BEMPEDOIC ACID (ETC-1002) 180 MG + EZETIMIBE 10 MG FIXED-DOSE COMBINATION

1002FDC-058

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 EZETIMIBE AND PLACEBO IN SUBJECTS WITH TYPE 2 DIABETES AND ELEVATED LDL-CHOLESTEROL

Study Phase: 2

IND Number: 130707

Indication: Treatment of hyperlipidemia

Investigators: Approximately 45 sites in the United States

Sponsor: Esperion Therapeutics, Inc.
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2. SYNOPSIS

Name of Sponsor/Company: 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 Ezetimibe and Placebo in Subjects With Type 2 Diabetes and Elevated LDL-Cholesterol

Study Number: 1002FDC-058

Phase of Development: 2

Clinical Sites: Approximately 45 sites in the United States

Name of Investigational Medicinal Product (IMP):

Bempedoic Acid 180 mg (BA) + Ezetimibe (EZE) 10 mg fixed-dose combination (FDC)
EZE 10 mg

Placebo (PBO)

Primary Objectives:

The Co-primary Objectives are:

- To assess the efficacy of FDC versus PBO on low-density-lipoprotein cholesterol (LDL-C) lowering in subjects with type 2 diabetes (T2D) treated for 12 weeks; and
- To assess the efficacy of FDC versus EZE on LDL-C lowering in subjects with T2D treated for 12 weeks.

Secondary Objectives:

- To assess the efficacy of EZE versus PBO on LDL-C lowering in subjects with T2D treated for 12 weeks;
- To assess the efficacy of FDC versus PBO, FDC versus and EZE, and EZE versus PBO on high-sensitivity C-reactive protein (hs-CRP), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (apoB), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) in subjects with T2D treated for 12 weeks;
- To assess the effect of FDC, EZE, and PBO on percent of subjects achieving LDL-C level <70 mg/dL;
- To assess the effect of FDC, EZE, and PBO on percent of subjects achieving LDL-C reduction ≥50%; and
- To characterize the safety and tolerability of FDC, EZE, and PBO in subjects with T2D treated for 12 weeks.

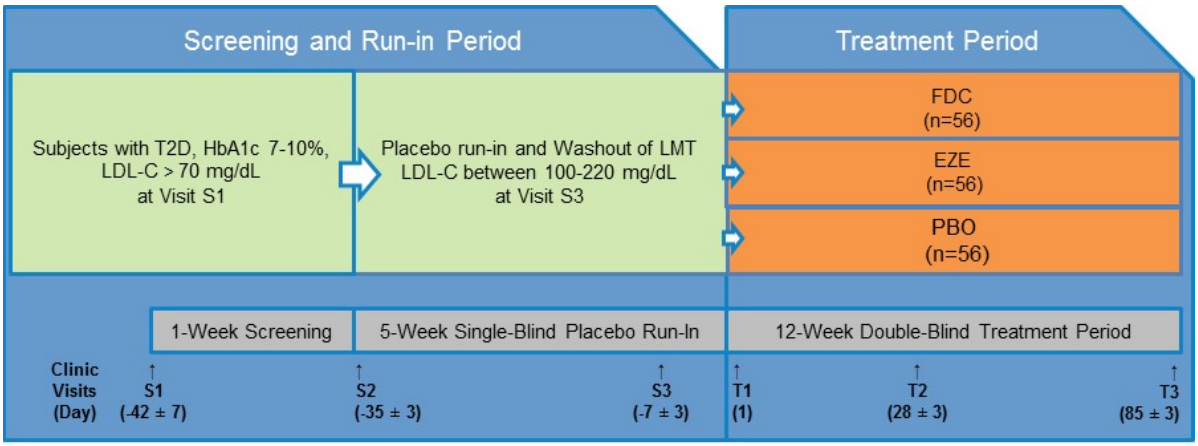
Exploratory Objectives:

- To assess the effect of FDC versus PBO, FDC versus EZE, and EZE versus PBO on hemoglobin A_{1C} (HbA_{1C}), fasting glucose, [redacted] homeostatic model assessment of insulin resistance (HOMA-IR) and [redacted], and 2-hour postprandial glucose (PPG) in subjects with T2D treated for 12 weeks.

Study Design:

This is a Phase 2, randomized, double-blind, parallel group, multicenter study of FDC versus EZE and PBO administered for 12 weeks in subjects with T2D and elevated LDL-C. An overview of the study design is presented below.

Overview of Study Design



T2D = type 2 diabetes; HbA_{1C} = hemoglobin A_{1C}; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; BA = bempedoic acid; EZE = ezetimibe; FDC = fixed-dose combination.

Subjects with a history of T2D for at least 6 months will be screened for eligibility at an initial screening visit (Visit S1), which will be conducted approximately 42 days before planned randomization into the study. Subjects who have an LDL-C level >70 mg/dL and who meet all other inclusion/exclusion criteria will be return for Visit S2 approximately 5 weeks prior to planned randomization into the study to washout of all LDL-C-lowering therapies and begin taking single-blind (subject) PBO. Subjects will return to the study site approximately 7 days before planned randomization into the study for Visit S3. Subjects who have an LDL-C level ≥100 mg/dL and who continue to meet the study inclusion/exclusion criteria will be scheduled for their first treatment visit.

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast. Subjects who continue to meet the study inclusion/exclusion criteria will be randomized in a 1:1:1 ratio to receive either FDC (n = 56), EZE (n = 56), or PBO (n = 56) once daily in the morning for 12 weeks. Randomized subjects will return for clinic visits at Week 4 (Visit T2) and Week 12 (Visit T3/End of Study [EOS]). Subjects 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.

Subjects will report to each of the study visits after a minimum 10-hour fast and without having taken their dose of IMP. Study site personnel will administer the IMP on these days after blood and urine samples have been drawn and other scheduled safety procedures have been completed. All other doses of IMP will be self-administered by the subjects; the last dose will be taken the day prior to the final clinical visit (Visit T3/EOS).

Study Population:

Approximately 168 male and female subjects with a history of T2D for at least 6 months and who meet the inclusion and exclusion criteria will be enrolled.

Subject Inclusion Criteria

Subjects must satisfy all the following criteria at Visit S1 (unless otherwise specified) for enrollment in the study:

1. The subject must be willing to provide written informed consent before any study-specific procedures are performed;
2. The subject must be aged 18-75 years or be of legal age of majority based on regional law, whichever is older;
3. The subject must have a history of T2D for 6 months or greater; and must be currently taking stable diabetes medication for 3 months or greater with HbA_{1C} between 7% and 10% at Visit S1;
4. The subject must have a fasting calculated LDL-C level >70 mg/dL at Visit S1;
5. The subject must have a fasting calculated LDL-C level between 100 and 220 mg/dL at Visit S3 after washout of all lipid-modifying therapy (LMT);
6. The subject must clinically stable and suitable to undergo washout of all LDL-C-lowering drugs and nutritional supplements for 17 weeks (with potential for 1-week extension if repeat assessments described in the protocol are required) based on investigator assessment;
7. The subject may be male or female. Women must not be pregnant (or planning to become pregnant within 30 days after the last dose of IMP) or lactating and must be:
   a. Naturally postmenopausal, defined as ≥1 year without menses and either:
      i. ≥55 years old, or
      ii. <55 years old with a follicle-stimulating hormone (FSH) level ≥40.0 IU/L;
   b. Surgically sterile by hysterectomy, bilateral oophorectomy, and/or tubal ligation; or
   c. Willing to use 1 acceptable method of birth control if of childbearing potential unless the subject agrees to follow the definition of true abstinence. The minimal requirement for use of acceptable contraception is from the time the informed consent form (ICF) is signed, during the study period, and for at least 30 days after the last dose of IMP. Acceptable methods of birth control include:
      i. placement of an intrauterine device (IUD) with or without hormones,
      ii. established use of oral, implanted, topical, or injectable, or hormonal method of contraception associated with inhibition of ovulation,
      iii. barrier methods, including condom or occlusive cap with spermicidal foam or spermicidal jelly,
      iv. vasectomized male partner who is the sole partner for the subject, or
      v. true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

   There are no protocol-specific birth control requirements for men who have partners that can become pregnant.

Subject Exclusion Criteria

Subjects who meet any of the following criteria at Visit S1 (unless otherwise specified) will be excluded from the study:

1. The subject has a body mass index (BMI) >40 kg/m^2;
2. The subject has a history of documented clinically significant cardiovascular disease including, but not limited to:
   a. myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease;
   b. uncontrolled hypertension, defined as mean systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg after sitting quietly for 5 minutes.

   Note: At the discretion of the investigator, a single repeat sitting systolic blood pressure and diastolic blood pressure may be obtained at another visit; the repeat values will be used to determine the subject's eligibility for the study;
   c. an arrhythmia requiring medical intervention;
   d. abdominal or thoracic aortic aneurysm;
   e. New York Heart Association (NYHA) Class III and IV heart failure;
3. The subject has a fasting TG level >400 mg/dL at Visit S3;

   Note: At the discretion of the investigator, a repeat TG measurement may be obtained once, and the screening period will be extended for up to 1 week. The repeat value will be used to determine the subject's eligibility for the study;
4. The subject has a history of type 1 diabetes;
5. The subject has uncontrolled hypothyroidism, including a value for thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN);
6. The subject has liver disease or dysfunction, including:
   a. positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C virus antibodies (HCV-AB) at Week -1 (Visit S2/Day -7), or
   b. serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value ≥2 × ULN and/or serum total bilirubin (TB) value ≥2 × ULN. If the serum TB value is ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and, if consistent with Gilbert's disease or if the subject has a history of Gilbert's disease, the subject may be enrolled in the study.

   Note: At the discretion of the investigator, a single repeat measurement of serum ALT, AST, and/or TB may be completed; the repeat value will be used to determine eligibility for the study. If a test for HCV-AB is positive, but an optional reflexive test for hepatitis C virus (HCV) ribonucleic acid (RNA) is negative, the subject can be enrolled in the study;
7. The subject has renal dysfunction or glomerulonephritis, including an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (as determined by the central laboratory using the Modification of Diet in Renal Disease [MDRD] formula);

   Note: At the discretion of the investigator, a single repeat eGFR may be obtained; the repeat value will be used to determine eligibility for the study;
8. The subject has gastrointestinal conditions or has undergone procedures (including weight loss surgery; eg, Lap-Band, gastric bypass) that may affect drug absorption;
9. The subject has hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL;

10. The subject had an active malignancy, including those requiring surgery, chemotherapy, and/or radiation, in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed;
11. The subject has an unexplained (ie, not associated with recent trauma or physically strenuous activity) serum creatine kinase (CK) value >3 × ULN at any time before randomization. Subjects with an explained elevation in serum CK must have single repeat serum CK value ≤3 × ULN before randomization;
12. The subject has a history of drug or alcohol abuse within the last 2 years or reports current consumption of >14 alcoholic drinks/week, uses any illicit drugs, or has a history of amphetamine or derivatives abuse or cocaine abuse. Subjects who are using amphetamine derivatives prescribed by and who are under the care of a health care practitioner can be enrolled after evaluation by the investigator;
13. The subject has donated blood, undergone multiple blood draws in a clinical study, experienced major trauma, received a blood transfusion, or undergone surgery, with or without blood loss, within 30 days before randomization;
14. The subject has used any experimental or investigational drugs within 30 days before screening and throughout the trial;
15. The subject has previously participated in a clinical study of BA;
16. The subject has experienced history of intolerance to EZE;
17. The subject has used prohibited drugs and/or nutritional supplements within 5 weeks prior to Visit T1 (unless otherwise specified) or plans to use any of the prohibited drugs and/or nutritional supplements during the study, including but not limited to:
    a. Statins;
    b. Fibrates (including fenofibrate);
    c. Niacin and derivatives;
    d. Bile acid sequestants;
    e. Ezetimibe (study-provided is allowed);
    f. Apheresis;
    g. Mipomersen or lomitapide (6 months prior to Visit S1);
    h. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (4 months prior to Visit S1, except PCSK9 small interfering RNA (siRNA), which are prohibited if used at any time in the past);
    i. Cholesteryl ester transfer protein (CETP) inhibitors (12 months prior to Visit S1);
    j. Red yeast rice extract-containing products;
    k. Omega 3 fatty acids and derivatives such as Lovaza® and over-the-counter (OTC) fish oil;
    l. Systemic corticosteroids (within 5 weeks prior to Visit T1); topical and inhaled corticosteroids are allowed;
    m. The following therapies for the treatment of T2D: rapid-acting and short-acting insulins including Lispro (HumaLog®), Aspart (Novalog®), Glulisine (Adipra®), Novolin R/ Novolin Regular, Humulin R/Humulin Regular (except when used for basal delivery by infusion pump); injectable GLP-1 agonists such as Exenatide (Byetta, Bydureon), liraglutide (Victoza®), albiglutide (Tanzeum®) and dulaglutide (Trulicity®); injectable synthetic forms of amylin such as Pramlintide (Symlin); and insulin glargine/lexisenatide (Soliqua®) (within 3 months prior to Visit T1).

18. The subject has planned initiation of or dosing changes in the following allowed drugs before or during the study:
    a. Oral diabetes medications (within 3 months prior to Visit T1);
    b. Intermediate-acting and long-acting insulin and insulin analogs when used for basal delivery of insulin including NPH, NovoLIN N, HumuLIN N, Glargine (Lantus), Determir (Levemir), NovoLIN 70/30, HumuLIN 70/30, NovoLog Mix 70/30 or HumuLOG Mix 70/30 (within 3 months prior to Visit T1);
    c. Rapid-acting and short-acting insulins only when used for basal infusion pump delivery (no bolus delivery allowed) including Lispro (HumaLog®), Aspart (Novalog®), Glulisine (Adipra®), Novolin R/Novolin Regular, Humulin R/Humulin Regular (within 3 months prior to Visit T1);
    d. Intermediate-acting and long-acting insulin and insulin analogs when used for basal delivery of insulin including NPH, NovoLIN N, HumuLIN N, Glargine (Lantus), Determir (Levemir), NovoLIN 70/30, HumuLIN 70/30, NovoLog Mix 70/30 or HumuLOG Mix 70/30 (within 3 months prior to Visit T1);
    e. Obesity medication (within 3 months prior to Visit T1);
    f. Hormone replacement (within 5 weeks prior to Visit T1); or
    g. Thyroid replacement (within 5 weeks prior to Visit T1).
19. The subject has a medical or situational (ie, geographical) finding that, in the investigator's opinion, may compromise the subject's safety or ability to complete the study;
20. The subject is an employee or contractor of the facility that is conducting the study or is a family member of the principal investigator, co-investigator, or any sponsor personnel.

IMP Dosage and Mode of Administration:

Bempedoic acid 180 mg + EZE 10 mg FDC tablets, EZE 10 mg overencapsulated tablets, and FDC-matching PBO tablet, and EZE-matching PBO capsules will be supplied by Esperion Therapeutics. All IMP will be ingested once daily at a similar time in the morning with or without food.

