BEMPEDOIC ACID (ETC-1002)

1002FDC-053

A RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BEMPEDOIC ACID 180 MG + EZETIMIBE 10 MG FIXED-DOSE COMBINATION COMPARED TO BEMPEDOIC ACID, EZETIMIBE, AND PLACEBO ALONE IN PATIENTS TREATED WITH MAXIMALLY TOLERATED STATIN THERAPY

Study Phase: 3

IND Number: 130707

Indication: Treatment of hyperlipidemia

Investigators: Approximately 125 sites located in North America

Sponsor: Esperion Therapeutics, Inc.
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2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.

Title of Study:

A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed-Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy

Study Number: 1002FDC-053

Phase of Development: 3

Clinical Sites: Approximately 125 sites located in North America

Primary Objective:

The co-primary objectives are to assess low-density lipoprotein cholesterol (LDL-C) lowering efficacy in patients receiving maximally tolerated statin therapy and treated for 12 weeks with bempedoic acid (BA) 180 mg + ezetimibe (EZE) 10 mg fixed-dose combination (FDC) versus each of the following:

- Placebo
- BA 180 mg
- EZE 10 mg

Secondary Objectives:

- To assess the efficacy of BA 180 mg + EZE 10 mg FDC versus placebo alone, BA alone, and EZE alone on high-sensitivity C-reactive protein (hs-CRP), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), triglycerides (TG), and apolipoprotein B (apoB) after 12 weeks of treatment;
- To characterize the safety and tolerability of BA 180 mg + EZE 10 mg FDC versus placebo alone, BA alone, and EZE alone through 12 weeks of treatment.

Exploratory Objectives:

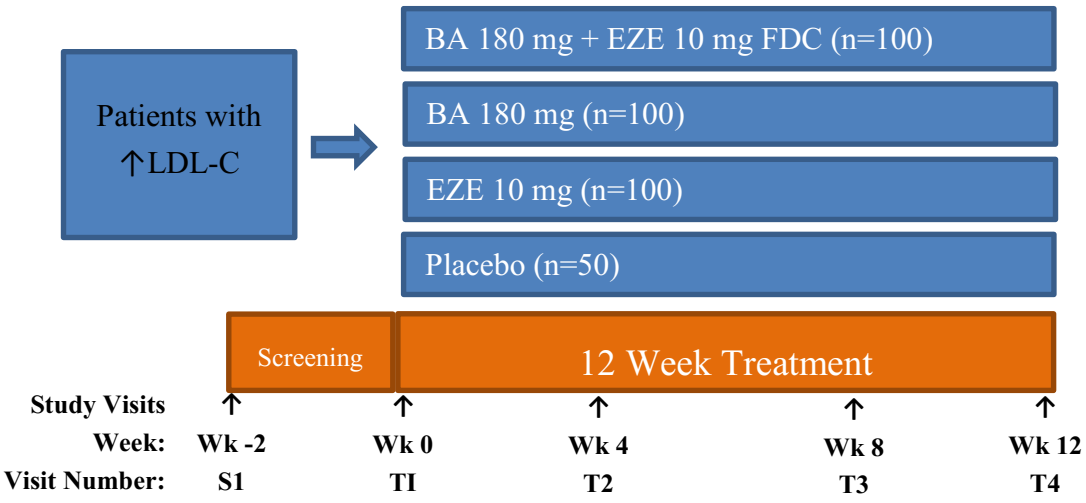
- To assess the efficacy BA 180 mg + EZE 10 mg FDC versus placebo alone, BA alone, and EZE alone on percentage of patients attaining LDL-C <70 mg/dL after 12 weeks of treatment;
- To characterize the plasma trough concentrations of BA and/or EZE when administered as BA 180 mg + EZE 10 mg FDC, BA alone, and EZE alone.

Study Design:

This is a Phase 3, randomized, double-blind, parallel group, multicenter study of BA + EZE versus its individual components and placebo. Screening (S1) will occur within approximately 2 weeks prior to randomization. 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. Approximately 350 eligible patients will be randomized 2:2:2:1 on Day 1/Week 0 (T1) to receive either BA 180 mg + EZE 10 mg FDC (N = 100), BA 180 mg (n = 100), EZE 10 mg (n = 100) or placebo (n = 50) for 12 weeks. Randomized patients will return for clinic visits at Week 4 (T2), Week 8 (T3), and Week 12 (T4). Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety and efficacy using the protocol-specified visit schedule and procedures.

Eligible patients will have 1) documented atherosclerotic cardiovascular diseases (ASCVD), and/or 2) heterozygous familial hypercholesterolemia (HeFH) and/or 3) multiple cardiovascular risk factors and will require additional LDL-C lowering therapy despite receiving maximally tolerated statin background therapy. Maximally tolerated statin therapy may include statin regimens other than daily dosing or no statin at all (if not tolerated); please note that simvastatin ≥40 mg/day is prohibited. A patient's currently used and maximally tolerated statin therapy will be determined by the investigator based on their medical judgment and local standard of care. Available sources, including the patient's self-reported history of lipid-modifying therapy will also be considered.

Patients will be stratified based on baseline/current statin intensity (high intensity statin versus other) and disease characteristics (ASCVD and/or HeFH versus multiple cardiovascular [CV] risk factors). High intensity statin includes atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day, all others will be categorized as 'other' for randomization and stratification purposes. Definition of ASCVD and/or HeFH or multiple CV risk factors are provided in inclusion criteria. Enrollment will be monitored and a cap may be placed, if necessary, to ensure appropriate distribution into either of the statin intensity categories.



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

Number of Patients (Planned): Approximately 350 adult male and female patients.

Duration of Study: Total study duration will be approximately 14 weeks (2 weeks [up to 16 days] of screening and 12 weeks of treatment).

Inclusion Criteria:

1. Provision of written informed consent prior to any study-specific procedure;
2. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Week -2 (Visit S1);
3. Men and nonpregnant, nonlactating women.

   Women must be either:

   - Naturally postmenopausal reported by the patient and defined as:
     - ≥55 years and ≥1 year without menses, or
     - <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L);

- Surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
- Women of childbearing potential willing to use at least 1 acceptable method of birth control. The minimal requirement for adequate contraception should be functional on Day 1, continuing during the study period and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:
  - oral, implantable, injectable or topical birth control medications;
  - placement of an intrauterine device with or without hormones;
  - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly;
  - vasectomized male partner who is the sole partner for this patient;
  - true abstinence: When this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

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

4. Treated with maximally tolerated statin therapy at stable dose for at least 4 weeks prior to screening. Maximally tolerated statin therapy may include statin regimens other than daily dosing, such as no statin to very low doses. A patient's maximally tolerated statin therapy will be determined by the investigator using their medical judgment and local standard of care. Available sources, including the patient's self-reported history of lipid-modifying therapy will also be considered.
5. Fasting LDL-C at Week -2 (Visit S1) while on maximally tolerated statin therapy:
   - ASCVD and or HeFH: ≥100 mg/dL (2.6 mmol/L);
   - Multiple cardiovascular risk factors: ≥130 mg/dL (3.4 mmol/L).

   Note: If a patient fails to meet LDL-C criterion, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat LDL-C measurement, the repeat value will be used to determine eligibility.
6. Meeting the definition for at least 1 of the following 3 categories (ASCVD, HeFH, multiple cardiovascular risk factors):
   a. Documented ASCVD including 1 or more of the following:
      - Acute MI;
      - Silent MI;
      - Unstable angina;
      - Coronary revascularization procedure (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery);
      - Clinically significant coronary heart disease (CHD) diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging);
      - Symptomatic peripheral arterial disease (PAD) defined as:
        - peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9, or
        - angiogram (including computed tomographic angiography [CTA]) showing ≥50% stenosis, or

- peripheral arterial revascularization (surgical or percutaneous) occurring greater than 90 days prior to Visit S1, or
- abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair occurring greater than 90 days prior to Visit S1, or
- lower extremity amputation due to peripheral vascular disease occurring greater than 90 days prior to Visit S1;

- Cerebrovascular atherosclerotic disease defined by:
  - ischemic stroke occurring greater than 90 days prior to Visit S1, or
  - Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram occurring greater than 90 days prior to Visit S1.

b. HeFH diagnosed by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria or the Dutch Lipid Clinical Network criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not also have ASCVD.

OR

c. Multiple cardiovascular risk factors defined as diabetes + 1 other risk factor or 3 risk factors that may include:
   a. Age (men ≥45 years; women ≥55 years) at Week -2 (Visit S1);
   b. Family history (coronary heart disease in a first degree relative, men <45 years; women <55 years);
   c. Smoking (current smoker);
   d. Hypertension (Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or on antihypertensive medications) at Week -2 (Visit S1);
   e. Low HDL-C (<40 mg/dL) at Week -2 (Visit S1);
   f. Coronary calcium score >95% for age/sex (see Appendix 6).

Exclusion Criteria:

1. Total fasting (minimum of 10 hours) TG ≥500 mg/dL (5.6 mmol/L) at Week -2 (Visit S1).

   Note: If a patient fails to meet TG criterion, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat TG measurement, the repeat value will be used to determine eligibility.
2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Week -2 (Visit S1) (Levey 2006).

   Note: If a patient fails to meet eGRF criterion, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat eGRF measurement, the repeat value will be used to determine eligibility.
3. Body mass index (BMI) ≥40 kg/m^2;
4. Recent (within 3 months prior to the screening visit [Week -2 (Visit S1)] or between screening and randomization visits) myocardial infarction (MI), unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or

dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease, or plans to undergo a major surgical or interventional procedure (e.g., PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.

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

   Note: If a patient fails to meet SBP and/or DBP criteria, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat blood pressure measurement, the repeat value will be used to determine eligibility.
6. Uncontrolled diabetes including hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -2 (Visit S1);
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -2 (Visit S1);
8. Liver disease or dysfunction, including:
   - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1), or
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥2 × ULN at Week -2 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

     Note: If a patient fails to meet ALT and/or AST criteria, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat ALT and/or AST measurement, the repeat value will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) that may affect drug absorption;
10. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL (100 g/L) at Week -2 (Visit S1);
11. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed;
12. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization;
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator;
14. Blood donation, blood transfusion, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization;
15. Use of any experimental or investigational drugs within 30 days prior to screening;
16. Previous enrollment in a BA clinical study;

17. Use of any of the following drugs within 5 weeks prior to screening (Visit S1) unless otherwise stated or a plan to use these drugs during the study is **prohibited**:
    - Systemic corticosteroids. Topical and inhaled corticosteroids are allowed;
    - Simvastatin ≥40 mg/day;
    - Non-statin LDL-C-modifying therapies:
        - Fibrates (including fenofibrate);
        - Niacin and derivatives;
        - Bile acid sequestants;
        - Ezetimibe;
        - Mipomersen or lomatipide (6 months prior to screening);
        - Apheresis;
        - Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (4 months prior to screening except PCSK9 small interfering RNA (siRNA), which are prohibited if used at any time in the past);
        - Cholesteryl ester transfer protein (CETP) inhibitors (12 months prior to screening);
        - Red yeast rice extract-containing products (2 weeks prior to screening);
18. Starting or adjusting the dose of the following permitted drugs within 5 weeks prior to screening. These drugs are **allowed as long as stable** at least 5 weeks prior to screening (Visit S1) unless otherwise noted:
    - Hormone replacement;
    - Thyroid replacement;
    - Obesity medication (6 months prior to screening);
    - Omega 3 fatty acids;
    - Diabetes medications;
19. Previous intolerance to ezetimibe;
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study;
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

Investigational Medicinal Product, Dosage and Mode of Administration:

- BA 180 mg + EZE 10-mg FDC tablet and matching placebo tablet
- BA 180-mg tablet and matching placebo tablet
- EZE 10-mg capsule and matching placebo capsule

All IMP will be ingested once daily at a similar time with or without food.

Non-Investigational Medicinal Product

All other background drugs including maximally tolerated statin therapy will be administered as prescribed by a physician.

Criteria for evaluation:

Lipid and Cardiometabolic Assessments:

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

Safety Assessments:

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) will be reported by treatment group. Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, HbA_{1C}, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram (ECG) readings, and weight.

Clinical Laboratory Assessments:

- Hematology: Hematocrit (Hct), Hgb, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute values only).
- Urinalysis (Dipstick): Clarity, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen.
- Urinalysis (Microscopic): Obtain centrally only if positive urine dipstick; bacteria, casts, crystals, epithelial cells, RBC, and WBC.
- Serum Chemistry (fasting): Albumin (ALB), alkaline phosphatase (ALK-P), ALT (or serum glutamic pyruvic transaminase [SGPT]), AST (or serum glutamic oxaloacetic transaminase [SGOT]), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO_2), chloride (Cl), creatinine, CK, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid.
- HbA_{1C}.

Other Screening Laboratories:

HBsAg, HCV, serum (Visit S1), and urine (Visit T1) pregnancy test (only for females who are of childbearing potential), FSH (only for postmenopausal females <55 years), TSH.

Plasma Trough IMP:

Plasma trough concentrations of BA (ETC-1002 and its active metabolite ESP15228) and EZE (glucuronidated EZE and unconjugated EZE).

Study Endpoints:

The primary objectives of this study are demonstrated by three co-primary endpoints:

- Percent change in LDL-C from baseline at Week 12 in BA 180 mg + EZE 10 mg FDC-treated arm compared to placebo arm;
- Percent change in LDL-C from baseline at Week 12 in BA 180 mg + EZE 10 mg FDC arm compared to BA 180 mg arm;
- Percent change in LDL-C from baseline at Week 12 in BA 180 mg + EZE 10 mg FDC-treated arm compared to EZE 10 mg arm.

The study is considered to have successfully demonstrated its primary objective IF all 3 co-primary endpoints achieve statistical significance.

Secondary endpoints:

- Percent change from baseline at Week 12 in parameters below between the BA 180 mg + EZE 10 mg FDC-treated arm and placebo arm, BA 180 mg-treated arm or EZE 10 mg arm:
  - hs-CRP;
  - Non-HDL-C;
  - TC;
  - ApoB;
  - TG;
  - HDL-C.

Exploratory endpoints:

- Proportion of patients attaining LDL <70 mg/dL at Week 12 in BA 180 mg + EZE 10 mg FDC-treated arm compared to BA 180 mg arm, EZE 10 mg arm and placebo arm;
- Plasma trough concentrations at Weeks 4, 8, and 12 of BA (ETC-1002 and its active metabolite ESP15228) and EZE (glucuronidated EZE and unconjugated EZE) in BA 180 mg + EZE 10 mg FDC-treated arm, BA-treated arm, and/or EZE alone treated arm.

Safety endpoints:

- Patient incidence of TEAE;
- Safety laboratory values, vital signs, PE findings, and ECGs.

Statistical Methods:

Sample Size

The sample size of 100 patients per active treatment group and 50 placebo patients (2:2:2:1) in this study (350 patients total) is selected to provide adequate power for each of the co-primary endpoint as well as the co-primary endpoint family as a whole.

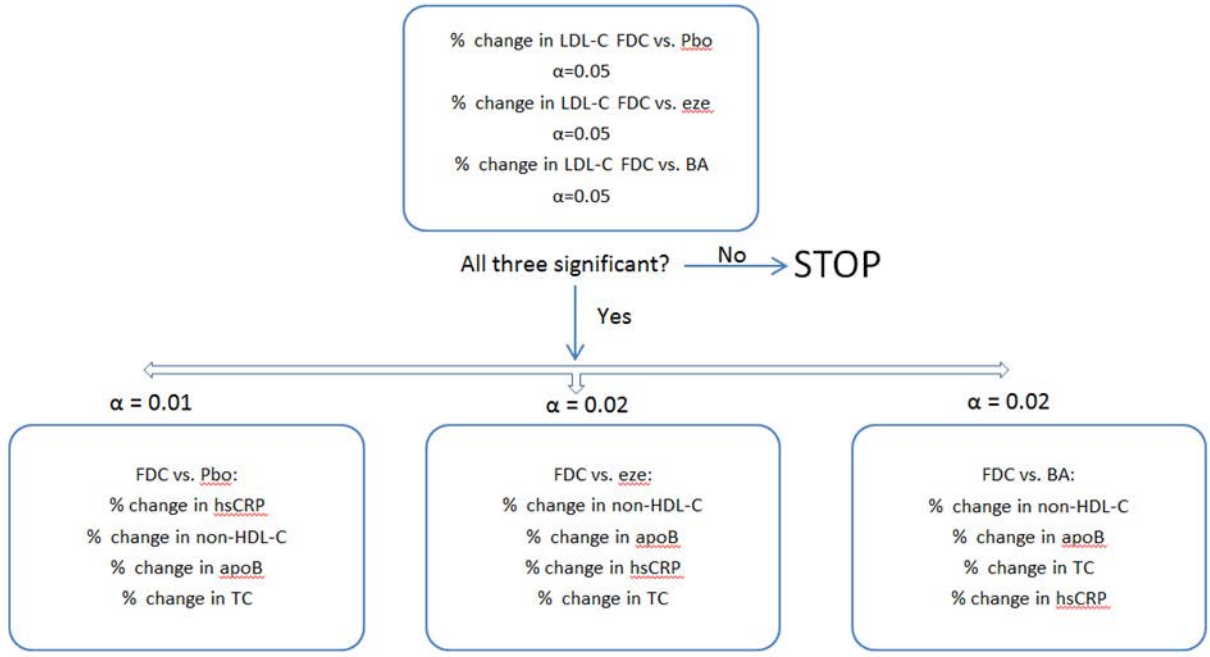
[redacted]

Testing Procedures

The co-primary endpoint family will be tested first, and each co-primary endpoint will be tested at alpha level of 0.05. The testing will stop if any of the co-primary endpoints does not achieve statistical significance. The secondary endpoints will only be tested when ALL of the co-primary endpoints are significant. A hierarchical testing procedure will be implemented within each comparison group on selected secondary endpoints.

Each of the secondary endpoint within a comparison group will be tested only if previous endpoint is significant at the alpha level assigned for that comparison group, i.e., via a step-down procedure.

A schematic representation for the statistical testing of the treatment comparisons and the co-primary and secondary efficacy endpoints is provided below.



Analysis Populations

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

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized patients who received at least 1 dose of blinded study medication (IMP).

The PK analysis set (PKS), used for all of the PK-related summaries, is defined as all patients in the SP who have at least 1 PK assessment unless major protocol deviations are identified to have affected the PK data or if key dosing or sampling information is missing.

Disposition and Baseline Characteristics

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

Primary Efficacy Analysis

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. Baseline is defined as the mean of the LDL-C values from Week -2 (Visit S1and predose Day 1/Week 0 (Visit T1). The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group and randomization stratification as factors and baseline LDL-C as a covariate.

Missing values for primary endpoint will be imputed using multiple imputation method, taking account for the adherence to the treatment. For patients with missing data and no longer receiving treatment at Week 12, their LDL-C will be imputed as their baseline value, for those with missing data but still receiving treatment, their LDL-C value will be imputed using a regression model based imputation including treatment, stratification factor, baseline LDL-C as auxiliary variables.

Secondary Efficacy Analysis

For the selected secondary endpoints (percent change from baseline to Week 12 in non-HDL-C, apoB, TC, and hsCRP), the data will be analyzed in the similar fashion as for the primary endpoints and then the step-down procedure as detailed above will be applied to the analysis results for each treatment comparison of interest (BA 180 mg + EZE 10 mg FDC versus placebo; BA 180 mg + EZE 10 mg FDC versus BA 180 mg; BA 180 mg + EZE 10 mg FDC versus EZE 10 mg). Other secondary endpoints based on HDL-C and TG will be analyzed separately outside of the step-down procedure. For HDL-C, non-HDL-C, TG, and TC, baseline is defined as the mean of the values from Week -2 (Visit S1) and predose Day 1/Week 0 (Visit T1), while baseline for apoB and hs-CRP is the predose Day 1/Week 0 value.

Safety Analyses

The summarization of AEs will include only TEAEs, any unfavorable and unintended sign, symptom, or disease occurred or worsened in severity since the first dose of the IMP until 30 days after study completion whether or not related to the product. An SAE is defined as any untoward medical occurrence that occurs at any dose that results in death, is life-threatening, requires inpatient hospitalization, results in persistent or significant disability, or results in a congenital anomaly/birth defect. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group.

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

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LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACL	Adenosine triphosphate-citrate lyase
ACSVL1	Very long-chain acyl-CoA synthetase 1
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular diseases
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the curve during 24 hours
BA	Bempedoic acid
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CABG	Coronary artery bypass graft
CEC	Clinical Event Committee
CETP	Cholesteryl ester transfer protein
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CNS	Central nervous system
CoA	Acetyl-coenzyme A

Abbreviation or Specialist Term	Explanation
CO_2	Carbon dioxide
CRF	Case report form
CRO	Contract research organization
CTA	Computed tomographic angiography
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EZE	Ezetimibe
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA_{1C}	Hemoglobin A_{1C}
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-ABVivi	Hepatitis C antibodies
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hs-CRP	High-sensitivity C-reactive protein

Abbreviation or Specialist Term	Explanation
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
LSM	Least squares mean
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MED ID	Medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Na	Sodium
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic analysis set
PT	Prothrombin time

Abbreviation or Specialist Term	Explanation
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
siRNA	Small interfering ribonucleic acid
SOC	System organ class
SOP	Standard operating procedures
SP	Safety population
SUSAR	Suspected and unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

Bempedoic acid (BA) 180 mg + ezetimibe (EZE) 10-mg fixed-dose combination (FDC) is being developed to lower low-density lipoprotein cholesterol (LDL-C).

Bempedoic acid (BA; ETC-1002) is an oral, first-in class, small molecule that is currently being investigated in Phase 3 clinical trials as a single agent in patients with primary hyperlipidemia who require additional LDL-C lowering. Bempedoic acid inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Bempedoic acid, like statins, up-regulates LDL-C receptors. However, unlike statins, BA does not inhibit cholesterol synthesis in muscle tissue, therefore it is anticipated that negative muscle-related adverse effects associated with statin use may be avoided by use of BA.

Ezetimibe (EZE; Zetia®) 10 mg was approved by the United States (US) Food and Drug Administration (FDA) for use to lower LDL-C, total cholesterol (TC), non-high-density lipoprotein-cholesterol (non-HDL-C), and apolipoprotein B (ApoB). Ezetimibe was approved as monotherapy and in combination with statins in patients with primary hyperlipidemia, and in combination with fenofibrate in patients with mixed hyperlipidemia. Ezetimibe has been approved as a FDC with more than 1 statin, and is currently marketed as an FDC of EZE and simvastatin (Vytorin®).

It is recommended that patients at high risk for future CVD events receive maximally tolerated statin therapy (Stone 2013; Catapano 2016). Despite receiving maximally tolerated statin therapy, many patients require additional therapy to further reduce LDL-C to an acceptable level. This Phase 3 study in patients treated with maximally tolerated statin background therapy is being conducted to characterize the magnitude of additional LDL-C lowering with an FDC of BA and EZE and to define the contribution to LDL-C lowering of each individual component.

4.1. Cardiovascular Disease and LDL-C-Lowering Drugs

Despite aggressive interventional and pharmacologic therapies, cardiovascular disease (CVD) is the number 1 cause of death globally (WHO 2015). The Global Burden of Disease study estimated that 29.6% of all deaths worldwide (approximately 15.6 million deaths) were caused by CVD in 2010, more than all communicable, maternal, neonatal and nutritional disorders combined, and double the number of deaths caused by cancers (Nichols 2014). In the US, based on 2011 death rate data, more than 2150 Americans die from CVD daily, an average of 1 death every 40 seconds (Mozaffarian 2015). Of great concern, approximately 155,000 Americans dying from CVD are less than 65 years of age (Mozaffarian 2015). In Europe, CVD remains the most common cause of deaths, resulting in almost 2 times as many deaths as cancer (Townsend 2015).

Elevated LDL-C is a major modifiable risk factor for the development of atherosclerosis and CVD (Sharrett 2001). Evidence supporting LDL-C as a therapeutic target and surrogate for cardiovascular (CV) outcomes comes from interventional studies with LDL-C-lowering therapies, epidemiological studies, and genetic variants (both gain of function and loss of function). Large randomized clinical studies aimed at lowering LDL-C show a consistent, log-linear relationship between LDL-C reduction and CV risk reduction, independent of the

mechanism for LDL-C lowering (Kathiresan 2008; Baigent 2010; Robinson 2005; Stamler 1986, Silverman 2016). A published patient-level meta-analysis including 26 statin trials and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and CV outcomes (Baigent 2010). This analysis showed that a 1 mmol/L (~39 mg/dL) reduction in LDL-C was associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. More recently, a meta-analysis in 312,175 patients from 49 trials assessed the relationship between LDL-C reduction and CV outcomes when LDL-C reduction was due to statin therapy versus established nonstatin interventions that work primarily by upregulation of the LDL receptor such as diet, bile acid sequestrants, ileal bypass, and EZE (Silverman 2016). This meta-analysis reported that the relationship between LDL-C reduction and CV outcomes was similar regardless of whether LDL-C reduction was derived from statin therapy or nonstatin interventions that upregulate the LDL receptor (Silverman 2016). Thus, LDL-C lowering via upregulation the LDL receptor is largely accepted as a valid surrogate endpoint of CV risk reduction by clinicians and regulatory authorities (Stone 2013).