Non-Investigation Medicinal Product:

All other background drugs including diabetes medications will be administered as prescribed by a physician.

Study Duration:

The expected study duration is approximately 126 days, including an approximate 42-day screening period (Visit S1/Day -42, followed by a 5-week single-blind PBO run-in / LMT washout period from Day -35 to Day -1), an 84-day treatment period beginning at Visit T1/Day 1, and an EOS visit (Visit T3/Day 85).

Criteria for evaluation:

Lipid, Cardiometabolic and Glycemic Assessments:

- Calculated fasting serum lipids LDL-C, non-HDL-C, TC, and apoB, TG, and HDL-C;
  - 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.
- Serum hs-CRP;
- Blood HbA_{1C};
- Plasma glucose (fasting and 2-hour post prandial);

[redacted]

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, and urinalysis), physical examination (PE) findings and vital signs.

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, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid.

Other Assessments:

HBsAg, HCV, serum (Visit S1) and urine (Visit T1) pregnancy test (only for females who are of childbearing potential), FSH (only for women <55 years old and ≥1 year without menses), TSH. Reserve blood samples (serum and plasma) for potential future measurement of potential biomarkers (Visit T1, T3).

Statistical Methods

Sample Size

The sample size of approximately 56 subjects per treatment arm (1:1:1) in this study (168 subjects 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]

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ACL	adenosine triphosphate-citrate lyase
ACS	acyl-coA synthetase
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoB	apolipoprotein B
ARIC	Atherosclerosis Risk in Communities
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{24}	area under the plasma concentration-time curve from time zero to 24 hours after dosing
BA	bempedoic acid
BMI	body mass index
BUN	blood urea nitrogen
C_{max}	maximum plasma drug concentration
Ca	calcium
CETP	cholesteryl ester transfer protein
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
Cl	chloride
cm	centimeter
CMV	cytomegalovirus
CO_2	carbon dioxide
CRO	contract research organization

Abbreviation or Specialist Term	Explanation
CTT	Cholesterol Treatment Trialists
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EENT	eyes, ears, nose, and throat
eGFR	estimated glomerular filtration rate
EOS	end of study
ESP15228	primary metabolite of bempedoic acid (ETC-1002)
ETC-1002	bempedoic acid
ETC-002-CoA	ETC-1002-coenzyme A
EZE	ezetimibe
FAS	full analysis set
FDA	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-AB	hepatitis C virus antibody
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
[redacted]	
HOMA-IR	homeostatic model of assessment of insulin resistance
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product(s)

Abbreviation or Specialist Term	Explanation
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
K	potassium
Kg/m^2	Kilograms per square meters
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LFT	liver function test
LMT	lipid-modifying therapy
LOCF	last observation carried forward
LSM	least squares mean
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
N/A	not available
Na	sodium
N/D	not done
NOAEL	no-observed-adverse-effect level
Non-HDL-C	non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
OTC	over-the-counter
PBO	placebo
PCSK9	proprotein convertase subtilisin/kexin type 9
PE	physical examination

Abbreviation or Specialist Term	Explanation
PK	pharmacokinetic
PPG	postprandial glucose
PT	prothrombin time
QTc	corrected QT interval
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
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
SP	Safety Population
SUBJECT ID	subject identification number
SUSARs	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination half-life
T2D	type 2 diabetes
TB	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglycerides
TQT	thorough QT/QTc
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell

5. INTRODUCTION

5.1. Lipid-Regulating Drugs and Cardiovascular Disease

Bempedoic acid (BA; ETC-1002) is an inhibitor of adenosine triphosphate-citrate lyase (ACL) (adenosine triphosphate [ATP] citrate lyase), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. It is an oral, first-in-class small molecule designed to lower low-density lipoprotein cholesterol (LDL-C) levels in patients with high cardiovascular risk who are unable to meet their treatment goals with currently available lipid-lowering therapies. Bempedoic acid is being evaluated as an adjunct to diet alone or in combination with other lipid-lowering therapies for treatment of adults with heterozygous familial hypercholesterolemia and/or clinical atherosclerotic cardiovascular disease who are on maximally tolerated statin therapy and who require additional lowering of LDL-C or who are unable to tolerate effective doses of currently available statin formulations.

Elevated LDL-C level is a major modifiable risk factor for the development of atherosclerosis and atherosclerotic cardiovascular diseases.[1] Despite aggressive interventional and pharmacologic therapies, cardiovascular disease is the number 1 cause of death globally.[2] An estimated 17.7 million people died from cardiovascular diseases in 2015, representing 31% of all deaths worldwide. Of these deaths, an estimated 7.4 million were due to coronary heart disease, and 6.7 million were due to stroke.[2] Cardiovascular disease remains the leading cause of death among Americans, Europeans, and around the world. The Global Burden of Disease study estimated that 29.6% of all deaths (approximately 15.6 million deaths) were caused by cardiovascular disease in 2010, more than all communicable, maternal, neonatal, and nutritional disorders combined, and double the number of deaths caused by cancers.[3] Based on 2011 death rate data, more than 2150 Americans die from cardiovascular diseases daily, for an average of 1 death every 40 seconds. Approximately 155,000 Americans who die from cardiovascular disease are younger than 65 years of age. In 2011, 34% of deaths due to cardiovascular disease occurred prior to the age of 75 years, less than the current 78.7-year average life expectancy.[4]

LDL-C is largely accepted as a valid surrogate endpoint of cardiovascular events by clinicians and regulatory authorities.[5] Long-term elevations in LDL-C lead to progressive accumulation of atherosclerotic lesions in the walls of arteries that require long-term management. While lifestyle changes are the primary intervention, these measures rarely decrease plasma LDL-C by >15%. Evidence supporting LDL-C as a therapeutic target and surrogate for cardiovascular 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 cardiovascular risk reduction, independent of the way LDL-C lowering was achieved based on mechanism of action.[6-9] A published patient-level meta-analysis, which includes 26 trials and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and cardiovascular outcomes.[7] This analysis showed that a 1 mmol/L reduction in LDL-C was associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. Intensive statin therapy relative to

low/moderate intensity statin treatment produces greater benefit in patients at high cardiovascular risk.[10]

Unfortunately, some patients with elevated LDL-C are unable to take high intensity statins due to dosing limits based on comorbidities, contraindications, and/or tolerance.[11] Nonstatin therapies may provide additional lowering of cardiovascular risk as demonstrated in the IMPROVE-IT trial, which added ezetimibe (EZE) to statin therapy.[12] Bempedoic acid and EZE are oral therapies that work by divergent mechanisms to lower LDL-C via up-regulation of LDL receptors. Coadministration of BA and EZE may, therefore, result in further reductions in LDL-C than can be obtained with either agent alone, thereby providing a therapeutic benefit to patients who do not achieve optimal lowering of LDL-C with either treatment alone.

The availability of a fixed-dose combination (FDC) tablet of BA 180 mg and EZE 10 mg (the recommended dose of each agent) would provide convenience to patients over coadministration of individual tablets, thereby enhancing treatment compliance. This 12-week study will evaluate the efficacy and safety of FDC compared to EZE 10 mg or placebo (PBO) in subjects with type 2 diabetes (T2D) and elevated LDL-C levels.

5.1.1. Overview of Bempedoic Acid

A complete summary of the available and nonclinical and clinical experience with BA is provided in the Investigator's Brochure.[13] The following sections provide information relevant to the current protocol.

5.1.2. Mechanism of Action

Bempedoic acid is a first-in-class small molecule inhibitor of ACL, an enzyme upstream of HMG-CoA in the cholesterol biosynthesis pathway. Bempedoic acid is a prodrug that requires activation in liver to ETC-1002-coenzyme A (ETC-1002-CoA), which mediates competitive inhibition of ACL. Inhibition of ACL by ETC-1002-CoA decreases cholesterol synthesis in the liver leading to increased low-density lipoprotein receptor (LDLR) expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC-1002-CoA decreases LDL-C via the same pathway as HMG-CoA reductase inhibition by statins.

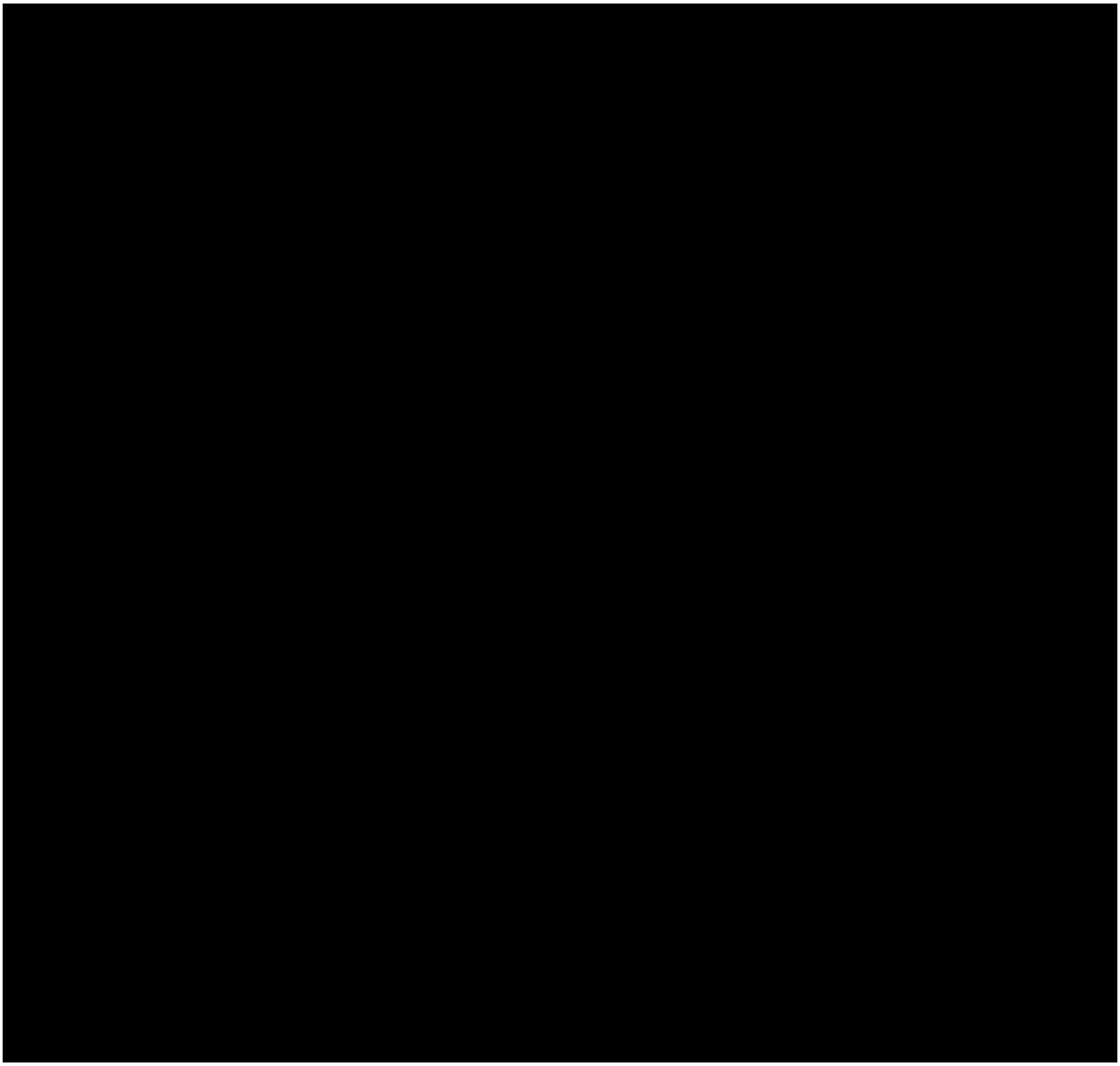
An important differentiating feature of BA is that, unlike statins, it does not inhibit cholesterol synthesis in skeletal muscle. The enzyme required to convert BA to ETC-1002-CoA is not present in skeletal muscle. Therefore, BA is not anticipated to mediate the adverse effects associated with inhibition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

5.1.3. Nonclinical Experience

[redacted]

5.1.4. Previous Human Experience

[redacted]



5.2. Risk-Benefit Assessment

Nonclinical and clinical data indicate that BA has a favorable risk-benefit profile. The ability of BA to achieve clinically meaningful LDL-C-lowering responses while demonstrating a favorable AE profile has been demonstrated in a variety of subject populations when given alone and as add-on therapy to statins. An ongoing Phase 3 trial of BA as add-on therapy to EZE therapy in subjects with elevated LDL-C levels who are on low or less-than-low doses of statins (Protocol 1002-048) has not identified any new safety concerns associated with coadministration of BA and EZE.

Information on the potential risks of BA is provided in the Investigator's Brochure for BA.[13] Information on the potential risks of EZE is provided in the prescribing information for EZE tablets.[14]

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objectives

- To assess the efficacy of FDC versus PBO on LDL-C lowering in subjects with T2D treated for 12 weeks; and
- To assess the efficacy of FDC versus EZE on LDL-C lowering in subjects with T2D treated for 12 weeks.

6.2. Secondary Objectives

- To assess the efficacy of EZE versus PBO on LDL-C lowering in subjects with T2D treated for 12 weeks;
- To assess the efficacy of FDC versus PBO, FDC versus EZE, and EZE versus PBO on high-sensitivity C-reactive protein (hs-CRP), non-HDL-C, total cholesterol (TC), apolipoprotein B (apoB), TG, and HDL-C in subjects with T2D treated for 12 weeks;
- To assess the effect of FDC, EZE, and PBO on percent of subjects achieving LDL-C level <70 mg/dL;
- To assess the effect of FDC, EZE, and PBO on percent of subjects achieving LDL-C reduction ≥50%; and
- To characterize the safety and tolerability of FDC, EZE, and PBO in subjects with T2D treated for 12 weeks.

6.3. Exploratory Objectives

- To assess the effect of FDC versus PBO and EZE on hemoglobin A_{1C} (HbA_{1C}), fasting glucose, [redacted] homeostatic model assessment of insulin sensitivity (HOMA-IR) and [redacted] and 2-hour postprandial glucose (PPG) in subjects with T2D treated for 12 weeks.

6.4. Study Endpoints

6.4.1. Primary Endpoint

- Percent change from baseline to Week 12/End of Study (EOS) in LDL-C.

6.4.2. Secondary Endpoints

- Percent change from baseline to Week 12 in hs-CRP, non-HDL-C, TC, apoB, TG, and HDL-C;
- Percent of subjects with LDL-C <70 mg/dL at Week 12;
- Percent of subjects with LDL-C reduction ≥50% from baseline to Week 12.

6.4.3. Exploratory Endpoints

- Percent change from baseline at [redacted] Week 12 in parameters below:
  - HbA_{1C};
  - Plasma glucose (fasting and 2-hour PPG);

  - HOMA-IR index;

6.4.4. Safety Endpoints

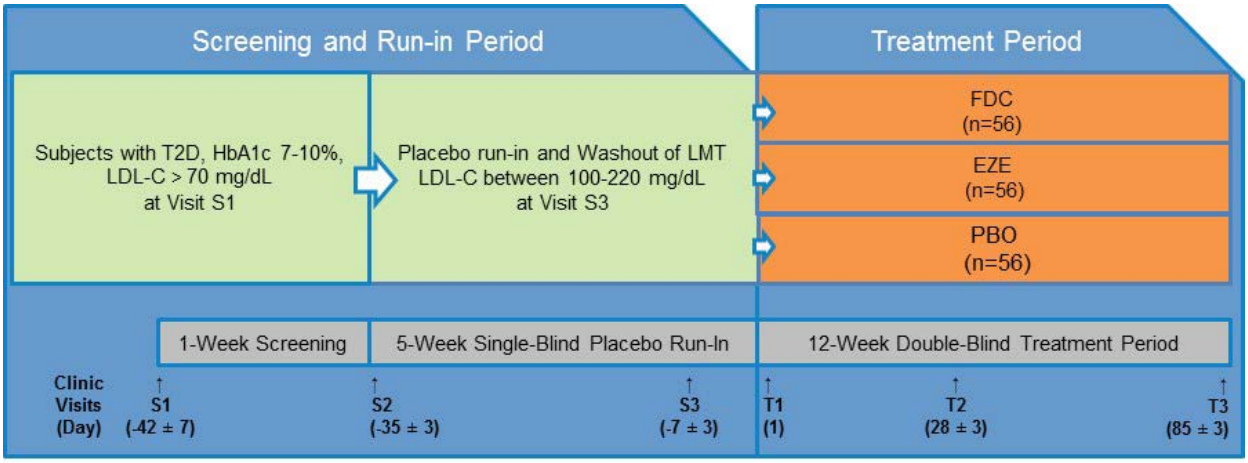
- TEAEs;
- SAEs;
- Clinical safety laboratories (hematology, clinical chemistry, and urinalysis);
- Vital signs;
- PEs.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 2, randomized, double-blind, parallel-group, multicenter study of BA 180 mg and EZE 10 mg FDC versus PBO and EZE 10 mg administered for 12 weeks in subjects with T2D and elevated LDL-C. An overview of the study design is presented in Figure 1.

Figure 1: Overview of Study Design



T2D= type 2 diabetes; HbA1c = hemoglobin A1c; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; BA = bempedoic acid; EZE = ezetimibe; FDC = fixed dose combination.

Subjects with a history of T2D for at least 6 months will be screened for eligibility at an initial screening visit (Visit S1), which will be conducted approximately 42 days before planned randomization into the study. Subjects who have an LDL-C level >70 mg/dL and who meet all other inclusion/exclusion criteria will be return for Visit S2 approximately 5 weeks prior to planned randomization into the study to washout of all LDL-C-lowering therapies and begin taking single-blind (subject) PBO. Subjects will return to the study site approximately 7 days before planned randomization into the study for Visit S3. Subjects who have an LDL-C level ≥100 mg/dL and who continue to meet the study inclusion/exclusion criteria will be scheduled for their first treatment visit.

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast. Subjects who continue to meet the study inclusion/exclusion criteria will be randomized in a 1:1:1 ratio to receive either FDC (n = 56), EZE (n = 56), or PBO (n = 56) once daily for 12 weeks. Randomized subjects will return for clinic visits at Week 4 (Visit T2) and Week 12 (Visit T3/EOS). Subjects who withdraw from IMP treatment will be asked to continue to be followed for safety and efficacy using the protocol-specified visit schedule and procedures. Subjects will be dispensed IMP at Visit T1/Day 1 and will be instructed to take the IMP in the morning at 24-hour intervals, with approximately 8 ounces of water with or without food.

Subjects will report to each of the study visits after a minimum 10-hour fast and without having taken their dose of IMP. Study site personnel will administer the IMP on these days after blood

and urine samples have been drawn and other scheduled safety procedures have been completed. All other doses of IMP will be self-administered by the subjects; the last dose will be taken the day prior to the final clinical visit (Visit T3/EOS).

7.2. Study Hypothesis

The clinical hypothesis for this study is that FDC therapy with BA180 mg, EZE 10 mg will significantly reduce LDL-C in subjects with T2D and elevated LDL-C treated daily for 12 weeks versus EZE 10 mg and versus PBO.

7.3. Rationale for Dose Selection

The daily dose of BA (180 mg) taken as an individual tablet or in combination with EZE in the FDC tablet represents the dose that is being evaluated in Phase 3 monotherapy and combination therapy trials of BA in subjects with hypercholesterolemia. The daily dose of EZE (10 mg) taken as an individual tablet or in combination with BA in the FDC tablets represents the recommended therapeutic dose for this drug.

7.4. Study Duration

The expected study duration is approximately 126 days, including an approximate 42-day screening period (Visit S1/Day -42, followed by a 5-week single-blind PBO run-in/lipid-modifying therapy (LMT) washout period from Day -35 to Day -1), an 84-day treatment period beginning at Visit T1/Day 1, and an EOS visit (Visit T3/Day 85).

7.5. Number of Subjects

Approximately 168 male and female subjects with a history of T2D for at least 6 months and who meet the inclusion and exclusion criteria will be enrolled and randomized in a 1:1:1 ratio to receive FDC (n = 56) or EZE (n = 56) or PBO (n = 56).

7.6. Replacement of Subjects

Subjects who are withdrawn from the study for any reason may be replaced at the discretion of the sponsor.

7.7. Number of Clinical Sites

Approximately 45 clinical sites in the United States (US) will participate in this study. Additional sites may be invited to participate to ensure study timelines are met.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects must satisfy all the following criteria at Visit S1 (unless otherwise specified) for enrollment in the study:

1. The subject must be willing to provide written informed consent before any study specific procedures are performed;
2. The subject must be aged 18-75 years or be of legal age of majority based on regional law, whichever is older;
3. The subject must have a history of T2D for 6 months or greater; and must be currently taking stable diabetes medication for 3 months or greater with HbA_{1C} between 7% and 10% at Visit S1;
4. The subject must have a fasting calculated LDL-C level >70 mg/dL at Visit S1;
5. The subject must have a fasting calculated LDL-C level between 100 and 220 mg/dL at Visit S3 after washout of all LMT;
6. The subject must clinically stable and suitable to undergo washout of all LDL-C-lowering drugs and nutritional supplements for 17 weeks (with potential for 1-week extension if repeat assessments described in the protocol are required) based on investigator assessment;
7. The subject may be male or female. Women must not be pregnant (or planning to become pregnant within 30 days after the last dose of IMP) or lactating and must be:
    a. Naturally postmenopausal, defined as ≥1 year without menses and either:
        i. ≥55 years old, or
        ii. <55 years old with a follicle-stimulating hormone (FSH) level ≥40.0 IU/L;
    b. Surgically sterile by hysterectomy, bilateral oophorectomy, and/or tubal ligation; or
    c. Willing to use 1 acceptable method of birth control if of childbearing potential unless the subject agrees to follow the definition of true abstinence. The minimal requirement for use of acceptable contraception is from the time the informed consent form (ICF) is signed, during the study period, and for at least 30 days after the last dose of IMP. Acceptable methods of birth control include:
        i. placement of an intrauterine device (IUD) with or without hormones,
        ii. established use of oral, implanted, topical, or injectable, or hormonal method of contraception associated with inhibition of ovulation,
        iii. barrier methods, including condom or occlusive cap with spermicidal foam or spermicidal jelly,
        iv. vasectomized male partner who is the sole partner for the subject, or

v. true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

There are no protocol-specific birth control requirements for men who have partners that can become pregnant.

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria at Visit S1 (unless otherwise specified) will be excluded from the study:

1. The subject has a body mass index (BMI) >40 kg/m^2;
2. The subject has a history of documented clinically significant cardiovascular disease including, but not limited to:
   a. myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease;
   b. uncontrolled hypertension, defined as mean systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg after sitting quietly for 5 minutes;

Note: At the discretion of the investigator, a single repeat sitting systolic blood pressure and diastolic blood pressure may be obtained at another visit; the repeat values will be used to determine the subject's eligibility for the study;

   c. an arrhythmia requiring medical intervention;
   d. abdominal or thoracic aortic aneurysm;
   e. New York Heart Association (NYHA) Class III and IV heart failure;
3. The subject has a fasting TG level >400 mg/dL at Visit S3;

Note: At the discretion of the investigator, a repeat TG measurement may be obtained once, and the screening period will be extended for up to 1 week. The repeat value will be used to determine the subject's eligibility for the study;

4. The subject has a history of type 1 diabetes;
5. The subject has uncontrolled hypothyroidism, including a value for thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN);
6. The subject has liver disease or dysfunction, including:
   a. positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C virus antibodies (HCV-AB) at Week -1 (Visit S2/Day 7), or
   b. serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value ≥2 × ULN and/or serum total bilirubin (TB) value ≥2 × ULN. If the serum TB value is ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and, if consistent with Gilbert's disease or if the subject has a history of Gilbert's disease, the subject may be enrolled in the study.

Note: At the discretion of the investigator, a single repeat measurement of serum ALT, AST, and/or TB may be completed; the repeat value will be used to determine eligibility for the study. If a test for HCV-AB is positive, but an optional reflexive test for hepatitis C virus (HCV) ribonucleic acid (RNA) is negative, the subject can be enrolled in the study;

7. The subject has renal dysfunction or glomerulonephritis, including an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (as determined by the central laboratory using the Modification of Diet in Renal Disease [MDRD] formula);

Note: At the discretion of the investigator, a single repeat eGFR may be obtained; the repeat value will be used to determine eligibility for the study;

8. The subject has gastrointestinal conditions or has undergone procedures (including weight loss surgery; eg, Lap-Band, gastric bypass) that may affect drug absorption;
9. The subject has hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL;
10. The subject had an active malignancy, including those requiring surgery, chemotherapy, and/or radiation, in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed;
11. The subject has an unexplained (ie, not associated with recent trauma or physically strenuous activity) serum creatine kinase (CK) value >3 × ULN at any time before randomization. Subjects with an explained elevation in serum CK must have single repeat serum CK value ≤3 × ULN before randomization;
12. The subject has a history of drug or alcohol abuse within the last 2 years or reports current consumption of >14 alcoholic drinks/week, uses any illicit drugs, or has a history of amphetamine or derivatives abuse or cocaine abuse. Subjects who are using amphetamine derivatives prescribed by and who are under the care of a health care practitioner can be enrolled after evaluation by the investigator;
13. The subject has donated blood, undergone multiple blood draws in a clinical study, experienced major trauma, received a blood transfusion, or undergone surgery, with or without blood loss, within 30 days before randomization;
14. The subject has used any experimental or investigational drugs within 30 days before screening and throughout the trial;
15. The subject has previously participated in a clinical study of BA;
16. The subject has experienced history of intolerance to EZE;
17. The subject has used prohibited drugs and/or nutritional supplements within 5 weeks prior to Visit T1 (unless otherwise specified) or plans to use any of the prohibited drugs and/or nutritional supplements during the study, including but not limited to:
    a. Statins;
    b. Fibrates (including fenofibrate);
    c. Niacin and derivatives;
    d. Bile acid sequestants;

e. Ezetimibe (study-provided is allowed);
f. Apheresis;
g. Mipomersen or lomitapide (6 months prior to Visit S1);
h. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (4 months prior to Visit S1, except PCSK9 small interfering RNA (siRNA), which are prohibited if used at any time in the past);
i. Cholesteryl ester transfer protein (CETP) inhibitors (12 months prior to Visit S1);
j. Red yeast rice extract-containing products;
k. Omega 3 fatty acids and derivatives such as Lovaza® and over-the-counter (OTC) fish oil;
l. Systemic corticosteroids (within 5 weeks prior to Visit T1; topical and inhaled corticosteroids are allowed);
m. The following therapies for the treatment of T2D: rapid-acting and short-acting insulins including Lispro (HumaLog®), Aspart (Novalog®), Glulisine (Adipra®), Novolin R/Novolin Regular, Humulin R/Humulin Regular (except when used for basal delivery by infusion pump); injectable GLP-1 agonists such as Exenatide (Byetta, Bydureon), liraglutide (Victoza®), albiglutide (Tanzeum®) and dulaglutide (Trulicity®); injectable synthetic forms of amylin such as Pramlintide (Symlin); and insulin glargine/lexisenatide (Soliqua®) (within 3 months prior to Visit T1);

18. The subject has planned initiation of or dosing changes in the following allowed drugs before or during the study:

a. Oral diabetes medications (within 3 months prior to Visit T1);
b. Intermediate-acting and long-acting insulin and insulin analogs when used for basal delivery of insulin including NPH, NovoLIN N, HumuLIN N, Glargine (Lantus), Determir (Levemir), NovoLIN 70/30, HumuLIN 70/30, NovoLog Mix 70/30 or HumuLOG Mix 70/30 (within 3 months prior to Visit T1),
c. Rapid-acting and short-acting insulins only when used for basal infusion pump delivery (no bolus delivery allowed) including Lispro (HumaLog®), Aspart (Novalog®), Glulisine (Adipra®), Novolin R/Novolin Regular, Humulin R/Humulin Regular (within 3 months prior to Visit T1),
d. Obesity medication (within 3 months prior to Visit T1);
e. Hormone replacement (within 5 weeks prior to Visit T1); or
f. Thyroid replacement (within 5 weeks prior to Visit T1);

19. The subject has a medical or situational (ie, geographical) finding that, in the investigator's opinion, may compromise the subject's safety or ability to complete the study;

20. The subject is an employee or contractor of the facility that is conducting the study or is a family member of the principal investigator, co-investigator, or any sponsor personnel.

8.3. Lifestyle and Dietary Guidelines

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

Beginning at screening, subjects will be counseled to follow a 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.

8.4. Investigator/Sponsor Suspension or Termination of Subject Enrollment

If, in the opinion of the investigator, the clinical observations in the study suggest that it may be unwise to continue, the investigator may suspend or terminate the study after consultation with Esperion Therapeutics. A written statement fully documenting the reasons for such a termination will be provided to Esperion Therapeutics (or designee) and to the institutional review board (IRB).

Esperion Therapeutics has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the investigator, the IRB, and regulatory authorities, if required.

Possible reasons for termination of the study 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, and
- lack of study oversight by the principal investigator and/or designee.

In the event any serious or nonserious AEs occur, all documentation relating to the event(s) must be obtained.

9. TREATMENT OF SUBJECTS

9.1. Investigational Medicinal Product Dosage and Mode of Administration

Subjects will receive one FDC-matched PBO tablet and one EZE-matching PBO capsule once daily for 35 ± 3 days during the run-in period prior to randomization.

Subjects will be randomized to receive treatment with:

- One (1) BA 180 mg + EZE 10 mg FDC tablet and 1 EZE-matching PBO capsule once daily for 84 ± 3 days, or
- One (1) EZE 10 mg overencapsulated tablet and 1 FDC-matched PBO tablet once daily for 84 ± 3 days; or
- One (1) FDC-matched PBO tablet and 1 EZE-matching PBO capsule once daily for 84 ± 3 days.