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

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

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

4.2. Background on Bempedoic Acid

4.2.1. Mechanism of Action

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

Both ETC-1002-CoA (via ACL inhibition) and statins (via HMG-CoA reductase inhibition) inhibit cholesterol synthesis in the liver, but an important differentiating feature is that unlike statins, BA is inactive in skeletal muscle. This is consistent with the absence of ACSVL1 (the synthetase required to activate BA to ETC-1002-CoA and inhibit ACL) expression in muscle tissue. Evidence suggests that muscle-related adverse effects associated with statin use is a result of HMG-CoA reductase inhibition directly in skeletal muscle leading to a reduction of several downstream biological intermediates within the cholesterol synthesis pathway important for muscle cell function. Since BA is not activated to ETC-1002-CoA and does not inhibit cholesterol synthesis in muscle tissue, it is anticipated that negative muscle-related adverse effects associated with statin use may be avoided by use of BA. The long-term safety of BA and its metabolites regarding human skeletal muscle is not yet established.

4.2.2. Nonclinical Experience

[redacted]

4.2.3. Previous Human Experience

[redacted]

[redacted]

4.2.4. Dose Selection

[redacted]

4.3. Background on Ezetimibe

Please see the EZE label.

4.4. Risk Benefit Summary

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

Several Phase 2 clinical studies have assessed the safety and efficacy of BA as add-on to statins or in combination with EZE. These studies showed significant LDL-C lowering and a favorable safety profile.

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

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Objectives

5.1.1. Primary Objectives

The co-primary objectives are to assess LDL-C lowering efficacy in patients receiving maximally tolerated statin therapy and treated for 12 weeks with BA 180 mg + EZE 10 mg FDC versus each of the following:

- Placebo;
- BA 180 mg;
- EZE 10 mg.

5.1.2. Secondary Objectives

- To assess the efficacy of BA 180 mg + EZE 10 mg FDC versus placebo alone, BA alone, and EZE alone on high-sensitivity C-reactive protein (hs-CRP), non-HDL-C, TC, apoB, HDL-C, and TG after 12 weeks of treatment;
- To characterize the safety and tolerability of BA 180 mg + EZE 10 mg FDC versus BA alone, EZE alone and placebo alone through 12 weeks of treatment.

5.1.3. Exploratory Objective:

- To assess the efficacy BA 180 mg + EZE 10 mg FDC versus placebo alone, BA alone, and EZE alone on percentage of patients attaining LDL-C <70 mg/dL after 12 weeks of treatment;
- To characterize the plasma trough concentrations of BA and/or EZE when administered as BA 180 mg + EZE 10 mg FDC, BA alone, and EZE alone.

5.2. Study Endpoints

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

5.2.1. Primary Endpoint

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

5.2.2. Secondary Endpoints

- Percent change from baseline to Week 12 in hsCRP, non-HDL-C, TC, ApoB, HDL-C, and TG.

5.2.3. Exploratory Endpoints

- Percentage of patients attaining LDL-C <70 mg/dL at Week 12;
- Plasma trough concentrations at Weeks 4, 8, and 12 of BA (ETC-1002 and its active metabolite ESP15228) and EZE (glucuronidated EZE and unconjugated EZE) in BA 180 mg + EZE 10 mg FDC-treated arm, BA-treated arm, and/or EZE alone treated arm.

5.2.4. Safety Endpoints

- Patient incidence of AEs;
- Clinical safety laboratory (including hematology, blood chemistry, and urinalysis) results;
- Vital signs, electrocardiograms (ECGs) and physical examination (PE) findings.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 3, randomized, double-blind, parallel group, multicenter study of BA + EZE versus its individual components and placebo. Screening (S1) will occur approximately within 2 weeks prior to randomization. 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. Approximately 350 eligible patients will be randomized 2:2:2:1 on Day 1/Week 0 (T1) to receive either BA 180 mg + EZE 10 mg FDC (N = 100), BA 180 mg (n = 100), EZE 10 mg (n = 100), or placebo (n = 50) for 12 weeks. Randomized patients will return for clinic visits at Week 4 (T2), Week 8 (T3) and Week 12 (T4). Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety and efficacy using the protocol-specified visit schedule and procedures.

Eligible patients will have documented atherosclerotic cardiovascular diseases (ASCVD), heterozygous familial hypercholesterolemia (HeFH), and/or multiple cardiovascular risk factors and require additional LDL-C-lowering therapy despite receiving maximally tolerated statin background therapy. Maximally tolerated statin therapy may include statin regimens other than daily dosing or no statin at all (if not tolerated); however, doses of simvastatin ≥40 mg/day are prohibited. A patient's currently used and maximally tolerated statin therapy will be determined by the investigator based on their medical judgment and local standard of care. Available sources, including the patient's self-reported history of lipid-modifying therapy will also be considered.

Patients will be stratified based on baseline/current statin intensity (high intensity statin versus other) and disease characteristics (ASCVD and/or HeFH versus multiple CV risk factors). High intensity statin includes atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day, all others will be categorized as 'other' for randomization and stratification purposes. Definition of ASCVD and/or HeFH or multiple CV risk factors are provided in inclusion criteria. Enrollment will be monitored and a cap may be placed, if necessary, to ensure appropriate distribution into either of the statin intensity categories.

6.2. Study Hypothesis

The clinical hypothesis for this study is that BA 180 mg + EZE 10 mg FDC will significantly reduce LDL-C versus placebo, BA, and EZE in patients receiving maximum statin background therapy treated daily for 12 weeks. Additionally, it is hypothesized that both BA and EZE significantly contribute to the LDL-C lowering efficacy of the FDC.

6.3. Estimated Study Duration

Total study duration will be approximately 14 weeks (2 weeks screening [up to 16 days] and 12 weeks treatment).

6.4. Number of Clinical Sites

Approximately 125 sites in North America will participate in this study. Additional sites may be invited to participate to ensure study timelines are met.

6.5. Number of Patients

The study will enroll approximately 350 adult male and female patients.

7. SELECTION OF PATIENTS

Please note that eligible patients will have either documented ASCVD, HeFH, and/or multiple cardiovascular risk factors.

7.1. Patient Inclusion Criteria

1. Provision of written informed consent prior to any study-specific procedure;
2. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Week -2 (Visit S1);
3. Men and nonpregnant, nonlactating women.

   Women must be either:

   - Naturally postmenopausal reported by the patient and defined as:
     - ≥55 years and ≥1 year without menses, or
     - <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L);
   - Surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential willing to use at least 1 acceptable method of birth control. The minimal requirement for adequate contraception should be functional on Day 1, continuing during the study period and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:
     - oral, implantable, injectable or topical birth control medications;
     - placement of an intrauterine device with or without hormones;
     - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly;
     - vasectomized male partner who is the sole partner for this patient;
     - true abstinence: When this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

   Note: There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
4. Treated with maximally tolerated statin therapy at stable dose for at least 4 weeks prior to screening. Maximally tolerated statin therapy may include statin regimens other than daily dosing, such as no statin to very low doses. A patient's maximally tolerated statin therapy will be determined by the investigator using their medical judgment and local

standard of care. Available sources, including the patient's self-reported history of lipid-modifying therapy will also be considered.

5. Fasting LDL-C at Week -2 (Visit S1) while on maximally tolerated statin therapy:
   - ASCVD and or HeFH: ≥100 mg/dL (2.6 mmol/L);
   - Multiple cardiovascular risk factors: ≥130 mg/dL (3.4 mmol/L).

   Note: If a patient fails to meet LDL-C criterion, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat LDL-C measurement, the repeat value will be used to determine eligibility.
6. Meeting the definition for at least 1 of the following 3 categories (ASCVD, HeFH, multiple cardiovascular risk factors):
   a. Documented ASCVD including 1 or more of the following:
      - Acute MI;
      - Silent MI;
      - Unstable angina;
      - Coronary revascularization procedure (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery);
      - Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging);
      - Symptomatic peripheral arterial disease (PAD) defined as:
        - peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9, or
        - angiogram (including computed tomographic angiography [CTA]) showing ≥50% stenosis, or
        - peripheral arterial revascularization (surgical or percutaneous) occurring greater than 90 days prior to Visit S1, or
        - abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair occurring greater than 90 days prior to Visit S1, or
        - lower extremity amputation due to peripheral vascular disease occurring greater than 90 days prior to Visit S1;

- Cerebrovascular atherosclerotic disease defined by:
  - ischemic stroke occurring greater than 90 days prior to Visit S1, or
  - Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram occurring greater than 90 days prior to Visit S1.

b. HeFH diagnosed by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria or the Dutch Lipid Clinical Network criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not also have ASCVD.

OR

c. Multiple cardiovascular risk factors defined as diabetes + 1 other risk factor or 3 risk factors that may include:

   a. Age (men ≥45 years; women ≥55 years) at Week -2 (Visit S1);

   b. Family history (coronary heart disease in a first degree relative, men <45 years; women <55 years);

   c. Smoking (current smoker);

   d. Hypertension (Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or on antihypertensive medications) at Week -2 (Visit S1);

   e. Low HDL-C (<40 mg/dL) at Week -2 (Visit S1);

   f. Coronary calcium score >95% for age/sex (see Appendix 6).

7.2. Patient Exclusion Criteria

1. Total fasting (minimum of 10 hours) TG ≥500 mg/dL (5.6 mmol/L) at Week -2 (Visit S1).

   Note: If a patient fails to meet TG criterion, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat TG measurement, the repeat value will be used to determine eligibility.

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

   Note: If a patient fails to meet eGRF criterion, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat eGRF measurement, the repeat value will be used to determine eligibility.

3. Body mass index (BMI) ≥40 kg/m^2;
4. Recent (within 3 months prior to the screening visit [Week -2 (Visit S1)] or between screening and randomization visits) myocardial infarction (MI), unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease, or plans to undergo a major surgical or interventional procedure (e.g., PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.
5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg after sitting quietly for 5 minutes.

   Note: If a patient fails to meet SBP and/or DBP criteria, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat blood pressure measurement, the repeat value will be used to determine eligibility.
6. Uncontrolled diabetes including hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -2 (Visit S1);
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -2 (Visit S1);
8. Liver disease or dysfunction, including:
   - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1), or
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥2 × ULN at Week -2 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

     Note: If a patient fails to meet ALT and/or AST criteria, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat ALT and/or AST measurement, the repeat value will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) that may affect drug absorption;
10. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL (100 g/L) at Week -2 (Visit S1);

11. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed
12. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (i.e., not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization;
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator;
14. Blood donation, blood transfusion, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization;
15. Use of any experimental or investigational drugs within 30 days prior to screening.;
16. Previous enrollment in a BA clinical study;
17. Use of any of the following drugs within 5 weeks prior to screening (Visit S1) unless otherwise stated or a plan to use these drugs during the study is **prohibited**:
    - Systemic corticosteroids. Topical and inhaled corticosteroids are allowed.
    - Simvastatin ≥40 mg/day;
    - Non-statin LDL-C-modifying therapies:
        - Fibrates (including fenofibrate);
        - Niacin and derivatives;
        - Bile acid sequestants;
        - Ezetimibe;
        - Mipomersen or lomatipide (6 months prior to screening);
        - Apheresis;
        - PCSK9 inhibitors (4 months prior to screening except PCSK9 small interfering RNA (siRNA), which are prohibited if used at any time in the past);
        - Cholesteryl ester transfer protein (CETP) inhibitors (12 months prior to screening);
        - Red yeast rice extract-containing products (2 weeks prior to screening);
18. Starting or adjusting the dose of the following permitted drugs within 5 weeks prior to screening. These drugs are **allowed as long as stable** at least 5 weeks prior to screening (Visit S1) unless otherwise noted:
    - Hormone replacement;
    - Thyroid replacement;

- Obesity medication (6 months prior to screening);
- Omega 3 fatty acids;
- Diabetes medications;

19. Previous intolerance to ezetimibe;
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study;
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

7.3. Patient Lifestyle and Dietary Guidelines

Patients will fast for a minimum of 10 hours prior to collection of all laboratory samples (water and concomitant medications are permitted).