All IMP will be taken orally, at a similar time (approximate 24-hour intervals), in the morning with or without food.

9.2. Description of Investigational Medicinal Product

9.2.1. Bempedoic Acid 180 mg + Ezetimibe 10 mg FDC Tablets, Ezetimibe 10 mg Overencapsulated Tablets, and Matching Placebo

Bempedoic acid 180 mg + EZE 10 mg FDC tablets, EZE 10 mg overencapsulated tablets, FDC-matched PBO tablets, and EZE-matching PBO capsules will be provided by Esperion Therapeutics. A description of the tablets is provided in Table 1.

Table 1: Description of Bempedoic Acid + Ezetimibe FDC Tablets, Ezetimibe Tablets and Placebo Tablets

Parameter	Bempedoic Acid + Ezetimibe FDC Tablet	Ezetimibe Overencapsulated Tablet	FDC-matched Placebo Tablet	Ezetimibe-matched Placebo Capsule
Dosage form:	Film-coated tablet	Over-encapsulated tablets	Film-coated tablet	Capsules
Unit dose:	180 mg bempedoic acid + 10 mg ezetimibe	10 mg	Not applicable	Not applicable
Container:	Blister cards with child-resistant closures	Blister cards with child-resistant closures	Blister cards with child-resistant closures	Blister cards with child-resistant closures
Route of administration:	Oral with water with or without food	Oral with water with or without food	Oral with water with or without food	Oral with water with or without food
Physical description:	[redacted]			

FDC = fixed-dose combination.

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

9.3. Concomitant Medications

Subjects will be instructed to report the use of any medication to the investigator and will be reminded about the importance of not taking any medications without consulting the investigator. Subjects will be questioned about concomitant medication use at each study visit during the screening and treatment periods. All prior medications, herbal remedies, dietary supplements, or vitamins that were taken within 3 months before screening (Visit S1) will be recorded. Any concomitant medication that is taken from the time the first dose of IMP is taken (Visit T1) through the EOS visit (Visit T3) or early termination from the study must be recorded, with indication, daily dose, and start and stop dates of administration.

9.3.1. Prohibited Medications

Use of any of the following drugs either in mono or combination therapy within 5 weeks prior to Visit T1 (unless otherwise stated) or a plan to use any of these drugs during the study is **prohibited**:

Lipid-Modifying Therapies (LMT)

- Statins including atorvastatin (Lipitor®), fluvastatin (Lescol®), lovastatin (Mevacor®, Altoprev™), pravastatin (Pravachol®), rosuvastatin Calcium (Crestor®), simvastatin (Zocor®) and pitavastatin (Livalo®);
- 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 OTC 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;
- Lipid altering nutritional supplements including berberine, psyllium (Metamucil®), green tea extract, sitostanol (found in oral nutritional supplements and some margarines, such as Benecol), beta-sitosterol (found in oral nutritional supplements and some margarines, such as Promise Activ), pantothine and policosanol;
- Apheresis;
- Mipomersen (Kynamro®) or lomitapide (Juxtapid®) (within 6 months prior to Visit S1);

- PCSK9 inhibitors including evolocumab (Repatha®) and alirocumab (Praluent®) (within 4 months prior to Visit S1, except PCSK9 siRNA, which are prohibited if used at any time in the past);
- CETP inhibitors (within 12 months prior to Visit S1);
- Red yeast rice extract (also known as monascus purpureus extract or Cholestin)-containing products (within 5 weeks prior to Visit T1);
- Omega 3 fatty acids and derivatives such as Lovaza and OTC fish oil;

Other Prohibited Medications

- Systemic corticosteroids (within 5 weeks prior to Visit T1); topical and inhaled corticosteroids are allowed;
- The following therapies for the treatment of type 1 or T2D: rapid-acting and short-acting insulins including Lispro (HumaLog®), Aspart (Novalog®), Glulisine (Adipra®), Novolin R/Novolin Regular, Humulin R/Humulin Regular (except when used for basal delivery by infusion pump); injectable GLP-1 agonists such as Exenatide (Byetta, Bydureon), liraglutide (Victoza®), albiglutide (Tanzeum®) and dulaglutide (Trulicity®); injectable synthetic forms of amylin such as Pramlintide (Symlin); and insulin glargine/lexisenatide (Soliqua®) within 3 months prior to Visit T1;
- Any experimental or investigational drugs within 30 days before screening (Week -6, Visit S1). Subjects who have enrolled in a study of an experimental siRNA inhibitor of PCSK9 are excluded.

9.3.2. Allowed Medications

Use of the following medications is allowed during the study:

- oral diabetes medications if no changes in dose are made within 3 months before randomization (Visit T1/Day 1) or during the study;
- Intermediate-acting and long-acting insulin and insulin analogs when used for basal delivery of insulin including NPH, NovoLIN N, HumuLIN N, Glargine (Lantus), Determir (Levemir), NovoLIN 70/30, HumuLIN 70/30, NovoLog Mix 70/30 or HumuLOG Mix 70/30 if no changes in dose are made within 3 months prior to Visit T1;
- Rapid-acting and short-acting insulins only when used for basal infusion pump delivery (no bolus delivery allowed) including Lispro (HumaLog®), Aspart (Novalog®), Glulisine (Adipra®), Novolin R/Novolin Regular, Humulin R/Humulin Regular if no changes in dose are made within 3 months prior to Visit T1;
- obesity medications if no changes in dose have been made within 3 months before randomization (at Visit T1/Day 1) or during the study;
- hormone replacement therapy if no changes in dose are made within 5 weeks before randomization (at Visit T1/Day 1) or during the study;

- thyroid placement therapy if no changes in dose are made within 5 weeks before randomization (at Visit T1/Day 1) or during the study; and
- topical corticosteroids.

Short-term use of a medication for a self-limiting indication (eg, acetaminophen for a headache) may be authorized by the investigator. The maximum allowable dose of acetaminophen is 2 g/day. The investigator must make the decision to authorize use of such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether use of the medication will compromise the outcome or validity of the study.

9.3.3. Contraception

Women of nonchildbearing potential are not required to use contraception. Women of nonchildbearing potential are defined as those who are naturally postmenopausal (defined as ≥1 year without menses and either a) ≥55 years old, or b) <55 years with an FSH level ≥40.0 IU/L) and those who are surgically sterile by hysterectomy, bilateral oophorectomy, and/or tubal ligation.

Women of childbearing potential must use 1 acceptable method of birth control, minimally, from the time the ICF is signed through at least 30 days after the last dose of IMP. Acceptable methods of birth control include:

a. placement of an IUD with or without hormones;
b. established use of oral, implanted, topical, or injectable, or hormonal method of contraception associated with inhibition of ovulation;
c. barrier methods, including condom or occlusive cap with spermicidal foam or spermicidal jelly;
d. vasectomized male partner who is the sole partner for the subject; and
e. true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

If a subject who is abstinent at the time the ICF is signed becomes sexually active, she must agree to use 1 acceptable method of contraception, as described above. There are no protocol-specific birth control requirements for men who have partners that can become pregnant. Contraceptive requirements do not apply to individuals who are exclusively in same-sex relationships.

9.4. Treatment Assignment, Randomization, and Blinding

During the Run-in Period, subjects will receive single-blind PBO beginning at Visit S2 and concluding with last dose on Day -1, the day prior to Visit T1. During the Treatment Period, subjects will receive double-blind IMP. On Day 1 (Visit T1), subjects will be randomized to receive either FDC or EZE or PBO, randomized 1:1:1. Randomized assigned blinded study drug will be dispensed to subjects according to the interactive web response system (IWRS). During

the Treatment Period, Sponsor, site personnel, contract research organization (CRO), and subject will all be unaware of subject's treatment assignment.

Blinding of treatment must be maintained for all subjects unless, in the opinion of the investigator, the safety of the subject 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 subject 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 subject'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, hs-CRP, non-HDL-C, TC, TG, and HDL-C that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the subject, 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 subjects 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.

9.5. Investigational Medicinal Product Adherence

Subjects will be instructed to bring their IMP to each study visit beginning at Visit S3 and completing at Visit T3/EOS. Compliance with dosing instructions will be assessed by counting the number of tablets and capsules remaining at each study visit. If the subject has not taken multiple doses as instructed, the subject will be queried for a reason, findings will be documented, and the subject will be counseled on the importance of carefully following all dosing instructions. Factors contributing to poor adherence will be determined and, if possible, remedied. Subjects 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.

9.6. Overdose

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

Ezetimibe has been generally well tolerated in clinical trials in which healthy subjects (N = 15) received 50 mg/day of EZE for 14 days, subjects with primary hyperlipidemia (N = 18) received 40 mg/day of EZE for up to 56 days, and subjects with homozygous sitosterolemia (N = 27) received 40 mg/day of EZE for up to 26 weeks.[14] One female subject with homozygous

sitosterolemia took an accidental overdose of EZE 120 mg/day for 28 days with no reported clinical or laboratory AEs. Symptomatic and supportive measures should be employed in the event of overdose.

10. INVESTIGATIONAL MEDICINAL PRODUCT

10.1. Investigational Medicinal Product Supply and Control

FDC, EZE, and PBO tablets and overencapsulated tablets will be supplied to the sites by Esperion Therapeutics. The IMP will be distributed and released in accordance with regional and local requirements during the conduct of the study. Study medication will be stored under lock and key, with access limited to those authorized by the investigator, and will be managed according to US Food and Drug Administration (FDA) regulations concerning the storage and administration of investigational drugs.

Additional information regarding packaging, labeling, storage, and distribution is provided in the pharmacy manual.

10.2. Administration of Investigational Medicinal Product

The dose of IMP will be administered to the subjects at the study site at each of the study visits. The first dose of single-blind PBO will be taken during Visit S2. Subsequent doses will be self-administered once daily by the subject at approximately the same time each day in the morning through Study Day -1 (the day prior to Visit T1). Double-blind IMP will be taken at Visit T1/Day 1 between 6 AM and 10 AM. The actual time of IMP administration during study visits will be recorded and will determine the target time of IMP administration for the subjects during the treatment period. Subjects will self-administer the IMP on all other days, once daily in the morning with or without food. The last dose of IMP will be taken on the morning of the day prior to Visit T3/EOS).

Subjects will be instructed on the importance of maintaining 24-hour intervals between doses. If the daily dose of IMP is not taken at the usual time due to unforeseen circumstances, the subject may take the dose as soon as possible after the target time but no later than noon. If the daily dose is not taken by noon, the subject will be instructed to skip the dose on that day and to resume dosing on schedule the next day.

10.3. Investigational Medicinal Product Accountability, Handling and Disposal

The Principal Investigator must maintain accurate records of the receipt of all study medication shipped by the sponsor/sponsor representative and the disposition of that study medication. 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 used and unused IMP (FDC, EZE, and PBO) will be returned to the sponsor (or designee) for destruction or disposed of by the study site, per

sponsor written instruction. All IMP returns must be accompanied by the appropriate documentation.

Investigational medicinal product 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;
- label identification or batch number;
- dates and initials of person responsible for product inventory (including entry/movement/disposition);
- date and amount dispensed to each subject, including unique subject identifier;
- data returned by subject, assessment of compliance, and relevant documentation of discrepancies;
- nonstudy disposition (eg, lost, broken, wasted); and
- amount returned to sponsor/sponsor designee.

The sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established quality system that meets the needs of this requirement.

11. STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

11.1. Informed Consent

The investigator is responsible for providing each subject with adequate explanations of the nature and risks of the study before any study procedures or assessments occur. The subject must be able to understand the ICF and to converse with the investigator in the language in which the ICF is written. No study-related procedures will be performed until the subject has been completely informed of the study risks and benefits, has freely consented to take part in the study, and has signed and dated an ICF that has been approved by a licensed IRB.

11.2. Subject Identification Numbers

A unique subject identification number (subject ID) will be assigned to identify each subject throughout the study and will be entered on all documentation. If a subject is not eligible to receive treatment or discontinues from the study, that subject's identification number cannot be assigned to another subject. Subject identification numbers will be assigned sequentially.

11.3. Rescreening

Subjects 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 subjects must also be re-consented and screening procedures must be repeated. If a subject is a screen failure, or if a subject discontinues from the study, their subject ID number will not be assigned to another subject. Rescreened subjects will be assigned a new subject ID number.

11.4. Procedures and Schedule of Assessments

The study is comprised of two distinct periods: the Screening and Run-in Period and the Treatment Period. The schedule of study events is provided in Appendix 1. However, a subject can be seen at any time for reasons of safety.

All relevant data will be captured on electronic case report forms (eCRFs) according to the eCRF completion guidelines.

11.5. General Visit Guidelines

Subjects will arrive fasted and having not taken study medication prior to the visit. The following assessments will be conducted while fasted and prior to taking study medication (unless otherwise specified):

- Review of medical history, prior and concomitant medications;
- Assess AEs and SAEs;
- PE;
- Vital signs;

- blood sampling for basic fasting lipid assessments (LDL-C, non-HDL-C, TC, TG, HDL-C);
- blood sampling for special lipids and other biomarkers (apoB, hs-CRP, glucose, [redacted] HbA_{1C});
- blood sampling for clinical safety laboratories.

11.6. Screening Period

11.6.1. Screening Period Visit 1 (Visit S1/Day -42 ± 7)

Subjects will be screened for study eligibility at Visit S1 (Day -42 ± 7). The following evaluations will be performed at this visit:

- Written informed consent will be obtained before any study-related procedures are conducted.
- Demographic data will be recorded.
- Recent clinically relevant medical history will be recorded.
- Prior, concomitant, and prohibited medications will be reviewed and recorded.
- Weight (in kilograms) and height (in centimeters) will be measured, and BMI will be calculated.
- PE
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded.
- Blood and urine specimens will be obtained for the following:
  - serum pregnancy test (for surgically sterile women and women of childbearing potential) or FSH test (women <55 years old and ≥1 year without menses);
  - basic fasting lipid panel;
  - special lipids and other biomarkers (HbA_{1C} only);
  - coagulation panel;
  - serum TSH;
  - clinical safety laboratories (hematology, clinical chemistry, and urinalysis;
  - urine drug screen.
- eGFR will be calculated (by central laboratory) using the MDRD formula.
- Conduct diet and exercise counseling.
- Contact IWRS to register subject.

Subjects with a history of T2D of at least 6 months with at least 3 months on stable diabetes medication, who have an HbA_{1C} between 7%-10%, an LDL-C level >70 mg/dL, and meet the other protocol inclusion/exclusion criteria based on initial screening will be contacted by phone to schedule the second screening visit (Visit S2) to occur approximately 7 days after Visit S1.

Subjects 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 subject can be seen at any time for safety reasons).

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

11.6.2. Screening Period Visit 2 (Visit S2/Day -35 ± 3)

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

- Review of all inclusion/exclusion criteria that can be assessed at this time;
- Concomitant and prohibited medication review (ongoing);
- Adverse events will be assessed (starting from signing of the informed consent);
- Electrocardiogram (ECG);
- Vital signs;
- Serology (including HBsAg, hepatitis C antibody);
- Conduct diet and exercise counseling;
- Instruct subject to stop taking all LMT and other prohibited medications (Section 9.3.1);
- Dispense single-blind PBO with instructions;
- Schedule next visit.

11.6.3. Screening Period Visit 3 (Visit S3/Day -7 ± 3)

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

- Review of all inclusion/exclusion criteria;
- Concomitant and prohibited medication review (ongoing);
- Adverse events will be assessed;
- Weight (in kilograms);
- Vital signs;
- Basic fasting lipids;
- Clinical safety laboratories;

- Conduct diet and exercise counseling;
- Assessment and recording of drug compliance with single-blind PBO;
- Schedule next visit.

11.7. Treatment Period

Enrollment criteria will be reviewed including select laboratory values from Visit S3. Subjects who have an LDL-C level between 100 to 220 mg/dL at Visit S3 and who meet all other inclusion/exclusion criteria will be scheduled for their first treatment visit (Visit T1/Day 1), and instructed to fast for a minimum of 10 hours (nothing but water) on the evening before reporting for Visit T1/Day 1.

11.7.1. Treatment Period Visit 1 (Visit T1/Day 1)

Subjects will be scheduled for their first treatment visit approximately 7 days after completion of Visit S3/Day -7. Subjects will arrive at the study site after a minimum 10-hour fast, will be administered their first dose of IMP at this visit.

Procedures and evaluations will be performed in the following order during this visit:

- Enrollment criteria will be reviewed.
- Concomitant and prohibited medications will be reviewed and recorded as needed.
- Adverse events will be assessed.
- Weight (in kilograms) will be recorded.
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded.
- Blood and urine specimens will be obtained for the following:
  - urine pregnancy test (for women of childbearing potential);
  - basic fasting lipid panel;
  - special lipids and other biomarkers;
  - clinical safety laboratories (hematology, clinical chemistry, and urinalysis);
  - reserve sample for potential exploratory biomarkers; and
  - urine drug screen.
- Subject will be given 1 serving of Ensure Original Vanilla® breakfast drink (Abbott Laboratories: 220 calories, 32 g of total carbohydrate) at approximately 9:00 AM and will record the time of the meal.
- Blood sample for PPG (glucose only) will be collected 2 hours ± 5 minutes after the subject consumes the Ensure breakfast drink for the 2-hour postprandial glucose assessment.

- Subjects will be randomized to a treatment (once daily dosing of FDC, EZE, or PBO IMP).
- Double-blind IMP will be dispensed and subject will be provided with dosing and storage instructions.
- Subjects will take their first dose of IMP, with approximately 8 ounces of water, following collection of the 2-hour PPG blood glucose sample collection.
- Conduct diet and exercise counseling.

11.7.2. Treatment Period Visit 2 (Visit T2/Day 28 ± 3)

Subjects will be scheduled for their second Treatment Period Visit approximately 27 days after completion of Visit T1/Day 1. Subjects will arrive at the study site after a minimum 10-hour fast, having not yet taken the daily dose of IMP.

Procedures and evaluations will be performed in the following order during this visit:

- Return of IMP; assessment and recording of IMP dosing adherence.
- Concomitant and prohibited medications will be reviewed and recorded as needed.
- Adverse events will be assessed.
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded.
- Blood and urine specimens will be obtained for the following:
  - basic fasting lipid panel;
  - special lipids and other biomarkers;
  - clinical safety laboratories (hematology, clinical chemistry, and urinalysis).
- Subject will be given 1 serving of Ensure Original Vanilla breakfast drink (Abbott Laboratories: 220 calories, 32 g of total carbohydrate) at approximately 9:00 AM and will record the time of the meal.
- Blood sample for PPG (glucose only) will be collected 2 hours ± 5 minutes after the subject consumes the Ensure breakfast drink for the 2-hour postprandial glucose assessment.
- Double-blind IMP dispensed.
- Subjects will take their daily dose of IMP, with approximately 8 ounces of water, following collection of the 2-hour PPG blood glucose sample collection.
- Conduct diet and exercise counseling.

11.7.3. Treatment Visit 3 (Visit T3/EOS/Day 85 ± 3)

Subjects will be scheduled for their final Treatment Period Visit approximately 84 days after completion of Visit S1/Day 1. Subjects will arrive at the study site after a minimum 10-hour fast, having taken the final dose of IMP approximately 24-hours earlier on the previous day.

Procedures and evaluations will be performed in the following order during this visit:

- Return of IMP; assessment and recording of IMP dosing adherence.
- Concomitant and prohibited medications will be reviewed and recorded as needed.
- Adverse events will be assessed.
- Weight (in kilograms) will be recorded.
- PE.
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded.
- Blood and urine specimens will be obtained for the following:
  - urine pregnancy test (for women of childbearing potential);
  - basic fasting lipid panel;
  - special lipids and other biomarkers;
  - clinical safety laboratories (hematology, clinical chemistry, and urinalysis)
  - reserve sample for potential exploratory biomarkers.
- Subject will be given 1 serving of Ensure Original Vanilla breakfast drink (Abbott Laboratories: 220 calories, 32 g of total carbohydrate) at approximately 9:00 AM and will record the time of the meal.
- Sample for PPG blood glucose will be collected 2 hours ± 5 minutes after the subject consumes the Ensure breakfast drink for the 2-hour postprandial glucose assessment.
- Subjects will be notified they may begin taking any LMT medications washed out during study participation at the conclusion of the visit.
- Complete study status in IWRS (ie, early withdrawal or completed study).

11.8. Subject Withdrawal Criteria

11.8.1. Early Withdrawal from Study

Subjects must remain in the study through Week 12 (Visit T3/Day 85 ± 3) to be considered as having completed the study. Subjects who prematurely withdraw from the study will be asked to continue to be followed for safety, as outlined in Appendix 1.

Participation in the study is voluntary. Subjects may refuse or withdraw from participation in this study at any time and for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

The investigator has the right and duty to interrupt the treatment of any subject whose health or well-being may be threatened by continued participation in this study. Such subjects should be withdrawn from the study and should not be continued under a modified regimen.

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

- Adverse event;
- Subject withdrawal of consent;
- Failure to comply with the protocol;
- Refusal to take IMP as indicated by the protocol;
- Illness, condition, or procedural complication that affects the subject's ability to participate in the study or that requires prohibited medication;
- Sponsor or investigator terminates the study;
- In the investigator's judgment, it is in the subject's best interest to discontinue participation in the study;
- Other (specify).

If a subject is lost to follow-up, study site personnel must make reasonable efforts to contact the subject to determine the reason for discontinuation/withdrawal. The measures that are taken to follow-up must be documented.

11.8.2. Procedures for Early Withdrawal

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

All effort should be made to have each subject complete all study visits on schedule according to the protocol. Accommodations for early or late visits in special circumstances will be considered by the Sponsor to prevent early withdrawal. Written notice (regardless of cause) is to be provided within 48 hours of the withdrawal to the Sponsor personnel or the Medical Monitor. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed. Except in the case of a medical emergency, the procedures and assessments detailed in Appendix 1 for Visit T3/EOS will be performed upon the discontinuation of the study.

12. ASSESSMENT OF PHARMACODYNAMICS

12.1. Pharmacodynamic Assessments

12.1.1. Sample Collection, Storage, and Shipping

Blood samples for Basic fasting lipids (LDL-C, non-HDL-C, TC, TG, and HDL-C), and Special lipids and biomarkers (apoB, hs-CRP, glucose, [redacted] and HbA_{1C}) will be drawn with the subject in the seated position according the schedule of events described in Appendix 1. All samples will be collected following a 10-hour fast with the exception of sample collected for the 2-hour postprandial glucose assessment as described in Section 12.1.3. Laboratory samples will be collected by appropriate clinical site personnel and then shipped according to the instructions in the laboratory manual (provided by the central laboratory). Reserve samples (serum and plasma) will be stored frozen for potential future measurement of additional BA safety and efficacy biomarkers.

12.1.2. Sample Collection, Storage, and Shipping

Blood samples for Basic fasting lipids, and Special lipids and biomarkers will be drawn with the subject in the seated position. All samples will be collected following a 10-hour fast with the exception of sample collected for the 2-hour postprandial glucose assessment as described in Section 12.1.2. Laboratory samples will be collected by appropriate clinical site personnel and then shipped according to the instructions in the laboratory manual (provided by the central laboratory).

12.1.3. Two-hour Postprandial Glucose (PPG) Assessment

At Visits T1, T2, and T3 following procedures described in Section 11.7; subjects will consume 1 serving of Ensure Original Vanilla breakfast drink (Abbott Laboratories: 220 calories, 32 g of total carbohydrate) at approximately 9:00 AM and site staff will record the time of the start and completion of the meal. The entire serving should be consumed within 5 minutes. A PPG blood glucose sample will be collected 2 hours ± 5 minutes after the subject begins to consume the Ensure breakfast drink and processed for plasma per the laboratory manual. The sample will be assessed by the central laboratory for glucose.

12.1.4. HOMA-IR and [redacted]

HOMA-IR and [redacted] will be calculated from fasting glucose and insulin levels determined at Visit T1 (baseline), Visit T2, and Visit T3/EOS using the following formulas described by Matthews et al.[15]

HOMA-IR = fasting glucose x fasting insulin / 22.5

[redacted]

12.1.5. Exploratory Biomarker Measurement

Additional exploratory safety, efficacy, or potential biomarkers may be assayed from serum and plasma blood samples collected at Visits T1 and T3 and stored frozen, reserved for potential future measurement of potential biomarkers.

12.1.6. Clinical Laboratory Parameters (Basic Fasting Lipids, Special Lipids and Other Biomarkers)

Blood specimens for basic fasting lipids, special lipids, and other biomarker laboratory assessments will be collected as shown in Table 2.

Table 2: Clinical Laboratory Parameters (Basic Fasting Lipids, Special Lipids and Other Biomarkers)

Clinical Laboratory Test	Clinical Laboratory Test
Basic Fasting Lipid Parameters • Calculated low-density lipoprotein cholesterol (LDL-C) • Non-high-density lipoprotein cholesterol (non-HDL-C) • Total cholesterol (TC) • Triglycerides (TG) • High-density lipoprotein cholesterol (HDL-C) Additional Samples • Reserve blood samples for potential future measurement of biomarkers	Special Lipids and Other Biomarkers • High-sensitivity C-reactive protein (hs-CRP) • Apolipoprotein B (apoB) • Glucose • [redacted] • Hemoglobin A_{1C} (HbA_{1C})

13. ASSESSMENT OF SAFETY

13.1. Demographics and Medical History

Demographic data and a medical history will be obtained from the subject at Visit S1/Day -42. Conditions that are relevant and/or clinically significant should be captured with at least a start date and an indication of whether the condition is ongoing or resolved. All surgeries, regardless of date, should be reported.

13.2. Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse rate will be recorded according to the schedule of events (Appendix 1). Measurements should be taken after subject has been seated quietly for at least 5 minutes in a chair with the back supported, the feet flat on the ground, and the arms bared and supported at heart level.

Blood pressure will be obtained using a calibrated, fully automated machine with a cuff that is appropriate to the size of the upper right arm. If a fully automated machine is not available, blood pressure may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study.

13.3. Weight, Height, and Body Mass Index

Height will be measured in centimeters (cm) at Visit S1 only. Weight will be measured in kilograms (kg) on a calibrated scale in the morning while fasting, in street clothing, and after voiding at Visit S1, T1, and T3/EOS.

Body mass index will be calculated as the weight in kilograms divided by the height in square meters (kg/m^2).

13.4. Physical Examination

A complete PE will be performed according to the schedule of events (Appendix 1) or at early termination from the study. A complete PE includes an assessment of the following:

- general appearance;
- skin;
- eyes, ears, nose, and throat (EENT);
- head/neck;
- extremities;
- musculoskeletal examination;
- respiratory examination;
- cardiovascular assessment, including rhythm and presence of cardiac abnormalities;

- abdominal examination;
- neurologic examination to record the presence of abnormalities in mental status, motor, and sensory function; and
- any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences.

Documentation of the PE will be included in the source documentation at the study site. Changes from baseline (Visit T1/Day 1) in PE findings that meet the definition of an AE will be recorded on the appropriate eCRF.

13.5. 12-Lead Electrocardiograms

A single 12-lead ECG will be obtained during screening at Visit S2. Additional 12-lead ECGs may be obtained at other times if clinically indicated. The ECG should be obtained after the subject has rested quietly in the supine position for at least 10 minutes.

13.6. Clinical Laboratory Tests

13.6.1. Clinical Safety Laboratory Parameters

Blood and urine specimens for safety laboratory assessments will be collected as shown in Table 3.

Table 3: Clinical Safety Laboratory Evaluations

Clinical Laboratory Test	**Clinical Laboratory Test**
Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %)	Blood Chemistry (serum, fasting) • Albumin (Alb) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT]) • Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT]) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total bilirubin (TB)[a] • Total protein • Uric acid
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen	
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC	Coagulation (Visit S1 for all subjects, Visit T1 and 3-7 days after Visit T1 in subjects receiving anticoagulation therapy only) • Prothrombin time (PT) • International normalized ratio (INR)

Table 3: Clinical Safety Laboratory Evaluations

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

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

Subjects will be instructed to fast for a minimum of 10 hours before each blood draw; only water will be permitted during the fasting period. If the subject has not fasted for a minimum of 10 hours before the study visit, the blood sample will not be drawn at that visit. The reason for any missing blood samples will be documented.

When vital signs and blood samples for safety laboratories are to be collected at the same time, measurement of vital signs should precede collection of blood samples.

13.6.2. Sample Collection, Storage, and Shipping

Blood samples will be drawn with the subject in the seated position. Laboratory samples will be collected by appropriate clinical site personnel and then shipped according to the instructions in the laboratory manual (provided by the central laboratory).

13.6.3. General Monitoring and Management of Abnormal Clinical Laboratory Values

The investigator will review the results of all laboratory tests as they become available and will sign and date the report to document their review. The investigator will ascertain if any laboratory value is abnormal or represents a clinically significant change from baseline for the individual subject, with baseline defined as the last value or observation before the first dose of IMP. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

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

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

- an action is taken with the imp because of the abnormality;
- intervention for management of the abnormality is required; or
- the abnormality be deemed clinically significant by the investigator.