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

8. TREATMENT OF PATIENTS

8.1. Administration of Investigational Medicinal Product

During the Treatment Period, patients will be randomized to receive IMP of either BA 180 mg + EZE 10 mg FDC, BA 180 mg, EZE 10 mg, or placebo once daily. Each daily allotment of IMP is comprised of 2 tablets and 1 capsule provided in a blister package. Patients will be instructed to ingest IMP orally once daily with or without food at a similar time every day. On clinic visit days, patients will be instructed to delay ingestion of IMP until all study procedures have been completed.

If the patient forgets to take IMP on nonclinic visit days, it may be taken up to 12 hours later the same day. After that time, the patient should not take IMP that day and should resume ingestion of IMP the following day. Details describing the reasons for missed doses should be documented in the patient's medical records and electronic case report form (eCRF). Extra IMP is provided and can be used, if needed, prior to the next visit or to replace an allotment of IMP that cannot be used because it is lost or damaged.

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

8.2. Prior and Concomitant Medications

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

The Prior/Concomitant case report form (CRF) will be used to record medications, herbal remedies, vitamins, other nutritional supplements, and over-the-counter medications taken within 6 weeks prior to screening and during the study, with the exception of statins (particularly those that were not tolerated due to an adverse effect), which will be recorded if taken at any point in the past.

8.2.1. Required Medications

Patients will be required to be on maximally tolerated statin therapy with dose stable for at least 4 weeks prior to screening (Visit S1). Maximally tolerated statin includes statin regimens other than daily dosing, including no to very low doses. A patient's currently used and maximally tolerated statin therapy will be determined by the investigator based on their medical judgment and local standard of care. Available sources, including the patient's self-reported history of lipid-modifying therapy will also be considered. Statins may include:

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

- Rosuvastatin Calcium (Crestor®)
- Simvastatin (Zocor®); please note that doses ≥40 mg/day are prohibited
- Pitavastatin (Livalo®)

8.2.2. Prohibited Medications and Dietary Supplement

Use of any of the following drugs either in mono or combination therapy within 5 weeks prior to Visit S1 (unless otherwise stated) or a plan to use these drugs during the study is **prohibited**:

- Systemic corticosteroids. Topical and inhaled corticosteroids are allowed;
- Simvastatin ≥40 mg/day;
- Select non-statin LDL-C-modifying therapies:
  - Fibrates including gemfibrozil (Lopid®), fenofibrate (Antara®, Lofibra®, Tricor®, and Triglide™, Lipantil®, Supralip®), clofibrate (Atromid-S), ciprofibrate (Modalim®), bezafibrate (Bezalip®);
  - Niacin and derivatives including Niaspan® Rx and over-the-counter niacin (crystalline >500 mg/day or slow release or timed release at any dose);
  - Bile acid sequestants including Cholestyramine (Questran®, Questran® Light, Prevalite®, Locholest®, Locholest® Light); colestipol (Colestid®); colesevelam HCl (WelChol®, Cholestagel®);
  - Ezetimibe (Zetia®, Ezetrol®) other than that which is study-supplied;
  - Mipomersen or lomatipide (6 months prior to screening);
  - Apheresis;
  - PCSK9 inhibitors (4 months prior to screening except PCSK9 siRNA, which are prohibited if used at any time in the past);
  - CETP inhibitors (12 months prior to screening);
  - Red yeast rice extract-containing products (2 weeks prior to screening).

Other Drugs:

- Probenecid or cyclosporine;
- Potent CYP3A4 inhibitors including amiodarone, azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole), bosentan, clarithromycin, cobicistat, conivaptan, danazol, daptomycin, diltiazem, domperidone, erlotinib, erythromycin, fusidic acid, mibefradil, nefazodone, piperaquine, protease inhibitors (atazanavir, boceprevir, darunavir, delavirdine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir), quinupristin/dalfopristin, telithromycin, verapamil.

8.2.3. Permitted Medications

Patients in this study may be using a wide range of concomitant medications, according to local standard of care for their medical conditions. Permitted medications must be stable for at least 2 weeks prior to Visit S1 (Week -2) with the exception of the medications described below.

The following permitted medications that may impact plasma lipid levels are allowed provided that they are stable at least 5 weeks prior to screening (Visit S1) unless otherwise noted:

- Hormone replacement;
- Thyroid replacement;
- Obesity medication (6 months prior to screening);
- Omega 3 fatty acids;
- Diabetes medications.

8.3. Treatment Assignment, Randomization, and Blinding

During the Treatment Period, patients will receive double-blind IMP. At Day 1 (Visit T1), patients will be randomized to receive either BA 180 mg + EZE 10 mg FDC, BA 180 mg, EZE 10 mg or placebo. The randomization will be stratified by baseline statin intensity (high intensity vs. other) and disease characteristics (ASCVD and/or HeFH vs. multiple CV risk factors). Only atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day are considered high intensity statin and all others will be considered as 'other' for randomization purpose. The criteria for determining these 2 stratification factors are further detailed in Section 7.1). The investigator or designee will utilize Interactive Web Response System (IWRS) during the visit to randomize the patient and obtain the appropriate IMP container via medication identification numbers (MED ID). A patient is considered to be randomized when the corresponding randomization box is checked within the eCRF.

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

During the Treatment Period, Sponsor, site personnel, CRO, and patient will all be unaware of patient's treatment assignment; an independent bio-analytical lab will be aware of treatment assignment only to support PK sample analysis.

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

consultation with the Medical Monitor, contact must be made within 24 hours of breaking the blind.

At the initiation of the study, the clinical site will be instructed on procedures for breaking the blind via the IWRS. In all cases of breaking the blind, the investigator must document in the patient's medical record the date, time, and reason for breaking the blind, and the names of personnel involved.

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

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Description of Investigational Medicinal Product

Table 2: Investigational Medicinal Products

Product Name:	**Investigational Medicinal Product**	
	Bempedoic acid	**Placebo to Match Bempedoic Acid**
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure:	9 count blister card with child resistant closures	9 count blister card with child resistant closures
Route of Administration:	Oral, daily at approximately the same time, with or without food	Oral, daily at approximately the same time, with or without food
Physical Description:	[redacted]	
Product Name:	**Investigational Medicinal Product**	
	Ezetimibe	**Placebo to Match Ezetimibe**
Dosage Form:	Over-encapsulated tablets	Capsules
Unit Dose:	10 mg	Not applicable
Container/Closure:	9-count blister card with child-resistant closures	9-count blister card with child-resistant closures
Route of Administration:	Oral, daily at approximately the same time, with or without food	Oral, daily at approximately the same time, with or without food
Physical Description:	[redacted]	
Product Name:	**Investigational Medicinal Product**	
	Bempedoic acid + ezetimibe FDC	**Placebo to Match Bempedoic acid + ezetimibe FDC**
Dosage Form:	Tablets	Tablets
Unit Dose:	180 mg/10 mg	Not applicable
Container/Closure:	9-count blister card with child-resistant closures	9-count blister card with child-resistant closures
Route of Administration:	Oral, daily at approximately the same time, with or without food	Oral, daily at approximately the same time, with or without food
Physical Description:	[redacted]	

Please see Pharmacy Manual for detailed storage requirements and instructions and additional information.

9.2. Investigational Medicinal Product Supply and Control

The Sponsor will supply the IMP for this study as described above. IMP will be distributed and released in accordance with regional and local requirements during the conduct of the study.

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

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

9.3. Packaging and Labeling

Double-blind IMP will be packaged in blister packs. Each blister pack will contain a 9-day supply and 4 blister packs will be provided in the drug kit.

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

9.4. Investigational Medicinal Product Adherence

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

9.5. Investigational Medicinal Product Accountability

Patients will be instructed to return all packaging and unused IMP at every visit for assessment of adherence and drug accountability.

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

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

- Amount received/placed in storage area;
- Amount currently in storage area;
- MED ID number for all IMP;
- Dates and initials of person(s) responsible for IMP inventory (including entry/movement/disposition);
- Date and amount of IMP dispensed to each patient, including unique patient identifiers;
- Date that IMP was returned by patient, assessment of adherence, and relevant documentation of discrepancies;

- Nonstudy disposition (e.g., lost, broken, wasted);
- Amount returned to Sponsor (or designee)/destroyed or amount destroyed per local standard operating procedure (SOP) following accountability by site monitor.

9.6. Investigational Medicinal Product Handling, Storage, and Disposal

The Principal Investigator will ensure that all IMP is stored in a secured area, under recommended storage conditions [redacted] in accordance with applicable regulatory requirements for investigational drugs. Access to IMP will be limited to those clinical site personnel authorized by the investigator. Upon completion or termination of the study, all IMP and used and unused IMP packaging must be returned to the Sponsor (or designee) for eventual destruction unless otherwise authorized by the Sponsor. All IMP returns must be accompanied by the appropriate documentation.

10. STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

10.1. Informed Consent

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

10.2. Interactive Web Response System and eCRFs

Data will be captured on eCRFs, and IWRS is contacted via eCRFs. Instructions for these systems and additional contact time points for IWRS will be provided separately.

10.3. Patient Identification Numbers

A unique patient identification number will be assigned to each patient to identify each patient throughout the study. Patient identification numbers will be assigned sequentially by IWRS and is comprised of protocol, site, and patient-specific numbers.

10.4. Rescreening

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

10.5. Procedures and Schedule of Assessments

The study is comprised of two distinct periods: screening and double-blind treatment.

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

10.5.1. Screening Week -2 (Visit S1; Day -16 to Day -5)

The screening period will begin with a screening visit that will occur within approximately 2 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:

- Assess AEs and serious adverse events (SAEs) (starting from signing the informed consent document);
- Demographics;
- Clinically relevant medical history;

- Prior and concomitant medication review;
- Review of all inclusion/exclusion criteria that can be assessed at this time;
- Height (cm), and weight (kg);
- Vital signs;
- Central clinical laboratory evaluations:
  - TSH;
  - Hematology, blood chemistry, and urinalysis;
  - Serology (including HBsAg, hepatitis C virus [HCV] antibody);
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG);
  - Serum pregnancy test (in female patients of childbearing potential) or FSH (only in postmenopausal women <55 years of age);
  - HbA_{1C};
- Contact IWRS to register the patient.

Patients who meet all enrollment criteria that can be assessed following review of the Visit S1 central clinical laboratory results (available several days after Visit S1) will be instructed to return for Visit T1 and to maintain consistent diet and exercise patterns throughout the study. Patients who fail to meet any entry criterion that can be assessed at Visit S1 are considered to be screen failures and are not required to return for additional visits (although a patient can be seen at any time for safety reasons).

Note: An unscheduled visit may be completed no more than 10 days after the screening visit if patient fails to meet entry criteria for LDL-C, TG, DBP, SBP, eGFR, ALT, AST, serology and/or CK entry criterion at the discretion of the investigator if warranted. For those patients who have a repeat measurement, the repeat value will be used to determine eligibility.

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

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

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

At randomization, patients will be stratified based on baseline/current statin intensity (High vs. Other) and disease characteristics (ASCVD and/or HeFH vs. multiple CV risk factors). High intensity statin includes atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day, all others will be categorized as ‘other’ for randomization and stratification purposes. Definition of ASCVD and/or HeFH or multiple CV risk factors are provided in inclusion criteria.

The patient will undergo the following assessments and procedures:

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

10.5.3. Treatment Week 4 (Visit T2; Day 29 ± 5 days)

Patients will undergo the following assessments and procedures:

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

10.5.4. Treatment Week 8 (Visit T3; Day 57 ± 5 days)

Patients will undergo the following assessments and procedures:

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

10.5.5. Treatment Week 12 (Visit T4; Day 85 ± 5 days)/End of Study or Early Termination

Patients will undergo the following assessments and procedures:

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

10.6. Discontinuations

10.6.1. Patients Inadvertently Enrolled

The inclusion and exclusion criteria for enrollment must be followed exactly and completely. If a patient who does not meet enrollment criteria is inadvertently enrolled, the Medical Monitor should be contacted within 24 hours of identification. If it is determined after discussion with the Medical Monitor that, in considering patient safety, it is appropriate to continue IMP (documentation of this is necessary), the patient will continue on IMP and be monitored for all visits and testing (including laboratory measures) for the duration of the study. If after discussion with the Medical Monitor it is determined that the patient should not continue IMP, IMP will be discontinued, but the patient will remain in the study to be evaluated for concomitant medications, and efficacy and safety endpoints until the end of the study visit.