13.6.3.1. Monitoring and Management of Elevated Liver Function Tests

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

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

- If the repeat LFT assessment confirms that the value for serum ALT and/or AST is >3 × ULN, consideration should be given to withdrawing the subject and administering no further doses of IMP. At the investigator's discretion, IMP may be interrupted and the subject may be rechallenged with the IMP after values for the LFTs have returned to baseline levels.
- If repeat LFT assessment confirms a value for serum ALT and/or AST >5 × ULN, the subject will be withdrawn from IMP treatment but will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1 or more frequently as determined by the investigator).
- If repeat LFT assessment confirms that the value for serum ALT and/or AST level is >3 × ULN and the subject has any of the following findings, the subject will be withdrawn from IMP treatment but will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1 or more frequently as determined by the investigator):
  - TB value >2 × ULN;

    Note: In the case of subjects with Gilbert's disease, TB will be fractionated and the determination of 2 × ULN will be based upon direct (conjugated) bilirubin.
  - INR value >1.5 × ULN (unless the subject is on a stable dose of anticoagulation medication);

- appearance or worsening of right upper abdominal discomfort, anorexia, fatigue, nausea, vomiting, fever, rash, or eosinophilia.

13.6.3.2. Monitoring and Management of Elevated Serum Creatinine Levels

If a subject experiences a decrease in eGFR to the level of 15 mL/min/1.73 m^2 or experiences acute renal failure, the subject will be withdrawn from IMP treatment but will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1).

13.6.3.3. Monitoring and Management of Changes in Hemoglobin Levels

If a subject experiences a decrease of >2.0 g/dL (20 g/L) from baseline in Hgb at any time after randomization, the subject will undergo a repeat confirmatory hematology testing as soon as is reasonably possible but preferably within 3 to 7 days after the laboratory test result becomes available.

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

- If a repeat assessment confirms a decrease >2.0 g/dL (20 g/L) from baseline in Hgb concentration, the subject should be monitored carefully during the study and return at 2-week intervals after study completion for additional Hgb measurements until the Hgb concentration returns to baseline or reaches a stable level.
- If a repeat assessment confirms a value <8 g/dL (80 g/L) for Hgb, the subject will be withdrawn from IMP treatment. The subject will return at 1-week intervals after withdrawal of IMP treatment for additional Hgb measurements until Hgb concentration returns to baseline or reaches a satisfactory conclusion.
- Subjects who are withdrawn from IMP treatment due to decreases in Hgb concentration will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1).

The investigator may choose to consult with a specialist at any time to further evaluate the cause of the alteration in hemoglobin.

13.6.3.4. Monitoring and Management of Elevated Creatine Kinase Levels

If a subject has a value >5 × ULN for serum CK at any time after randomization, the subject will undergo a repeat confirmatory assessment as soon as is reasonably possible but preferably within 3 to 7 days after the laboratory result is available. This assessment will include questioning for related symptoms.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality (value >5 × ULN), the subject should, if asymptomatic, receive further assessment and investigation into the cause. The presence of renal injury should be assessed, and serum CK levels should be measured approximately weekly or more frequently, if clinically indicated, until resolution. If serum CK levels continue to rise, treatment with the IMP should be discontinued.
- If symptomatic, the following steps should be completed:
  - Hold dosing with the IMP;
  - Clarify the nature, duration, and intensity of muscle symptoms;
  - Review possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology);
  - Evaluate for additional diagnoses or other conditions, which can cause myopathy, including muscle tenderness (by PE), weakness, rash, measurement of serum creatinine level, and dipstick urinalysis with microscopy, if indicated;
  - Obtain clinical chemistries to assess the possibility of lactic acidosis; and
  - Follow symptoms and serum CK levels until the abnormality has resolved.

    If, based on the above evaluation, an alternative explanation is suspected, consider resuming IMP once the serum CK level returns to baseline levels. If no alternative explanation exists, consider withdrawing the subject from IMP treatment.
- If the repeat assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality (serum CK value >10 × ULN) even in the absence of symptoms, the subject should be withdrawn from the study and given no further doses of IMP. In all cases, signs/symptoms and laboratory evaluations, as outlined in the bulleted point above, should be evaluated.
- If the subject is withdrawn from IMP treatment, the subject should be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1).

13.6.3.5. Monitoring and Management of Potential Hypoglycemia and Metabolic Acidosis

Subjects will be educated on the signs and symptoms of hypoglycemia and will be instructed to report any signs and symptoms of hypoglycemia to the investigator.

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

Clinical laboratories will be assessed to determine any signs of anion gap metabolic acidosis. If laboratory test results are consistent with metabolic acidosis, the subject will be immediately contacted for further medical evaluation of the acidosis, and the event will be captured as an AE.

13.6.4. Total Blood Volume

The total number of venipunctures and total volume of blood collected during the study will be limited to that needed for safety assessments. The total whole blood volume collected during the study will not exceed approximately 300 mL for each subject.

13.7. Adverse and Serious Adverse Events

13.7.1. Adverse Events

13.7.1.1. Definition of Adverse Events

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

An AE can be:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- any new disease or exacerbation of an existing disease;
- any deterioration in nonprotocol-required measurements of laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from IMP; or
- an adverse drug reaction (ADR; see Section 13.7.1.2).

Treatment-emergent AEs are defined as AEs that begin or worsen after the first dose of IMP.

13.7.1.2. 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 (ie, the relationship cannot be ruled out).

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

13.7.1.3. Reporting of Adverse Events

All AEs that occur from the time the ICF is signed through 30 days after the last study visit should be recorded on the eCRF. Any SAE that occurs from the time the ICF is signed through 30 days after the last study visit should be reported to the sponsor per Section 13.7.2.4.

Subjects should be instructed to report any AE that they experience from the time the ICF is signed through 30 days after the last dose of IMP to the investigator. Investigators should make an assessment for AEs at each visit and record the event on the appropriate eCRF.

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

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

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

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

- description of the event (eg, headache);
- date of onset;
- date of resolution (or that the event is continuing);
- action taken because of the event;
- seriousness of the event;
- severity of the event;
- outcome of the event; and

- investigator's assessment of relationship to IMP.

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

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

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.

13.7.1.4. 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 subject's daily activities.
- Moderate: Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe: Events interrupt the subject'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.

13.7.1.5. Relationship

It is the investigator's responsibility to assess the relationship of the AE to both the IMP and EZE. The degree of "relatedness" of the AE to the IMP and EZE should be described using the following scale:

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

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

13.7.1.6. Monitoring and Follow-up of Adverse Events

Subjects 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 subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject 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 subject is lost to follow-up or dies.

Subjects 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.

13.7.1.7. Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as AEs that begin or worsen after the first dose of IMP.

13.7.2. Serious Adverse Events

13.7.2.1. Definition of Serious Adverse Event

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

- results in death;
- is life threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions;
- is a congenital anomaly/birth defect; or
- is an important medical event.

Note: Hospitalization is defined as a formal inpatient admission. This will not include admissions under "23-hour Observational Status," an emergency room visit without hospital admission, or an urgent care visit and therefore such events will not be recorded as an SAE under this criterion, nor will hospitalization for an elective or outpatient procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective or outpatient surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational

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

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

Any clinical endpoints that meet SAE criteria will be also reported as SAEs.

13.7.2.2. Definition of Adverse Events or Outcomes Not Qualifying as Serious Adverse Events

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

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

13.7.2.3. 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 local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment. Laboratory abnormalities should be reported as an AE if they meet any of the following criteria:

- Intervention is required to treat the abnormality.
- Modification of study treatment is required due to the abnormality.
- Based on the investigator's medical judgement.

13.7.2.4. Reporting Serious Adverse Events

All SAEs, regardless of relationship to IMP, occurring from the time of informed consent until 30 days following the last dose of IMP (for most subjects 30 days after Visit T3, must be reported by the principal investigator or designee to the authorized safety designee within 24 hours of the principal investigator or the clinical site becoming aware of the occurrence. All SAEs that the investigator considers related to IMP that occur after the 30-day follow-up of the study period must be reported to the sponsor.

To report the SAE, complete the provided SAE form and submit it to the safety designee within 24 hours of becoming aware of the occurrence.

The investigator is required to submit SAE reports to the IRB in accordance with local requirements. All investigators involved in studies using the same investigational product will

receive any safety alert notifications for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

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

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

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to the safety designee.

13.7.2.5. 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 IMP will be notified by the sponsor (or designee) of SUSARs. SUSARS must be communicated as soon as possible to the appropriate IRB by the investigator, as applicable and/or reported in accordance with local laws and regulations. Investigators should provide written documentation of IRB notification for each report to the sponsor.

Serious AEs that are anticipated to occur in this subject population will be collected and reported by the investigator as described in Section 13.7.2.4 . However, these events will not be submitted to the regulatory authorities as expedited reports unless they meet SUSAR criteria. The events that are considered exempt from expedited reporting include the following clinical endpoints:

- cardiovascular death;
- nonfatal myocardial infarction;
- nonfatal stroke;
- unstable angina requiring hospitalization;
- coronary revascularization;
- heart failure requiring hospitalization; and
- noncoronary arterial revascularization.

13.7.2.6. Reporting of Subject Death

The death of any subject 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 above.

13.7.2.7. Reports of Pregnancy

Although not considered an SAE (unless the event occurs with a serious outcome), pregnancy information on female subjects will be collected by the authorized safety designee. If a female

subject becomes pregnant during the study, study treatment should be discontinued immediately. The principal investigator or designee must complete and submit the Pregnancy Report Form within 24 hours of awareness of the pregnancy. In addition, subjects who become pregnant will complete the EOS evaluations according to the schedule in Appendix 1. Whenever possible, pregnancies should be followed until outcome and the Pregnancy Outcome Reporting Form submitted to the safety designee once the outcome is known.

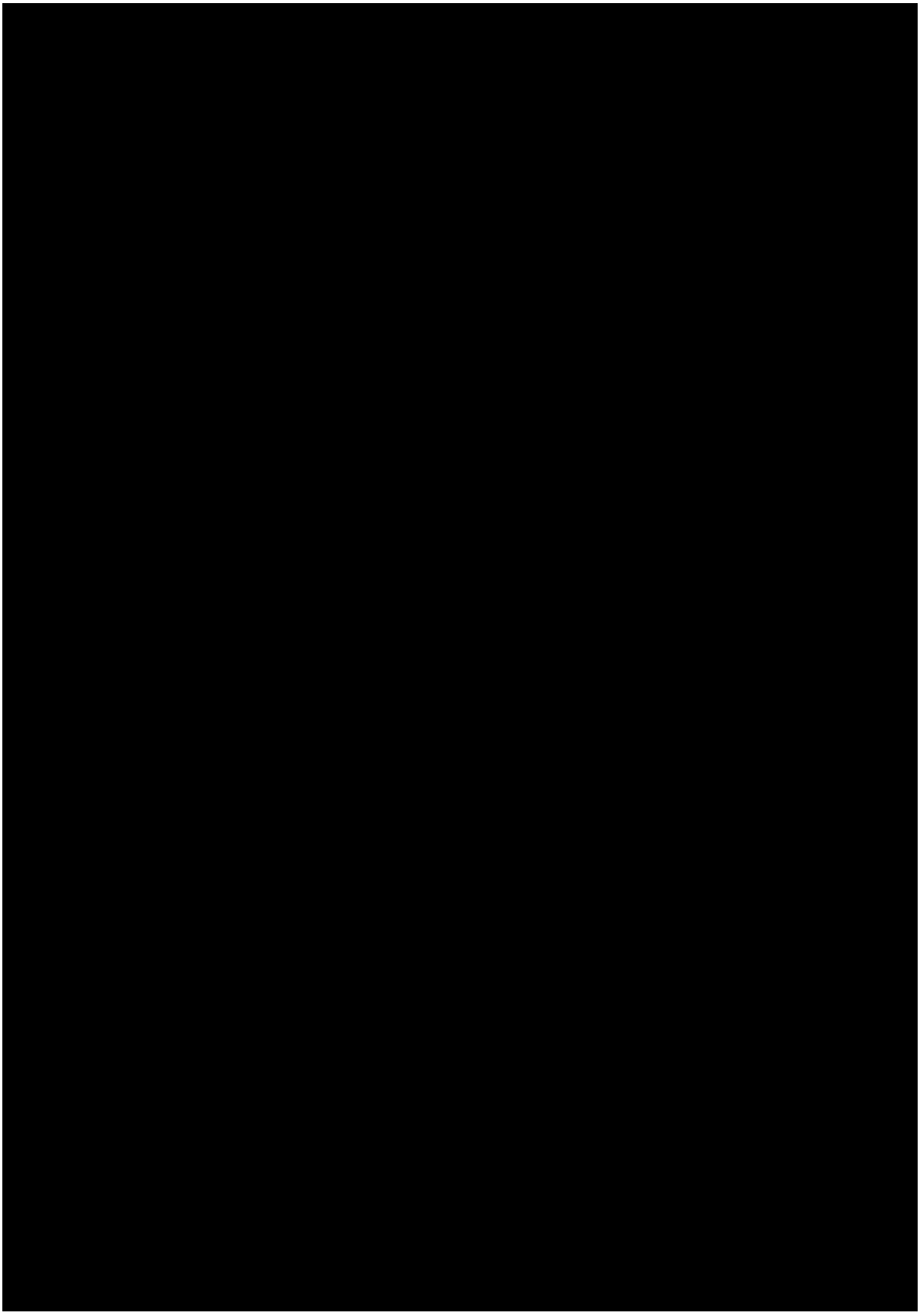
13.7.3. Adverse Events of Special Interest

[redacted]

The protocol procedures that are included in clinical studies of BA are part of standard clinical care for subjects with elevated LDL-C levels and, in addition, address the potential and theoretic risks of BA.

All BA studies will include standard pharmacovigilance including evaluation of AEs, PE findings, vital signs, and laboratory assessments. [redacted]

[redacted]



14. STATISTICS

14.1. General Considerations

The analyses described in this section will be performed as further outlined in the Statistical Analysis Plan, which will be finalized before the end of the study. The analyses specified in the Statistical Analysis Plan will supersede those specified in the protocol in the event of any differences between the two documents. A copy of the Statistical Analysis Plan will be included as an appendix in the clinical study report for this protocol.

14.2. Determination of Sample Size

The sample size of approximately 56 subjects per treatment arm (1:1:1) in this study (168 subjects 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.

14.3. Analysis Populations

The following analysis populations will be defined:

- The full analysis set (FAS) will be used for the pharmacodynamic analyses and will include all randomized subjects who receive at least 1 dose of study drug and have a baseline and at least 1 measurable postbaseline lipid value, and having taken their study drug within 2 days of the lipid measurement. Subjects in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received.
- Treatment Completer analysis set is a subset of full analysis set and will include subjects who complete 12-week treatment as indicated on the end of treatment CRF and have non-missing LDL-C value at Week 12
- The safety population (SP) will include all subjects who receive at least 1 dose of IMP. Subjects in the SP will be included in the treatment group that they actually received, regardless of their randomized treatment.

14.4. Disposition, Demographic, and Baseline Characteristics

Disposition, including reason for withdrawal from the study, will be summarized by treatment group. Demographic and other baseline characteristics will be summarized by treatment group

using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) for continuous variables and counts and percentages for categorical variables.

14.5. Study Endpoints

The primary objectives of this study are demonstrated by 2 co-primary endpoints:

- Percent change in LDL-C from baseline at Week 12 in FDC-treated arm compared to PBO-treated arm;
- Percent change in LDL-C from baseline at Week 12 in FDC-treated arm compared to EZE-treated arm.

The study is considered to have successfully demonstrated its primary objective if both co-primary endpoints achieve statistical significance.

Secondary Endpoints

- Percent change from baseline at Week 12 in parameters below between the FDC treated arm and EZE treated arm and PBO treated arm:
  - hs-CRP;
  - Non-HDL-C;
  - TC;
  - apoB;
  - TG;
  - HDL-C;
- Proportion of subjects attaining LDL-C <70 mg/dL at Week 12 in FDC-treated arm and EZE-treated arm and PBO-treated arm;
- Proportion of subjects achieving LDL-C reductions ≥50% from baseline at Week 12 in FDC-treated arm and EZE-treated arm and PBO-treated arm.

Safety Endpoints

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

Exploratory Assessments

- Percent change from baseline at [redacted] Week 12 in parameters below between the FDC-treated arm and EZE-treated arm and PBO-treated arm:
  - HbA_{1C};
  - Plasma glucose (fasting and 2-hour post-prandial);

[redacted]

[redacted]

– HOMA-IR index;

[redacted]

14.6. Pharmacodynamic Analyses

Descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) will be used to summarize LDL-C, TC, HDL-C, non-HDL-C, TGs, apoB, hs-CRP, glucose, [redacted] HbA_{1C}, HOMA-IR, [redacted], and 2-hour PPG levels at each assessment by treatment group and to summarize the change from baseline and the percent change from baseline by treatment group at each postbaseline assessment.

The primary and secondary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline value as a covariate. The ANCOVA will be performed using the FAS, with subjects included in their randomized treatment group regardless of the treatment they actually received. Subjects who are missing their Week 12 LDL-C will have their Week 12 value imputed by last postbaseline observation carried forward (LOCF). The least squares mean (LSM) and standard error (SE) for percent change estimate will be provided for both treatment groups, along with the PBO-corrected LSM, its 95% confidence interval (CI) and associated p-value. We will analyze observed data and LOCF data separately.

The same analysis will be performed as sensitivity analysis on treatment completer set for primary and secondary efficacy endpoints.

14.7. Exploratory Analyses

For exploratory endpoints (change from baseline to Week 4 and Week 12 in HbA_{1C}, fasting glucose, [redacted] HOMA-IR index, [redacted] and 2-hour PPG), the data will be analyzed in the similar fashion as for the primary endpoints. For fasting plasma glucose, [redacted] baseline is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1); while baseline for HbA_{1C}, 2-hour PPG and [redacted] is the predose Day 1/Week 0 (Visit T1) value.

14.8. Safety Analyses

Treatment-emergent AEs will be coded using MedDRA and will be categorized by System Organ Class and Preferred Term. The subject incidence of all TEAE, SAEs, related AEs, AEs leading to withdrawal of study drug and/or study, fatal AEs, and AESI will be tabulated by system organ class (SOC) and preferred term in descending order of frequency and by treatment group.

Descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) will be used to summarize actual values and change-from-baseline values for clinical laboratories and vital signs at each postbaseline assessment by cohort. All values will be evaluated for clinically notable results. Data for additional safety parameters (eg, PE findings) will be listed by subject.

The AESI will be summarized as below.

Hepatic Safety

For liver-associated enzymes and TB, the number and percent of subjects with abnormal values for ALT, AST, and TB will be summarized. All liver-associated laboratory abnormalities will be assessed for Hy's Law criteria (>3 × ULN for either ALT or AST, with accompanying TB >2 × ULN in the absence of other known causes) will also be applied to the data; any potential Hy's law cases will be listed separately.

Musculoskeletal Safety

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

Hyperglycemia/Hypoglycemia/

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

Renal Safety

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

Neurocognitive Events

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

Metabolic Acidosis

Metabolic Acidosis events will be monitored by clinical safety laboratory chemistries.

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 Good Clinical Practice (GCP) guidelines, national regulatory requirements, and the current Declaration of Helsinki throughout its duration by means of personal visits to the investigator's facilities and other communications.

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

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA 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, eCRFs, medical records and source documents, drug disposition records, ICFs, etc), as well as discussion on the conduct of the study with the investigator and staff. These documents should be redacted by the site in accordance with local law.

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

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

15.2. Audits and Inspections

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

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

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 (see also Section 15.1).

17. ETHICS

17.1. Institutional Review Board/Independent Ethics Committee Approval

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

Institutional review boards must be constituted according to the applicable laws. It is the responsibility of each investigational site to submit the protocol, Investigator's Brochure, subject ICF for the study, subject recruitment materials (if applicable), and other documentation as required to its IRB for review and approval. A copy of the written approval must be provided to the sponsor.

The documentation should clearly mention the approval/favorable opinion of the protocol, the subject ICF, and subject 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 IRB and provided to the sponsor before the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

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

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

The investigator must promptly inform the IRB of all SAEs or other safety information reported from the subject or sponsor.

17.2. Ethical Conduct of the Study

The investigator agrees, when signing the protocol, to conduct the study in accordance with ethical principles (21 CFR Parts 11, 50, 54, 56, 312, 314, and 320) that have their origin in the current revision of the Declaration of Helsinki and that are consistent with GCPs, applicable regulatory requirements, and policies and procedures as outlined by the ethical requirements for IRB review and ICFs.

The investigator agrees to allow monitoring and auditing of all essential clinical study documents by the sponsor or its authorized representatives and inspection by the FDA. Monitoring and auditing visits by the sponsor or authorized designee will be scheduled with the appropriate staff at mutually agreeable times periodically throughout the study.

The investigator will ensure proper implementation and conduct of the study, including those study-related duties delegated to other appropriately qualified individuals. The investigator will ensure that the study staff cooperates with monitoring and audits and will demonstrate due diligence in recruiting and screening study subjects. The investigator must sign the "Investigator Signature" page (Appendix 3) and return it and a copy of a current curriculum vitae to the sponsor. For this study and all studies conducted under an investigational new drug application (IND), the investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to the sponsor (or designee).

17.3. Written Informed Consent

The investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Subjects must also clearly understand that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures on the sponsor-approved ICF.

The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject in accordance with the IRB reporting guidelines.

17.4. Subject Confidentiality

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

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

18. DATA HANDLING AND RECORD KEEPING

18.1. Inspection of Records

Applicable regulations require the sponsor (or 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 subjects in this study. These regulations also allow the sponsor records to be inspected by authorized representatives of the regulatory agencies. The investigator will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

18.2. Retention of Records

In compliance with the ICH/GCP guidelines, the investigator/institution agrees to retain and maintain all study records that support the data collected from each subject, 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 subject ICFs, 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. Electronic 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 subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

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

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

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

Data reflecting the subject's participation with the IMP under investigation are to be reported to the sponsor. The data is to be recorded on the eCRFs and/or other media provided or approved by the sponsor.

A completed eCRF must be submitted for each subject who receives IMP, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject 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 (N/A) not available or (N/D) not done; do not leave a space blank.

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

It is essential that all dates appearing on the sponsor's subject 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 signed or countersigned by the investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed within a timely manner, according to the eCRF completion guidelines, following the evaluation.

19. ADMINISTRATIVE CONSIDERATIONS

19.1. Investigators

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

- Agree to conduct the study in accordance with the relevant current protocol;
- Agree to personally conduct or supervise the described investigation(s);
- Agree to inform any subjects, or persons used as controls, that the investigational medicinal products are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met;
- Agree to report adverse experiences that occur during the investigation;
- Read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the investigational medicinal product;
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments;
- Maintain adequate and accurate records and make those records available for inspection;
- Ensure that an appropriate IRB will be responsible for the initial and continuing review and approval of the clinical investigation;
- Agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others;
- Agree not to make changes in the research without IRB approval, except where necessary to eliminate apparent hazards to subjects;
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements.

Refer also to:

- FDA Regulations Related to GCP and Clinical Trials: http://www.fda.gov/oc/gcp/regulations.html
- Guidance and Information Sheets on GCP in FDA-Regulated Clinical Trials: http://www.fda.gov/oc/gcp/guidance.html
- Guidance for IRBs and Clinical Investigators: http://www.fda.gov/oc/ohrt/irbs/default.htm
- Guidance for Industry – E Good Clinical Practice: Consolidated Guidance: http://www.fda.gov/cder/guidance/959fnl.pdf

19.2. Study Administrative Structure

Medical and Safety Monitoring: [redacted]
Cell phone: [redacted]
Email: [redacted]

Central Laboratory: Details are provided in the laboratory manual

Bioanalytical Laboratory: [redacted]

IMP Supply Chain Details are provided in the pharmacy manual

eCRF and Database: Details are provided in the CRF Completion Guidelines

19.3. Amendments

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

In situations in which 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, to other government agencies, or in connection with intellectual property filings or publications. 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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22. APPENDICES

Appendix 1 Schedule of Assessments

Appendix 2 Sponsor Signature

Appendix 3 Investigator Signature

Appendix 4 Summary of Changes Amendment 1

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Period:	**Screening and Run-in**			**Treatment**		
Study Visit:	**S1**	**S2**	**S3**	**T1**	**T2**	**T3/EOS[a]**
Study Week:	**-6**	**-5**	**-1**	**1**	**4**	**12**
Procedure Study Day:	**-42 ± 7**	**-35 ± 3**	**-7 ± 3**	**1**	**28 ± 3**	**85 ± 3**
Informed consent	X					
Inclusion/Exclusion criteria[b]	X	X	X	X		
Demographics	X					
Medical history	X					
Prior and/or Concomitant medications	X	X	X	X	X	X
Adverse event recording		X	X	X	X	X
Physical examination	X					X
Weight/BMI [c]	X		X	X		X
Height	X					
12-Lead ECG[d]		X				
Vital signs[e]	X	X	X	X	X	X
Serum pregnancy test/FSH[f]	X					
Urine pregnancy test[h]				X		X
Basic fasting lipid panel[g]	X		X	X	X	X
Special lipids and other biomarkers[h]	X			X	X	X
Coagulation panel[i]	X					
TSH	X					
Serology[j]		X				
Clinical safety laboratories[k]	X		X	X	X	X
Urine drug screen	X			X		

Study Period:	**Screening and Run-in**			**Treatment**		
Study Visit:	**S1**	**S2**	**S3**	**T1**	**T2**	**T3/EOS[a]**
Study Week:	**-6**	**-5**	**-1**	**1**	**4**	**12**
Procedure **Study Day:**	**-42 ± 7**	**-35 ± 3**	**-7 ± 3**	**1**	**28 ± 3**	**85 ± 3**
Reserve Sample for Potential Exploratory Biomarkers[l]				X		X
Calculate eGFR	X					
Washout LMT		X	X	X	X	X
Randomization				X		
Ensure breakfast drink[m]				X	X	X
PPG glucose sample[n]				X	X	X
Diet and exercise counseling	X	X	X	X	X	
Dispense single-blind IMP		X				
Return single-blind IMP and assess dosing adherence			X	X		
Dispense double-blind IMP				X	X	
Return double-blind IMP and assess dosing adherence					X	X

ApoB = apoprotein B; BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HbsAg = hepatitis B surface antigen; HCV-AB = hepatitis C virus antibody; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; IMP = investigational medicinal product; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.

[a] All procedures will be completed at EOS or at time of early termination from the study. The last dose of IMP will be taken on the morning of Day 84 or the day prior to Visit T3/EOS. Visit T3/Day 85 represents 24 hours after the last dose of IMP.

[b] Subject must have a fasting calculated LDL-C level between 100 and 220 mg/dL after 5-week washout of all LDL-C-lowering drugs and nutritional supplements. If TG level is >400 mg/dL, a repeat assessment may be obtained; the repeat assessment will be used to determine study eligibility and screening will be extended by 1 week.

[c] Weight will be measured on a calibrated scale in the morning while fasting, in street clothing, and after voiding. BMI will be calculated using height from Visit S1 and measured weight at respective visits.

[d] A single 12-lead ECG will be obtained after the subject has rested quietly in the supine position for at least 10 minutes

[e] Systolic blood pressure, diastolic blood pressure, and pulse rate will be obtained after the subject has been seated quietly for at least 5 minutes in a chair with the back supported, the feet flat on the ground, and the arms bared and supported at heart level.

[f] Pregnancy tests will be obtained for women of childbearing potential and for surgically sterile women; FSH level will be obtained for women <55 years old and ≥1 year without menses.
[g] Basic fasting lipid panel includes calculated TC, calculated LDL-C, HDL-C, calculated non-HDL-C, and TGs.
[h] Special lipids and other biomarkers include apoB, hs-CRP, glucose, [redacted] and HbA_{1C}.
[i] Coagulation panel (see Table 3) will be performed only at Visit S1/Day -42 unless the subject is receiving an anticoagulant agent in which case the coagulation panel will be repeated at Visit T1/Day 1 and 3 to 7 days after starting the IMP.
[j] The serology assessment includes HbsAg and HCV-AB.
[k] Clinical safety laboratories include hematology, clinical chemistry, and urinalysis; the required assays are listed in Table 3.
[l] Reserve blood sample for potential future exploratory biomarkers will be collected at Visits T1 and T3; separated into K2-edta plasma and serum separator tubes; and processed plasma and serum samples will be stored frozen for potential future analysis.
[m] Subjects will consume 1 serving of Ensure Original Vanilla® breakfast drink (Abbott Laboratories: 220 calories, 32 g of total carbohydrate) at approximately 9:00 AM and site staff will record the time of the start and completion of the meal. The entire serving should be consumed within 5 minutes.
[n] PPG blood glucose sample will be collected 2 hours ± 5 minutes after the subject begins to consumes the Ensure breakfast drink

APPENDIX 2. SPONSOR 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 Ezetimibe and Placebo in Subjects With Type 2 Diabetes and Elevated LDL-Cholesterol

Study Number: 1002FDC-058

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

(e-signature on file)

[redacted]

Date

APPENDIX 3. INVESTIGATOR 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 Ezetimibe and Placebo in Subjects With Type 2 Diabetes and Elevated LDL-Cholesterol

Study Number: 1002FDC-058

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.

Name:
Title:
Affiliation:
Address:
Phone:
Fax:

Date

APPENDIX 4. SUMMARY OF CHANGES AMENDMENT 1

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002FDC-058
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 Ezetimibe and Placebo in Subjects with Type 2 Diabetes and Elevated LDL-C
Protocol Version Incorporating Current Summary of Changes:	Amendment 1: 14 March 2018
Preceding Protocol Version:	Original Protocol: 18 December 2017
Investigational Product Name:	Bempedoic Acid 180 mg + Ezetimibe 10 mg FDC

Conventions used in this Summary of Changes Document

- 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.
- All locations (i.e., section numbers and/or header text) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.
- The original text is from the preceding protocol version.
- In the "New Text", all substantive text added to the protocol is bolded and italicized.
- 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:

1. Added a line for Amendment 1 version and date to reflect amendment version details.
2. Revise page headers for Amendment 1 version and date to reflect amendment version details.
3. Revised text to indicate that IMP should be taken "in the morning" in the Synopsis and Section 7.1 for consistency across all sections of the protocol
4. Revised text to indicate subjects may take IMP "with or without food" rather than after a minimum 10-hour fast" in Sections 7.1 and 9.2.1 (Table 1) for consistency across all sections of the protocol.