Patients inadvertently enrolled under the following criteria should be discontinued from IMP (but remain in the study):

- Female patients who are pregnant or are breastfeeding or who do not agree to use at least 1 reliable methods of birth control during the study (unless they have agreed to follow the definition of true abstinence);
- Any clinically significant medical condition that according to the investigator could interfere with participation in the study;
- Unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study;
- Have a history of drug, alcohol, or substance abuse within the past 6 months, as assessed by the investigator.

If a patient stops IMP for any of the above exclusion criteria following discussion with the Medical Monitor, then investigators should notify the Sponsor (or designee). The reason for the patient's inadvertent enrollment should be documented in the patient's record.

10.6.2. Temporary Discontinuation of Investigational Medicinal Product

There may be situations in which IMP is temporarily discontinued at the discretion of the investigator. IMP should be restarted as soon as possible based on investigator judgment. The number of days the IMP was not taken, and the reason for temporary discontinuation, should be documented in the patient's medical record. There is no limit to the amount of time patient can be off IMP prior to restarting.

Investigators should contact the Medical Monitor if IMP is temporarily discontinued and this should occur prior to IMP discontinuation if possible.

10.6.3. Permanent Discontinuation of Investigational Medicinal Product

There may be situations where it may be necessary for a patient to permanently discontinue IMP.

Investigators should contact the Medical Monitor prior to permanent IMP discontinuation to discuss the situation. **If IMP is permanently discontinued, the patient will remain in the**

study to be evaluated for concomitant medications, efficacy and safety endpoints until the final study visit. If the patient is unwilling or unable to return for follow-up visits in person, alternatives such as telephone contact visits per the Schedule of Events, or telephone follow up at the end of the study should be used to collect as much data as possible. The follow-up frequency will be documented in the eCRF.

The reason for permanent discontinuation of IMP should be documented in the eCRF. If the discontinuation of IMP is due to an AE, the event should be documented in the eCRF. Some possible reasons that may lead to permanent early IMP discontinuation include:

- In the opinion of the investigator, any AE or a significant change in a laboratory value that warrants permanent discontinuation of IMP therapy. Investigators are advised to call the Medical Monitor prior to making such a decision;
- Illness, condition, or procedural complication (including AEs) affecting the patient's ability to participate or requiring prohibited medication. Investigators are advised to call the Medical Monitor prior to making such a decision;
- Female patients who become pregnant or are breastfeeding or who do not agree to use at least 1 reliable methods of birth control during the study (unless they have agreed to follow the definition of true abstinence) will be permanently discontinued from IMP;
- The patient requests to stop IMP permanently;
- The patient study blind is broken;
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study. If after discussion with the study Medical Monitor it is determined that the patient should not continue IMP, IMP will be discontinued;
- Patient moves away and it is impossible to come to this or any other trial site for visits as required by protocol.

10.6.4. Patient Discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be uncommon, occurring only if the patient explicitly withdraws consent. At the time of discontinuing from the study, the Medical Monitor should be contacted, and, if possible, an early discontinuation visit should be conducted, per the Study Schedule. The patient will be permanently discontinued both from the IMP and from the study at that time. During the study closeout period, survival (vital) status will be collected within legal and ethical boundaries for all patients randomized who withdrew their participation from the study.

10.6.5. Patients Lost to Follow-Up

A patient would be considered potentially lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected

to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Investigators are advised to call the Medical Monitor prior to concluding patient is lost to follow-up. Vital status will be collected within legal and ethical boundaries during the study closeout period. If vital status is determined, the patient will not be considered lost to follow-up.

10.6.6. Discontinuation of Study Sites or the Study

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

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

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

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

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

11. ASSESSMENT OF EFFICACY

11.1. Assessments of Lipids and hs-CRP

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

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

- Blood samples will be drawn after a minimum 10-hour fast (water and concomitant medications are allowed)

Patients are to be in a seated position during the blood collection. Collection schedule and instructions are provided in the Central Clinical Laboratory Manual. A description of the sample collection, storage, and shipping as well as monitoring and management of abnormal laboratories are described in Section 12.1.6.

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

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

Clinical Laboratory Test	Clinical Laboratory Test
Basic Lipid Parameters • Total cholesterol (TC) • Calculated low-density lipoprotein cholesterol (LDL-C) and non-HDL-C • High-density lipoprotein cholesterol (HDL-C) • Triglycerides (TG)	Other Parameters • High-sensitivity C-reactive protein (hs-CRP) • Apolipoprotein B (ApoB)

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

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

12.1.1. Demographic/Medical History

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

12.1.2. Vital Signs

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

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

12.1.3. Weight and Height

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

Height will be measured using standard clinic procedures.

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

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

12.1.4. Physical Examination

Physical examinations will include an assessment of the following:

- General appearance;
- Skin;
- Eyes, ears, nose, and throat;
- Head and neck;
- Extremities;

- Musculoskeletal examination;
- Respiratory examination;
- Cardiovascular assessment, including rhythm and presence of cardiac abnormalities;
- Abdominal examination;
- Neurologic examination including documentation of the presence of abnormalities in mental status and motor and sensory function;
- Any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences.

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

12.1.5. Electrocardiogram

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

12.1.5.1. Monitoring and Management of Abnormal Electrocardiograms

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

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

12.1.6. Central Clinical Laboratory Tests

12.1.6.1. Central Clinical Laboratory Parameters (Safety)

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

Table 4: Central Clinical Laboratory Parameters (Safety)

<table>
<tr><th>Clinical Laboratory Test</th><th>Clinical Laboratory Test</th></tr>
<tr><td><u>Hematology</u>
• Hematocrit (Hct)
• Hemoglobin (Hgb)
• Mean corpuscular hemoglobin (MCH)
• Mean corpuscular hemoglobin concentration (MCHC)
• Mean corpuscular volume (MCV)
• Platelet count
• Red blood (RBC) cell count
• White blood (WBC) cell count with differential (absolute values only)</td><td rowspan="2"><u>Blood Chemistry (serum, fasting)</u>
• Albumin (ALB)
• Alkaline phosphatase (ALK-P)
• Alanine aminotransferase (ALT; SGPT)
• Aspartate aminotransferase (AST; SGOT)
• Blood urea nitrogen (BUN)
• Calcium (Ca)
• Carbon dioxide (CO_2)
• Chloride (Cl)
• Creatinine
• Creatine kinase (CK)
• Glucose
• Lactate dehydrogenase (LDH)
• Phosphorus
• Potassium (K)
• Sodium (Na)
• Total and direct bilirubin (TB)
• Total protein
• Uric acid</td></tr>
<tr><td><u>Urinalysis (Dipstick)</u>
• Clarity
• Bilirubin
• Color
• Glucose
• Ketones
• Leukocyte esterase
• Nitrite
• Occult blood
• pH
• Protein
• Specific gravity
• Urobilinogen</td></tr>
<tr><td><u>Urinalysis (Microscopic) – only if urine dipstick abnormal</u>
• Bacteria
• Casts
• Crystals
• Epithelial cells
• Red blood cells (RBC)
• White blood cells (WBC)</td><td><u>Coagulation – ONLY in patients receiving anticoagulant therapy that in the investigator's judgment requires monitoring, measured only at Visit T1 and 3 to 5 days post Visit T1</u>
• Prothrombin time (PT)
• International normalized ratio (INR)</td></tr>
</table>

Table 4: Central Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), optional reflexive hepatitis C RNA only if HCV is positive • Serum and urine pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; only for postmenopausal females <55 years old >1 year without menses) • Thyroid-stimulating hormone (TSH)	Other Sample Collection • Plasma trough investigational medicinal product (IMP)

12.1.6.2. Sample Collection, Storage, and Shipping

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

12.1.6.3. Collection and Assessment of Plasma Trough IMP

Plasma trough IMP will be measured at Weeks 4, 8, and 12. A single 6-mL whole blood sample will be collected and processed by the site according to instructions provided in the manual provided by the Central Laboratory. At the time of sample collection, the date and time of blood draw and the last 2 doses of study medication will also be collected. Samples will be shipped to the central clinical laboratory and subsequently forwarded to a bio-analytical lab for measurement and analysis.

Plasma trough IMP concentrations will be measured and analyzed using validated methods and will include BA (ETC-1002 and its active metabolite ESP15228) and EZE (glucuronidated EZE and unconjugated EZE).

12.1.6.4. General Monitoring and Management of Abnormal Clinical Labs

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

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

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

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

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

12.1.6.4.1. 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; 2) history of concomitant medication use; 3) history of exposure to environmental chemical agents, including ethanol; and 4) query for related symptoms. Although samples will be collected, some repeat LFT parameters may not be measured until elevation is confirmed.

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN but ≤5 × ULN, consideration should be given to administering no further doses of IMP. At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >5 × ULN and no alternative reason for elevation is identified, patient should discontinue IMP. At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following and no alternative reason for elevation is identified, patient should discontinued IMP and be given no further IMP treatment:
  - TB >2 × ULN;
  - INR >1.5 × ULN (unless the patient is on stable dose of anticoagulation medication);
  - Appearance or worsening of right upper abdominal discomfort, anorexia, fatigue, nausea, vomiting, fever, rash, or eosinophilia.

12.1.6.4.2. Monitoring and Management of Elevated Creatine Kinase

If at any time after randomization a patient experiences a marked CK elevation >5 × ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available. If initial CK elevation is >10 × ULN, patients will be instructed to discontinue IMP immediately (instead of continuing IMP until repeat lab value is assessed). It is very important that repeat confirmatory assessment occur as soon as possible (within a day of stopping IMP).

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

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN, if asymptomatic the 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 the repeat CK assessment confirms an unexplained (i.e., not associated with recent trauma or physically strenuous activity) CK abnormality as listed below, the patient should discontinue IMP:
  - >5 × ULN that is associated with symptoms of muscle pain, muscle weakness, or dark urine; or
  - >10 × ULN, even in the absence of symptoms.
- At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after CK has returned to the baseline level.

12.1.6.4.3. Monitoring and Management of Elevated TG

Patients may continue to use stable doses of TG-lowering medications (except fibrates) during the study. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. If the TG level exceeds 1000 mg/dL (11.3 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol defined threshold criteria for TG.

- Any patient with initial report of TG >1000 mg/dL (11.3 mmol/L), will be counseled on healthy dietary guidelines, and reminded to take IMP and other background medications as directed and fast for at least 10 hours prior to repeat TG assessment.
- Patient will return to clinic within 1 week for a repeat, fasting TG assessment to confirm the TG value meets the threshold criteria.

- Any patient with a confirmed TG >1000 mg/dL (11.3 mmol/L) will have TG lowering medications (except fibrates) adjusted or added if possible to lower TG. Changes in medications will be documented on the case report form. These medications will not be provided by the sponsor.

12.1.6.4.4. Monitoring and Management of Potential Hypoglycemia and Metabolic Acidosis

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

Clinical laboratories will be assessed by the Investigator or designee to determine any signs of anion gap metabolic acidosis. If laboratories are consistent with metabolic acidosis, immediate follow up with the patient for further medical evaluation of the acidosis will occur (see Section 13.3 for additional details). This event should be captured as an AE.

12.1.6.5. Total Blood Volume of Central Clinical Laboratory Samples

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

13. ADVERSE AND SERIOUS ADVERSE EVENTS

13.1. Adverse Events

13.1.1. Definition of Adverse Events

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

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Any new disease or exacerbation of an existing disease;
- Any deterioration in nonprotocol-required measurements of laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug;
- TEAEs are defined as AEs that begin or worsen after the first dose of study drug;
- Adverse drug reaction (ADR; see Section 13.1.2).

13.1.2. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., 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 (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

13.1.3. Reporting for Adverse Events

All AEs occurring during the course of the study (starting from signing informed consent to study completion or discontinuation) will be collected on the AE eCRF. Patients should be instructed to report any AE that they experience to the Investigator through 30 days following study completion or discontinuation. Beginning with Visit S1 (Week -2), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. Any SAE that occurs from the time of signing informed consent through 30 days following study completion should be reported to the Sponsor per Section 13.2.4.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally,

the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure. Any medical condition already present at screening or baseline should not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

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

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

- Description of the event (e.g., headache);
- Date of onset;
- Date of resolution (or that the event is continuing);
- Action taken as a result of the event;
- Seriousness of the event;
- Severity of the event;
- Outcome of the event;
- Investigator's assessment of relationship to study drug.

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

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

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

13.1.4. Severity

It is the Investigator's responsibility to assess the intensity (severity) of an AE. The severity of the AE will be characterized as mild, moderate, or severe according to the following definitions:

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

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

13.1.5. Relationship

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

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

13.1.6. Monitoring and Follow-up of Adverse Events

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

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

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

13.1.7. Treatment-Emergent Adverse Events

TEAE are defined as AEs that begin or worsen after the first dose of study drug until 30 days after study completion or as defined in the study-specific statistical analysis plan.