5. Revised text to indicate container for IMP are "blister cards with child-resistant closures" rather than "HDPE container with screw-on, child-proof cap" in Section 9.2.1 (Table 1) and removed references to HDPE in Sections 4 and 9.2.1 (Table 1) to reflect final packaging of IMP.
6. Revised text to remove general order of scheduled assessments at study visits (unless otherwise specified); and to indicate scheduled assessments should be completed on subjects while fasted and prior to taking study medication in Section 11.5 for clarity on intended general visit guidelines.
7. Specified that FSH is for women "<55 years old and ≥1 year without menses" in Synopsis "Other Assessments" subsection, Section 11.6.1, Section 13.6.1 Table 3, and Appendix 1 footer superscript "f" for consistency across all sections of the protocol.
8. For study procedures and schedule of assessments, added "weight (in kilograms) will be recorded" for Visit T1 (Section 11.7.1) and Visit T3/EOS (Section 11.7.3) for consistency across all sections of the protocol.
9. Remove references to Pharmacokinetic (PK) samples in Sections 12.1.5, 12.1.6, and 13.6.4 since PK analyses are not planned for this study.
10. Correct requirement for repeat coagulation testing if subject is receiving an anticoagulant agent in Section 13.6.1 Table 3 for consistency across all sections of the protocol.
11. Correct reporting requirements for AEs to the period of the time the ICF is signed through 30 days after the last study visit in Section 13.7.1.3 for consistency across all sections of the protocol.

CHANGE 1: REVISION OF TITLE PAGE VERSION INFORMATION

Location:

Title Page: Version

Original Text:

Version	Date
Original Protocol	18 December 2017 (Final)

New Text:

Version	Date
Original Protocol	18 December 2017 (Final)
Amendment 1	***14 March 2018***

CHANGE 2: REVISION OF PAGE HEADER VERSION INFORMATION

Location:

Page headers, all pages

Original Text:

Bempedoic Acid 180 mg + Ezetimibe 10 mg
Fixed-Dose Combination — Esperion Therapeutics, Inc.
Clinical Study Protocol 1002FDC-058 — Original Protocol, Final, 18 December 2017

New Text:

Bempedoic Acid 180 mg + Ezetimibe 10 mg
Fixed-Dose Combination — Esperion Therapeutics, Inc.
Clinical Study Protocol 1002FDC-058 — ***Amendment 1, 14 March 2018***
~~Original Protocol, Final, 18 December 2017~~

CHANGE 3: INDICATE THAT IMP SHOULD BE TAKEN "IN THE MORNING"

Location:

Synopsis; Subsection Study Design

Original Text:

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast. Subjects who continue to meet the study inclusion/exclusion criteria will be randomized in a 1:1:1 ratio to receive either FDC (n = 56), EZE (n = 56), or PBO (n = 56) once daily for 12 weeks.

New Text:

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast. Subjects who continue to meet the study inclusion/exclusion criteria will be randomized in a 1:1:1 ratio to receive either FDC (n = 56), EZE (n = 56), or PBO (n = 56) once daily ***in the morning*** for 12 weeks.

Location:

Synopsis; Subsection IMP Dosage and Mode of Administration

Original Text:

Bempedoic acid 180 mg + EZE 10 mg FDC tablets, EZE 10 mg overencapsulated tablets, and FDC-matching PBO tablet, and EZE-matching PBO capsules will be supplied by Esperion Therapeutics. All IMP will be ingested once daily at a similar time with or without food.

New Text:

Bempedoic acid 180 mg + EZE 10 mg FDC tablets, EZE 10 mg overencapsulated tablets, and FDC-matching PBO tablet, and EZE-matching PBO capsules will be supplied by Esperion Therapeutics. All IMP will be ingested once daily at a similar time ***in the morning*** with or without food.

Location:

Section 7.1

Original Text:

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast…Subjects will be dispensed IMP at Visit T1/Day 1 and will be instructed to take the IMP at 24-hour intervals, with approximately 8 ounces of water, after a minimum 10 hour fast (only water allowed) and to continue fasting for 1 hour after ingesting the IMP.

New Text:

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast… Subjects will be dispensed IMP at Visit T1/Day 1 and will be instructed to take the IMP ***in the morning*** at 24-hour intervals, with approximately 8 ounces of water~~, after a minimum 10 hour fast (only water allowed) and to continue fasting for 1 hour after ingesting the IMP~~ ***with or without food.***

CHANGE 4: INDICATE SUBJECTS MAY TAKE IMP "WITH OR WITHOUT FOOD"

Location:

Section 7.1

Original Text:

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast…Subjects will be dispensed IMP at Visit T1/Day 1 and will be instructed to take the IMP at 24-hour intervals, with approximately 8 ounces of water, after a minimum 10 hour fast (only water allowed) and to continue fasting for 1 hour after ingesting the IMP.

New Text:

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast… Subjects will be dispensed IMP at Visit T1/Day 1 and will be instructed to take the IMP ***in the morning*** at 24-hour intervals, with approximately 8 ounces of water~~, after a minimum 10 hour fast (only water allowed) and to continue fasting for 1 hour after ingesting the IMP~~ ***with or without food.***

Location:

Section 9.2.1 (Table 1)

Original Text:

Parameter	**Bempedoic Acid + Ezetimibe FDC Tablet**	**Ezetimibe Overencapsulated Tablet**	**FDC-matched Placebo Tablet**	**Ezetimibe-matched Placebo Capsule**
Dosage form:	Film-coated tablet	Over-encapsulated tablets	Film-coated tablet	Capsules
Unit dose:	180 mg bempedoic acid + 10 mg ezetimibe	10 mg	Not applicable	Not applicable
Container:	HDPE container with screw-on, child proof cap	HDPE container with screw-on, child proof cap	HDPE container with screw-on, child proof cap	HDPE container with screw-on, child proof cap
Route of administration:	Oral with water after a minimum 10 hour fast	Oral with water after a minimum 10 hour fast	Oral with water after a minimum 10 hour fast	Oral with water after a minimum 10 hour fast
Physical description:	[redacted]			

New Text:

Parameter	**Bempedoic Acid + Ezetimibe FDC Tablet**	**Ezetimibe Overencapsulated Tablet**	**FDC-matched Placebo Tablet**	**Ezetimibe-matched Placebo Capsule**
Dosage form:	Film-coated tablet	Over-encapsulated tablets	Film-coated tablet	Capsules
Unit dose:	180 mg bempedoic acid + 10 mg ezetimibe	10 mg	Not applicable	Not applicable
Container:	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***
Route of administration:	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***

Parameter	Bempedoic Acid + Ezetimibe FDC Tablet	Ezetimibe Overencapsulated Tablet	FDC-matched Placebo Tablet	Ezetimibe-matched Placebo Capsule
Physical description:	[redacted]			

CHANGE 5: INDICATE CONTAINER FOR IMP ARE "BLISTER CARDS WITH CHILD-RESISTANT CLOSURES" AND REMOVE REFERENCES TO HDPE CONTAINERS

Location:

Section 4. List of Abbreviations and Definitions of Terms

Original Text:

HDL-C	high-density lipoprotein cholesterol
HDPE	high density polyethylene
Hgb	hemoglobin

New Text:

HDL-C	high-density lipoprotein cholesterol
~~HDPE~~	~~high density polyethylene~~
Hgb	hemoglobin

Location:

Section 9.2.1 (Table 1)

Original Text:

Parameter	Bempedoic Acid + Ezetimibe FDC Tablet	Ezetimibe Overencapsulated Tablet	FDC-matched Placebo Tablet	Ezetimibe-matched Placebo Capsule
Dosage form:	Film-coated tablet	Over-encapsulated tablets	Film-coated tablet	Capsules
Unit dose:	180 mg bempedoic acid + 10 mg ezetimibe	10 mg	Not applicable	Not applicable
Container:	HDPE container with screw-on, child proof cap	HDPE container with screw-on, child proof cap	HDPE container with screw-on, child proof cap	HDPE container with screw-on, child proof cap
Route of administration:	Oral with water after a minimum 10 hour fast	Oral with water after a minimum 10 hour fast	Oral with water after a minimum 10 hour fast	Oral with water after a minimum 10 hour fast
Physical description:	[redacted]			

FDC = fixed-dose combination; HDPE = high density polyethylene

New Text:

Parameter	Bempedoic Acid + Ezetimibe FDC Tablet	Ezetimibe Overencapsulated Tablet	FDC-matched Placebo Tablet	Ezetimibe-matched Placebo Capsule
Dosage form:	Film-coated tablet	Over-encapsulated tablets	Film-coated tablet	Capsules
Unit dose:	180 mg bempedoic acid + 10 mg ezetimibe	10 mg	Not applicable	Not applicable
Container:	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***	~~HDPE container with screw-on, child proof cap~~ ***Blister cards with child-resistant closures***

Parameter	**Bempedoic Acid + Ezetimibe FDC Tablet**	**Ezetimibe Overencapsulated Tablet**	**FDC-matched Placebo Tablet**	**Ezetimibe-matched Placebo Capsule**
Route of administration:	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***	Oral with water ~~after a minimum 10 hour fast~~ ***with or without food***
Physical description:	[redacted]			

FDC = fixed-dose combination~~; HDPE = high density polyethylene~~.

CHANGE 6: CLARIFICATION OF INTENDED GENERAL VISIT GUIDELINES

Location:

Section 11.5

Original Text:

When multiple procedures are scheduled for the same visit, the following order should be followed (unless otherwise specified):

New Text:

~~When multiple procedures are scheduled for the same visit, the following order should be followed~~ ***Subjects will arrive fasted and having not taken study medication prior to the visit. The following assessments will be conducted while fasted and prior to taking study medication*** (unless otherwise specified):

CHANGE 7: CLARIFY THAT FSH IS FOR WOMEN "<55 YEARS OLD AND >1 YEAR WITHOUT MENSES"

Location:

Synopsis; Subsection Criteria for evaluation, Other Assessments

Original Text:

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. Reserve blood samples (serum and plasma) for potential future measurement of potential biomarkers (Visit T1, T3).

New Text:

HBsAg, HCV, serum (Visit S1) and urine (Visit T1) pregnancy test (only for females who are of childbearing potential), FSH (only for ~~postmenopausal females~~ ***women*** <55 years ***old and ≥1 year without menses***), TSH. Reserve blood samples (serum and plasma) for potential future measurement of potential biomarkers (Visit T1, T3).

Location:

Section 11.6.1

Original Text:

- Blood and urine specimens will be obtained for the following:
  - serum pregnancy test (for surgically sterile women and women of childbearing potential) or FSH test (postmenopausal women);

New Text:

- Blood and urine specimens will be obtained for the following:
  - serum pregnancy test (for surgically sterile women and women of childbearing potential) or FSH test (~~postmenopausal~~ women ***<55 years old and ≥1 year without menses***);

Location:

Section 13.6.1, Table 3

Original Text:

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

New Text:

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

Location:

Appendix 1. Schedule of Assessments; Footer Superscript "f"

Original Text:

[f] Pregnancy tests will be obtained for women of childbearing potential and for surgically sterile women; FSH level will be obtained for postmenopausal women.

New Text:

[f] Pregnancy tests will be obtained for women of childbearing potential and for surgically sterile women; FSH level will be obtained for ~~postmenopausal~~ women ***<55 years old and ≥1 year without menses***.

CHANGE 8: ADD "WEIGHT (IN KILOGRAMS) WILL BE RECORDED" FOR VISIT T1 (SECTION 11.7.1) AND VISIT T3/EOS (SECTION 11.7.3)

Location:

Section 11.7.1

Original Text:

- Adverse events will be assessed.
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded.

New Text:

- Adverse events will be assessed.
- ***Weight (in kilograms) will be recorded.***
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded.

Location:

Section 11.7.3

Original Text:

- Adverse events will be assessed.
- PE.

New Text:

- Adverse events will be assessed.
- ***Weight (in kilograms) will be recorded.***
- PE.

CHANGE 9: REMOVE REFERENCES TO PK SAMPLES

Location:

Section 12.1.5

Original Text:

Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from serum and plasma blood samples collected at Visits T1 and T3 and stored frozen, reserved for potential future measurement of potential biomarkers.

New Text:

Additional exploratory safety, efficacy, ~~PK,~~ or potential biomarkers may be assayed from serum and plasma blood samples collected at Visits T1 and T3 and stored frozen, reserved for potential future measurement of potential biomarkers.

Location:

Section 12.1.6

Original Text:

Blood specimens for PK laboratory assessments will be collected as shown in Table 2.

New Text:

Blood specimens for ~~PK~~ ***basic fasting lipids, special lipids, and other biomarker*** laboratory assessments will be collected as shown in Table 2.

Location:

Section 13.6.4

Original Text:

The total number of venipunctures and total volume of blood collected during the study will be limited to that needed for PK and safety assessments.

New Text:

The total number of venipunctures and total volume of blood collected during the study will be limited to that needed for ~~PK and~~ safety assessments.

CHANGE 10: CORRECT REPORTING REQUIREMENTS FOR AES TO THE PERIOD OF THE TIME OF ICF IS SIGNED THROUGH 30 DAYS AFTER THE LAST STUDY VISIT

Location:

Section 13.6.1, Table 3

Original Text:

Coagulation (Visit S1 for all subjects, Visit T1 and 3-5 days after Visit T1 in subjects receiving anticoagulation therapy only) • Prothrombin time (PT) • International normalized ratio (INR)

New Text:

Coagulation (Visit S1 for all subjects, Visit T1 and 3-~~5~~*7* days after Visit T1 in subjects receiving anticoagulation therapy only) • Prothrombin time (PT) • International normalized ratio (INR)

CHANGE 11: CORRECT REPORTING REQUIREMENTS FOR AES TO THE PERIOD OF THE TIME OF ICF IS SIGNED THROUGH 30 DAYS AFTER THE LAST STUDY VISIT

Location:

Section 13.7.1.3

Original Text:

All AEs that occur from the time the ICF is signed through 20 days after the last study visit should be recorded on the eCRF. Any SAE that occurs from the time the ICF is signed through 30 days after the last study visit should be reported to the sponsor per Section 13.7.2.4.

New Text:

All AEs that occur from the time the ICF is signed through ~~20~~***30*** days after the last study visit should be recorded on the eCRF. Any SAE that occurs from the time the ICF is signed through 30 days after the last study visit should be reported to the sponsor per Section 13.7.2.4.

Signature Page for VV-CLIN-000963 v0.1

Approval	[redacted] 15-Mar-2018 22:18:34 GMT+0000
Approval	[redacted] 15-Mar-2018 22:24:48 GMT+0000
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