13.2. Serious Adverse Events

13.2.1. Definition of Serious Adverse Event

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

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

NOTE: Hospitalization is defined as a formal inpatient admission. This will not include admissions under "23-hour Observational Status", an Emergency Room visit without hospital admission or an Urgent Care visit and therefore, such events will not be recorded as an SAE under this criterion. Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

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

13.2.2. Events not Qualifying as Serious Adverse Events

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

- Overdose of either Esperion study drug or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a nonserious AE on the appropriate eCRF page

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

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the central (or local where appropriate) laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment. For criteria of reporting abnormal lab values as AE, see Section 12.1.6.4.

13.2.4. Reporting Serious Adverse Events

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following study completion, must be reported by the Principal Investigator or designee to the authorized Medical and Safety Services within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. For most patients this will be 30 days following their Week 12 (Visit T4) visit. All SAEs that the Investigator considers related to study drug that occur after the 30-day follow-up of the study period must be reported to the Sponsor.

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

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

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

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

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

13.2.5. Reporting of Serious Adverse Events to Regulatory Authorities

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

SAEs that are anticipated to occur in this patient population will be collected and reported by the Investigator as described in Section 13.2.4. However, these events will not be submitted to the

regulatory authorities as expedited reports unless they meet SUSAR criteria. These events that are considered to be exempt from expedited reporting include the following clinical endpoints:

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

13.2.6. Reporting of Patient Death

The death of any patient during the study, or within the 30-day follow-up period after they have completed the study (regardless of the cause), must be reported as detailed in Section 13.2.4.

13.2.7. Reports of Pregnancy

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

13.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) include metabolic acidosis (clinical laboratories), hepatic, muscular (AE and CK evaluation), new onset diabetes/hyperglycemia, renal, cardiovascular, and neurocognitive/neurologic events. Specific monitoring guidelines are provided in the case of AEs uncovered through laboratory evaluations.

13.4. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) responsible for monitoring Phase 3 BA studies will be informed of this study and available for ad hoc review of specific data if needed. However, due to the study's relatively short enrollment period and treatment duration, the DMC will not review data from this study on an ongoing basis.

13.5. Clinical Event Committee (CEC)

A blinded independent expert Clinical Event Committee (CEC) responsible for adjudicating clinical endpoints including all major cardiovascular events from Phase 3 BA studies will be informed of this study and available for ad hoc review of specific data if needed. However, due to the study's relatively short enrollment period and treatment duration, the CEC will not routinely adjudicate clinical endpoints from this study.

14. STATISTICS

14.1. General Considerations

The statistical analyses described in this section will be performed as further outlined in the statistical analysis plan (SAP). The SAP will supersede the protocol if there are any differences between the 2 documents in the plans or descriptions for data analysis. The SAP will be included as an appendix in the clinical study report for this protocol.

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

14.2. Determination of Sample Size

The sample size of 100 patients per active treatment group and 50 patients in the placebo arm (2:2:2:1) of this study (350 patients total) was selected to provide adequate power for each of the co-primary endpoint as well as the co-primary endpoint family as a whole.

14.3. Analysis Populations

The full analysis set (FAS), used for all of the efficacy analyses, is defined as all randomized patients. Patients in FAS will be analyzed in the treatment group they are randomized to regardless of the treatment received.

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

The PK analysis set (PKS), used for all of the PK-related summaries, is defined as all patients in the SP who have at least 1 PK assessment unless major protocol deviations are identified to have affected the PK data or if key dosing or sampling information is missing.

14.4. Disposition, Demographics, and Baseline Characteristics

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

14.5. Co-Primary Endpoint Analysis

The co-primary efficacy endpoints consist of three comparisons of the percent change from baseline to Week 12 in LDL-C: FDC vs. placebo, FDC vs. EZE; and FDC vs. BA.

Each of the comparisons will be carried out using an analysis of covariance (ANCOVA) model including treatment group and stratification factors as factors and baseline LDL-C as covariate.

Baseline LDL-C is defined as the mean of the values from Week -2 (Visit S1) and pre-dose Day 1/Week 0 (Visit T1).

Missing values for primary endpoint will be imputed using multiple imputation (MI) method (MI), taking account for the adherence to the treatment. For patients with missing data and no longer receive treatment at Week 12, their LDL-C will be imputed as their baseline value; for those with missing data but still receiving treatment, their LDL-C value will be imputed using a regression based model including treatment, stratification factors, baseline LDL-C as auxiliary variables. Approximately 200 datasets will be imputed. The imputed datasets will be analyzed using the ANCOVA model described above and the results from the analysis of each imputed dataset will be combined using Rubin's method. The final results will include the least squares mean (LSM), SE, 95% confidence interval (CI) and associated p-values for each treatment group, as well as for each treatment group comparison of interests.

The details of the ANCOVA model and multiple imputations will be further described in the SAP.

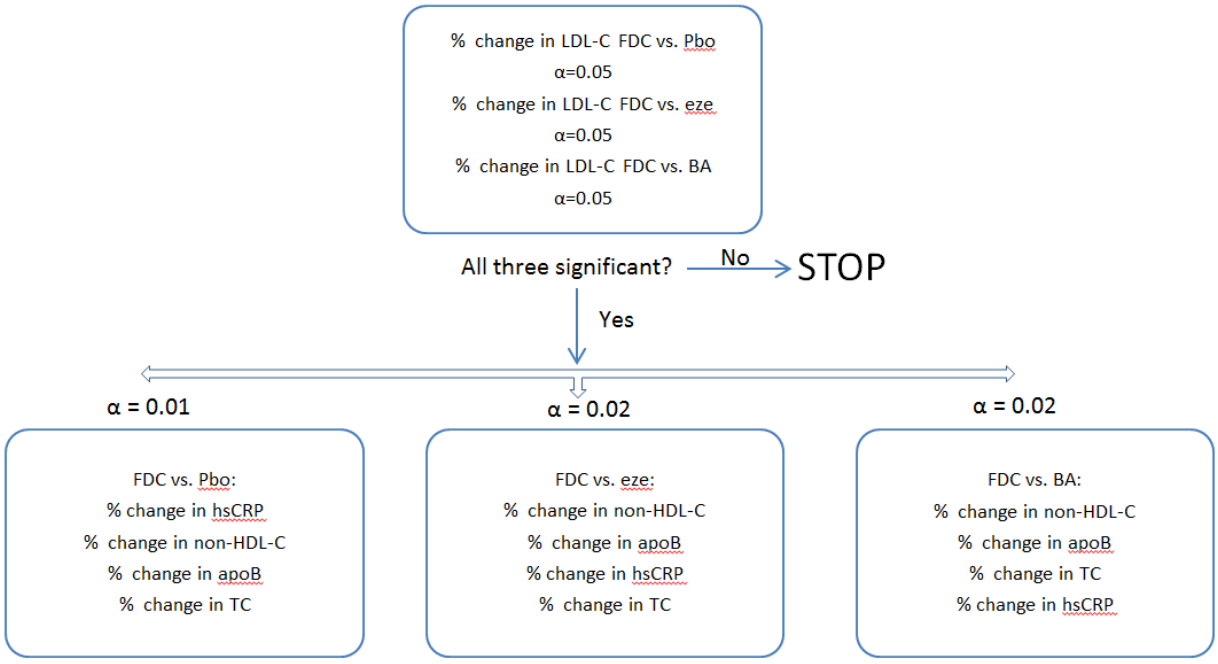
Each of the comparisons within the co-primary endpoint family will be conducted at a significance level of 0.05. If and only if all three testing achieve statistical significance, the study is claimed to meet its primary objective and the hypothesis testing will continue to secondary endpoints, otherwise all statistical comparisons for secondary endpoints are considered descriptive only.

14.6. Secondary Efficacy Endpoint Analyses

Secondary efficacy endpoints, which include the percent change from baseline to Week 12 in additional lipid and cardiometabolic biomarkers, will be analyzed in a similar manner as the primary efficacy endpoint.

Baseline for non-HDL-C, HDL-C, TC, and TG is defined as the mean of the values from Week -2 (Visit S1) and predose Day 1/Week 0 (Visit T1), while baseline for ApoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value.

As described in Section 14.5, if co-primary endpoint family achieves statistical significance, a list of selected secondary endpoints will be tested in sequential order within each comparison group. The alpha allocation among the three comparison groups is: alpha = 0.02 for FDC vs. EZE or FDC vs. BA; alpha = 0.01 for FDC vs. Pbo



All other secondary endpoints not included in the step-down procedure will be tested at significant level of 0.05 without multiplicity adjustment.

14.7. Exploratory Endpoints

The proportion of patients achieving an LDL-C <70 mg/dL after 12-week treatment will be summarized for each treatment group and the comparison between FDC vs. EZE; FDC vs. BA, and FDC vs. placebo will be based on Chi-sq test or Fisher's exact test. No missing data imputation will be applied to this analysis.

Descriptive summary for plasma trough concentrations of BA and/or EZE will be provided at Weeks 4, 8, and 12 by treatment group.

Further details will be provided in the SAP.

14.8. Safety Endpoints

Descriptive statistics will be provided for summary of TEAEs and other safety assessments.

TEAEs, SAEs, related AEs, and AESIs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. Fatal AE, AEs leading to discontinuation of IMP or study, will each be summarized by treatment group.

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

Hepatic Safety

Liver-associated enzymes and TB will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST and TB. Hy's law criteria (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN) will also be applied to the data; any potential Hy's law cases will be listed separately. *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.*

Musculoskeletal Safety

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

Diabetes and *Hyperglycemia*

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

Renal Safety

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

Neurocognitive Events

Neurocognitive events will be evaluated by routine safety monitoring of PE findings and AEs. Neurocognitive events will be identified using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms and will be summarized by SOC, severity, and relationship to IMP for each treatment group.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

The Sponsor (or its authorized representative) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, International Council for 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 (e.g., laboratory reports, clinic notes, study drug dispensing log, pharmacy records, patient sign-in sheets, patient-completed questionnaires, telephone logs, ECGs) required to confirm information contained in the eCRFs.

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

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

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

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

15.2. Audits and Inspections

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

16. 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 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Institutional Review Board Approval

Before initiation of the study, the Investigator must obtain approval or favorable opinion of the research protocol, ICD, and any material related to patient recruitment from an IRB 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.

17.2. Ethical Conduct of the Study

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

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

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

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

17.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also 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.

17.4. 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.

18. DATA HANDLING AND RECORDKEEPING

18.1. 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.

18.2. Retention of Records

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

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

Essential records (including eCRFs, source documents, 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.

18.3. Case Report Forms and Study Records

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

Study records are comprised of source documents, eCRFs, and all other administrative documents (e.g., 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 (e.g., laboratory reports, clinic notes, study drug disposition log, pharmacy records, patient sign-in sheets, patient completed questionnaires, telephone logs, X-rays, and ECGs). All draft, preliminary, and pre/final iterations of a final report are also considered to be source documents (e.g., 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 for each patient must be signed and dated by the Investigator acknowledging review and that the data are accurate and complete. The completed database is to be returned to the Sponsor as soon as practical after completion by the mechanism prescribed for the protocol.

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

19. ADMINISTRATIVE CONSIDERATIONS

19.1. 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

19.2. Study Administrative Structure

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

Central Laboratory:

TBD

Bio-analytic Laboratory:

Randomization, IWRS, Medical Writing:

TBD

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

TBD

Medical and Safety Services including Medical Monitoring:


Cell phone #:
Email:

TBD – Corresponding CRO Medical and Safety Monitoring

19.3. Amendments and Study Termination

Changes to the research covered by this protocol must be implemented by formal protocol amendment. All amendments to the protocol must be initiated by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IRB 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.

19.4. Financial Disclosure

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

20. PUBLICATION AND DISCLOSURE POLICY

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

All information derived from this clinical study will be used by the Sponsor (or designee) and therefore, may be disclosed by the Sponsor (or designee) as required to other clinical Investigators, to the FDA, 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.

21. LIST OF REFERENCES

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

22. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS

Visit	**S1[1]**	**T1**	**T2**	**T3**	**T4[2]**
Week	**-2**	**0**	**4**	**8**	**12/EOS**
Procedure	**Day -16 to -5**	**Day 1**	**Day 29 ± 5**	**Day 57 ± 5**	**Day 85 ± 5**
Informed Consent	X				
Enrollment Criteria	X	X			
Demographics	X				
Medical History	X				
Concomitant\Prohibited Medications	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X
Physical Exam		X			X
Weight[3]	X	X[3]	X	X	X
Height/BMI	X				
12-Lead ECG[4]		X			X
Vital Signs[5]	X	X	X	X	X
Serology[6]	X				
Serum Pregnancy/FSH [7]	X				
Urine Pregnancy		X			
TSH	X				
Clinical Safety Labs[8]	X	X	X	X	X
Basic Fasting Lipids[9]	X	X	X	X	X
Special Fasting Lipids and Other Biomarkers[10]		X			X
HbA_{1C}	X				
Plasma Trough Study Drug			X	X	X
Randomization		X			
Double Blind Drug Dispensing		X	X	X	
Drug Return			X	X	X

BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone, HbA_{1C} = hemoglobin A_{1C}; TSH = thyroid-stimulating hormone.

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

[1] An optional visit approximately 10 days later MAY be completed if patient fails to meet specified entry criteria. If this optional visit is completed, the repeat value will be used to determine eligibility.

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

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

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

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

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

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

[8] Clinical safety labs include hematology, blood chemistry, and urinalysis. Coagulation panel only if receiving anticoagulants that in the investigator's judgement requires monitoring (then test at T1 and repeat 3-5 days after starting IMP).

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

[10] Includes apoB and hs-CRP.

APPENDIX 2. SPONSOR'S SIGNATURE

Study Title:	A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed-Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy
Study Number:	1002FDC-053
Final Date:	18 October 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: _____

[redacted]

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title:	A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed-Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy
Study Number:	1002FDC-053
Final Date:	18 October 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. DUTCH LIPID CLINIC NETWORK CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

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

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

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

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

Scoring:

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

References:

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

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

Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia[1]

Definite Familial Hypercholesterolemia:

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

  OR

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

Possible Familial Hypercholesterolemia:

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

  OR

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

References:

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

APPENDIX 6. ESTIMATED PERCENTILES OF CAC BY AGE CATEGORY, GENDER, AND RACE/ETHNICITY

Percentiles by Race	**Women, n**				**Men, n**			
	Age, y				**Age, y**			
	45–54	**55–64**	**65–74**	**75–84**	**45–54**	**55–64**	**65–74**	**75–84**
White, n	379	356	379	194	321	325	375	174
25th	0	0	0	20	0	0	21	103
50th	0	0	13	106	0	28	145	385
75th	0	16	119	370	22	155	540	1200
90th	8	102	391	921	110	452	1345	2933
95th	31	209	674	1535	207	743	2271	4619
Chinese, n	109	107	103	52	102	94	102	50
25th	0	0	0	0	0	0	0	11
50th	0	0	5	32	0	5	34	81
75th	0	18	70	146	14	67	174	305
90th	12	105	246	398	89	242	487	769
95th	44	213	436	656	184	429	803	1299
Black, n	274	241	278	110	214	192	206	98
25th	0	0	0	0	0	0	0	23
50th	0	0	0	47	0	0	32	141
75th	0	5	77	214	2	40	191	516
90th	9	74	310	582	45	173	575	1281
95th	38	173	561	953	105	318	945	2176
Hispanic, n	218	196	169	86	205	177	149	75
25th	0	0	0	0	0	0	1	36
50th	0	0	1	45	0	3	56	153
75th	0	2	51	205	9	75	247	494
90th	2	50	203	557	88	291	666	1221
95th	18	118	361	917	195	512	1091	1943

Reference:

McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006;113:30-7.

APPENDIX 7. SUMMARY OF CHANGES IN AMENDMENT 1

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002FDC-053
Study Title:	A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed-Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy
Protocol Version Incorporating Current Summary of Changes:	Amendment 1: 18 October 2017
Preceding Protocol Version:	Original Protocol: 03 August 2017
Investigational Product Name:	ETC-1002

Conventions used in this Summary of Changes Document

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

Summary and Justification of Changes

The protocol was amended for the following:

- Made administrative changes throughout protocol where required to correct inconsistencies, add clarification, or correct errors.
- Added instructions for collection, processing, and analysis of plasma trough bempedoic acid and ezetimibe concentrations. This new assessment was added to generate additional data describing these plasma trough IMP concentrations in a large clinical study.

- Added instruction to delay ingestion of IMP on clinic visit days until all study procedures have been completed. This instruction was added to enable accurate analysis of plasma trough IMP concentrations.
- Modified description of drug kit to indicate that 4, not 3, blister packs would be provided in each kit. Four blister packs are needed to supply sufficient drug for 4-week intervals between treatment visits.
- Modified instruction for acceptable contraception to functional, not started, on Day 1 to ensure adequate coverage while IMP is being administered.
- Added instruction to record prior use of statin at any point in the past, not just within 6 weeks prior to screening. Extended statin history will provide additional details regarding statins that may have been stopped in the past due to intolerable adverse effects.
- Added comment to exclusion criterion that if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C RNA is negative, patient can be enrolled.
- Removed erroneous statements that DMC and CEC would review data from this study on an ongoing basis.
- Added instruction to inclusion criteria that multiple risk factors of blood pressure, age and HDL-C should be assessed at Week -2 (Visit S1).
- Added clarification that ezetimibe is prohibited unless it is study supplied.
- Removed reference to randomization number since no specific number is generated.
- Added a definition for the PK analysis population.
- Added detail that an independent bio-analytical lab will be aware of treatment assignment during the treatment period only to support pharmacokinetic sample analysis.

CHANGE 1 REVISION OF TITLE PAGE VERSION INFORMATION

Location:

Title Page

Original Text:

Version	Date
Original Protocol:	03 August 2017

New Text:

Version	Date
Original Protocol:	03 August 2017
Amendment 1:	***18 October 2017***

CHANGE 2 REVISION TO EXPLORATORY OBJECTIVES

Location:

Section 2, Synopsis; Section 5.1.3, Exploratory Objective

Original Text:

- To assess the efficacy BA 180 mg + EZE 10 mg FDC versus placebo alone, BA alone, and EZE alone on percentage of patients attaining LDL-C <70 mg/dL after 12 weeks of treatment

New Text:

- To assess the efficacy BA 180 mg + EZE 10 mg FDC versus placebo alone, BA alone, and EZE alone on percentage of patients attaining LDL-C <70 mg/dL after 12 weeks of treatment***;***
- ***To characterize the plasma trough concentrations of BA and/or EZE when administered as BA 180 mg + EZE 10 mg FDC, BA alone, and EZE alone.***

CHANGE 3 ADDITION OF CRITERIA FOR EVALUATION

Location:

Section 2, Synopsis

New Text:

Plasma Trough IMP

Plasma trough concentrations of BA (ETC-1002 and its active metabolite ESP15228) and EZE (glucuronidated EZE and unconjugated EZE)

CHANGE 4 REVISION TO STUDY ENDPOINTS

Location:

Section 2, Synopsis; Section 5.2.3, Exploratory Endpoints

Original Text:

Exploratory endpoints:

- Proportion of patients attaining LDL <70 mg/dL at Week 12 in BA 180 mg + EZE 10 mg FDC-treated arm compared to BA 180 mg arm, EZE 10 mg arm and placebo arm

New Text:

Exploratory endpoints:

- Proportion of patients attaining LDL <70 mg/dL at Week 12 in BA 180 mg + EZE 10 mg FDC-treated arm compared to BA 180 mg arm, EZE 10 mg arm and placebo arm***;***
- ***Plasma trough concentrations at Weeks 4, 8, and 12 of BA (ETC-1002 and its active metabolite ESP15228) and EZE (glucuronidated EZE and unconjugated EZE) in BA 180 mg + EZE 10 mg FDC-treated arm, BA-treated arm, and/or EZE alone treated arm.***

CHANGE 5 REVISION TO INCLUSION CRITERIA

Location:

Section 2, Synopsis; Section 7.1, Patient Inclusion Criteria

Original Text:

3. Men and nonpregnant, nonlactating women,

   Women must be either:

   - Naturally postmenopausal reported by the patient and defined as:
     - ≥55 years and ≥1 year without menses, or
     - <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L),
   - Surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential willing to use at least 1 acceptable method of birth control. The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:

6. Meeting the definition for at least 1 of the following 3 categories (ASCVD, HeFH, multiple cardiovascular risk factors):
   c. Multiple cardiovascular risk factors defined as diabetes + 1 other risk factor or 3 risk factors that may include:
      a. Age (men ≥45 years; women ≥55 years)
      b. Family history (coronary heart disease in a first degree relative, men <45 years; women <55 years)
      c. Smoking (current smoker)
      d. Hypertension (Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or on antihypertensive medications)
      e. Low HDL-C (<40 mg/dL)
      f. Coronary calcium score >95% for age/sex (see Appendix 6)

New Text:

3. Men and nonpregnant, nonlactating women,

   Women must be either:

   - Naturally postmenopausal reported by the patient and defined as:
     - ≥55 years and ≥1 year without menses, or
     - <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L),
   - Surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential willing to use at least 1 acceptable method of birth control. The minimal requirement for adequate contraception should be ~~started~~***functional*** on Day 1, continuing during the study period and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:

6. Meeting the definition for at least 1 of the following 3 categories (ASCVD, HeFH, multiple cardiovascular risk factors):
   c. Multiple cardiovascular risk factors defined as diabetes + 1 other risk factor or 3 risk factors that may include:
      a. Age (men ≥45 years; women ≥55 years) ***at Week -2 (Visit S1);***
      b. Family history (coronary heart disease in a first degree relative, men <45 years; women <55 years);
      c. Smoking (current smoker);

d. Hypertension (Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or on antihypertensive medications) ***at Week -2 (Visit S1);***

e. Low HDL-C (<40 mg/dL) ***at Week -2 (Visit S1);***

f. Coronary calcium score >95% for age/sex (see Appendix 6)

CHANGE 6 REVISION TO EXCLUSION CRITERIA

Location:

Section 2, Synopsis; Section 7.2, Patient Exclusion Criteria

Original Text:

8. Liver disease or dysfunction, including:

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥2 × ULN at Week -2 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

  Note: If a patient fails to meet ALT and/or AST criteria, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat ALT and/or AST measurement, the repeat value will be used to determine eligibility.

New Text:

8. Liver disease or dysfunction, including:

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥2 × ULN at Week -2 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

  Note: If a patient fails to meet ALT and/or AST criteria, an optional single repeat visit/measurement can, at the discretion of the investigator, be completed up to a maximum of 10 days later. For those patients who have a repeat ALT and/or AST measurement, the repeat value will be used to determine eligibility. ***Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.***

CHANGE 7 REMOVAL OF CEC AND DMC REVIEW STATEMENTS

Location:

Section 2, Synopsis, Criteria for Evaluation; Section 13.2.1, Definition of Serious Adverse Event

Original Text:

Lipid and Cardiometabolic Assessments:

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

Safety Assessments:

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) will be reported by treatment group. Clinical endpoints will be collected and adjudicated by an independent Clinical Event Committee (CEC). Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, HbA_{1C}, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram (ECG) readings, and weight.

New Text:

Lipid and Cardiometabolic Assessments:

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

Safety Assessments:

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) will be reported by treatment group. ~~Clinical endpoints will be collected and adjudicated by an independent Clinical Event Committee (CEC).~~ Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, HbA_{1C}, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram (ECG) readings, and weight.

Original Text:

13.2.1 Definitions of Serious Adverse Event

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

New Text:

13.2.1 Definitions of Serious Adverse Event

~~Any clinical endpoints that meet SAE criteria will be reported as SAEs. The Clinical Event Committee (CEC) will adjudicate clinical endpoints in a blinded fashion, but the Data Monitoring Committee (DMC) will review clinical endpoints and SAEs in an unblinded fashion.~~

CHANGE 8 REVISIONS TO ANALYSIS POPULATIONS

Location:

Section 2, Synopsis, Analysis Population; Section 14.3, Analysis Populations

Original Text:

Analysis Populations

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

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized patients who received at least 1 dose of blinded study medication (IMP).

New Text:

Analysis Populations

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

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized patients who received at least 1 dose of blinded study medication (IMP).

The PK analysis set (PKS), used for all of the PK-related summaries, is defined as all patients in the SP who have at least 1 PK assessment unless major protocol deviations are identified to have affected the PK data or if key dosing or sampling information is missing.

Original Text:

14.3 Analysis Population

The full analysis set (FAS), used for all of the efficacy analyses, is defined as all randomized patients. Patients in FAS will be analyzed in the treatment group they are randomized to regardless of the treatment received.

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

New Text:

14.3 Analysis Population

The full analysis set (FAS), used for all of the efficacy analyses, is defined as all randomized patients. Patients in FAS will be analyzed in the treatment group they are randomized to regardless of the treatment received.

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

The PK analysis set (PKS), used for all of the PK-related summaries, is defined as all patients in the SP who have at least 1 PK assessment unless major protocol deviations are identified to have affected the PK data or if key dosing or sampling information is missing.

CHANGE 9 REVISION TO ADMINISTRATION OF IMP

Location:

Section 8.1, Administration of Investigational Medicinal Product

Original Text:

During the Treatment Period, patients will be randomized to receive IMP of either BA 180 mg + EZE 10 mg FDC, BA 180 mg, EZE 10 mg, or placebo once daily. Each daily allotment of IMP is comprised of 2 tablets and 1 capsule provided in a blister package. Patients will be instructed to ingest IMP orally once daily with or without food at a similar time every day.

New Text:

During the Treatment Period, patients will be randomized to receive IMP of either BA 180 mg + EZE 10 mg FDC, BA 180 mg, EZE 10 mg, or placebo once daily. Each daily allotment of IMP is comprised of 2 tablets and 1 capsule provided in a blister package. Patients will be instructed to ingest IMP orally once daily with or without food at a similar time every day. ***On clinic visit days, patients will be instructed to delay ingestion of IMP until all study procedures have been completed.***

CHANGE 10 REVISION TO PRIOR AND CONCOMITANT MEDICATIONS

Location:

Section 8.2, Concomitant Medications

Original Text:

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

New Text:

The Prior/Concomitant case report form (CRF) will be used to record medications, herbal remedies, vitamins, other nutritional supplements, and over-the-counter medications taken within 6 weeks prior to screening and during the study***, with the exception of statins (particularly those that were not tolerated due to an adverse effect), which will be recorded if taken at any point in the past***.

CHANGE 11 REVISION TO PROHIBITED MEDICATIONS AND DIETARY SUPPLEMENT

Location:

Section 8.2.2, Prohibited Medications and Dietary Supplement

Original Text:

- Ezetimibe (Zetia®, Ezetrol®)

New Text:

- Ezetimibe (Zetia®, Ezetrol®) ***other than that which is study supplied;***

CHANGE 12 REVISION TO TREATMENT ASSIGNMENT, RANDOMIZATION, AND BLINDING

Location:

Section 8.3, Treatment Assignment, Randomization, and Blinding

Original Text:

During the Treatment Period, patients will receive double-blind IMP. At Day 1 (Visit T1), patients will be randomized to receive either BA 180 mg + EZE 10 mg FDC, BA 180 mg, EZE 10 mg or placebo. The investigator or designee will utilize Interactive Web Response System (IWRS) during the visit to obtain a randomization number and the appropriate IMP container via medication identification numbers (MED ID). A patient is considered to be randomized when they have been assigned a randomization number by IWRS.

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

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

New Text

During the Treatment Period, patients will receive double-blind IMP. At Day 1 (Visit T1), patients will be randomized to receive either BA 180 mg + EZE 10 mg FDC, BA 180 mg, EZE 10 mg or placebo. ***The randomization will be stratified by baseline statin intensity (high intensity vs. other) and disease characteristics (ASCVD and/or HeFH vs. multiple CV risk factors). Only atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day are considered high intensity statin and all others will be considered as 'other' for randomization purpose. The criteria for determining these 2 stratification factors are further detailed in Section 7.1).*** The investigator or designee will utilize Interactive Web Response System (IWRS) during the visit to ~~obtain a randomization number~~***randomize the patient*** and ***obtain*** the appropriate IMP container via medication identification numbers (MED ID). A patient is considered to be randomized when ~~they have been assigned a randomization number by IWRS~~***the corresponding randomization box is checked within the eCRF***.

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

During the Treatment Period, Sponsor, site personnel, CRO, and patient will all be unaware of patient's treatment assignment***; an independent bio-analytical lab will be aware of treatment assignment only to support PK sample analysis***.

CHANGE 13 REVISION TO PACKAGING AND LABELING

Location:

Section 9.3, Packaging and Labeling

Original Text:

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

New Text:

Double-blind IMP will be packaged in blister packs. Each blister pack will contain a 9-day supply and ~~3~~***4*** blister packs will be provided in the drug kit.

CHANGE 14 REVISION TO IWRS AND ECRFS

Location:

Section 10.2, Interactive Web Response System and eCRFs

Original Text:

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

New Text:

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

CHANGE 15 REVISION TO STUDY PROCEDURES

Location:

Section 10.5.2, Treatment Week 0 (Visit T1; Day 1)

Original Text:

At randomization, patients will be stratified based on baseline/current statin intensity (High vs. Other) and disease characteristics (ASCVD and/or HeFH vs. multiple cardiovascular [CV] risk factors). High intensity statin includes atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day, all others will be categorized as 'other' for randomization and stratification purposes. Definition of ASCVD and/or HeFH or multiple CV risk factors are provided in inclusion criteria. 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:

- Concomitant medication review (ongoing)
- Assess AEs and SAEs
- PE
- ECG
- Urine pregnancy test (in female patients of childbearing potential)
- Review inclusion/exclusion criteria to establish patient eligibility
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind IMP
- Weight
- Vital signs

- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - ApoB and hs-CRP
- Dispense double-blind IMP and provide dosing and storage instructions

New Text:

At randomization, patients will be stratified based on baseline/current statin intensity (High vs. Other) and disease characteristics (ASCVD and/or HeFH vs. multiple ~~cardiovascular [~~CV~~]~~ risk factors). High intensity statin includes atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day, all others will be categorized as 'other' for randomization and stratification purposes. Definition of ASCVD and/or HeFH or multiple CV risk factors are provided in inclusion criteria. ~~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:

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

CHANGE 16 REVISION TO STUDY PROCEDURES

Location:

Section 10.5.3, Treatment Week 4 (Visit T2; Day 29 ± 5 days)

Original Text:

Patients will undergo the following assessments and procedures:

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

New Text:

Patients will undergo the following assessments and procedures:

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

Location:

Section 10.5.4, Treatment Week 8 (Visit T3; Day 57 ± 5 days)

Original Text:

Patients will undergo the following assessments and procedures:

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

New Text:

Patients will undergo the following assessments and procedures:

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

Location:

Section 10.5.5, Treatment Week 12 (Visit T4; Day 85 ± 5 days)/End of Study or Early Termination

Original Text:

Patients will undergo the following assessments and procedures:

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

New Text:

Patients will undergo the following assessments and procedures:

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

CHANGE 17 REVISION TO CENTRAL CLINICAL LABORATORY PARAMETERS (SAFETY)

Location:

Section 12.1.6.1, Table 4, Central Clinical Laboratory Parameters (Safety)

Original Text:

Table 4: Central 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 values only)	Blood Chemistry (serum, fasting) • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB) • Total protein • Uric acid
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen	

Table 4: Central Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Urinalysis (Microscopic) – only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cells (RBC) • White blood cells (WBC)	Coagulation – ONLY in patients receiving anticoagulant therapy that in the investigator's judgment requires monitoring, measured only at Visit T1 and 3 to 5 days post Visit T1 • Prothrombin time (PT) • International normalized ratio (INR)
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), optional reflexive hepatitis C RNA only if HCV is positive • Serum and urine pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; only for postmenopausal females <55 years old >1 year without menses) • Thyroid-stimulating hormone (TSH)	

New Text:

Table 4: Central 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 values only)	Blood Chemistry (serum, fasting) • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine

Table 4: Central Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	**Clinical Laboratory Test**
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen	• Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB) • Total protein • Uric acid
Urinalysis (Microscopic) – only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cells (RBC) • White blood cells (WBC)	Coagulation – ONLY in patients receiving anticoagulant therapy that in the investigator's judgment requires monitoring, measured only at Visit T1 and 3 to 5 days post Visit T1 • Prothrombin time (PT) • International normalized ratio (INR)
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), optional reflexive hepatitis C RNA only if HCV is positive • Serum and urine pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; only for postmenopausal females <55 years old >1 year without menses) • Thyroid-stimulating hormone (TSH)	***Other Sample Collection*** • ***Plasma trough investigational medicinal product (IMP)***

CHANGE 18 ADDITION OF CENTRAL CLINICAL LABORATORY PARAMETER

Location:

Section 12.1.6.3, Collection and Assessment of Plasma Trough IMP

New Text:

12.1.6.3. Collection and Assessment of Plasma Trough IMP

Plasma trough IMP will be measured at Weeks 4, 8, and 12. A single 6-mL whole blood sample will be collected and processed by the site according to instructions provided in the manual provided by the Central Laboratory. At the time of sample collection, the date and time of blood draw and the last 2 doses of study medication will also be collected. Samples will be shipped to the central clinical laboratory and subsequently forwarded to a bio-analytical lab for measurement and analysis.

Plasma trough IMP concentrations will be measured and analyzed using validated methods and will include BA (ETC-1002 and its active metabolite ESP15228) and EZE (glucuronidated EZE and unconjugated EZE).

CHANGE 19 REVISIONS TO TOTAL BLOOD VOLUME SAMPLES

Location:

Section 12.1.6.5, Total Blood Volume of Central Clinical Laboratory Sample

Original Text:

12.1.6.4 Total Blood Volume of Central Clinical Laboratory Samples

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

New Text:

12.1.6.4***5*** Total Blood Volume of Central Clinical Laboratory Samples

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

CHANGE 20 REVISIONS TO EXPLORATORY ENDPOINTS

Location:

Section 14.7, Exploratory Endpoints

Original Text:

The proportion of patients achieving an LDL-C <70 mg/dL will be summarized for each treatment group and the comparison between FDC vs. EZE; FDC vs. BA, and FDC vs. placebo will be based on Chi-Sq test or Fisher's exact test. No multiplicity adjustment will be performed.

Further details will be provided in the SAP.

New Text:

The proportion of patients achieving an LDL-C <70 mg/dL ***after 12-week treatment*** will be summarized for each treatment group and the comparison between FDC vs. EZE; FDC vs. BA, and FDC vs. placebo will be based on Chi-~~S~~***s***q test or Fisher's exact test. No ***missing data imputation will be applied to this analysis***~~multiplicity adjustment will be performed~~.

Descriptive summary for plasma trough concentrations of BA and/or EZE will be provided at Weeks 4, 8, and 12 by treatment group.

Further details will be provided in the SAP.

CHANGE 21 REVISIONS TO SCHEDULE OF EVENTS

Location:

Appendix 1, Schedule of Events table

Original Text:

Visit	**S1[1]**	**T1**	**T2**	**T3**	**T4[2]**
Week	**-2**	**0**	**4**	**8**	**12/EOS**
Procedure	**Day -16 to -5**	**Day 1**	**Day 29 ± 5**	**Day 57 ± 5**	**Day 85 ± 5**
Informed Consent	X				
Enrollment Criteria	X	X			
Demographics	X				
Medical History	X				
Concomitant\Prohibited Medications	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X
Physical Exam		X			X
Weight[3]	X	X[3]	X	X	X
Height/BMI	X				
12-Lead ECG[4]		X			X
Vital Signs[5]	X	X	X	X	X
Serology[6]	X				
Serum Pregnancy/FSH [7]	X				
Urine Pregnancy		X			
TSH	X				
Clinical Safety Labs[8]	X	X	X	X	X
Basic Fasting Lipids[9]	X	X	X	X	X
Special Fasting Lipids and Other Biomarkers[10]		X			X
HbA_{1C}	X				
Randomization		X			
Double Blind Drug Dispensing		X	X	X	
Drug Return			X	X	X

New Text:

Visit	**S1[1]**	**T1**	**T2**	**T3**	**T4[2]**
Week	**-2**	**0**	**4**	**8**	**12/EOS**
Procedure	**Day -16 to -5**	**Day 1**	**Day 29 ± 5**	**Day 57 ± 5**	**Day 85 ± 5**
Informed Consent	X				
Enrollment Criteria	X	X			
Demographics	X				
Medical History	X				
Concomitant\Prohibited Medications	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X
Physical Exam		X			X
Weight[3]	X	X[3]	X	X	X
Height/BMI	X				
12-Lead ECG[4]		X			X
Vital Signs[5]	X	X	X	X	X
Serology[6]	X				
Serum Pregnancy/FSH [7]	X				
Urine Pregnancy		X			
TSH	X				
Clinical Safety Labs[8]	X	X	X	X	X
Basic Fasting Lipids[9]	X	X	X	X	X
Special Fasting Lipids and Other Biomarkers[10]		X			X
HbA_{1C}	X				
Plasma Trough Study Drug			***X***	***X***	***X***
Randomization		X			
Double Blind Drug Dispensing		X	X	X	
Drug Return			X	X	X

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