BEMPEDOIC ACID

1002-050

A MULTICENTER OPEN-LABEL EXTENSION (OLE) STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF BEMPEDOIC ACID (ETC-1002) 180 MG

Study Phase:	3
IND Number:	106,654
EudraCT Number:	2016-004115-12
Indication:	Treatment of hyperlipidemia
Investigators:	Approximately 125 sites located in the United States, Canada, Germany, Netherlands, Poland, United Kingdom
Sponsor:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 Ann Arbor, MI 48108 Phone: 734-862-4840 Fax: 734-582-9720
Sponsor Contact:	[redacted]
Medical Monitor:	

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Original Protocol:	01 November 2016
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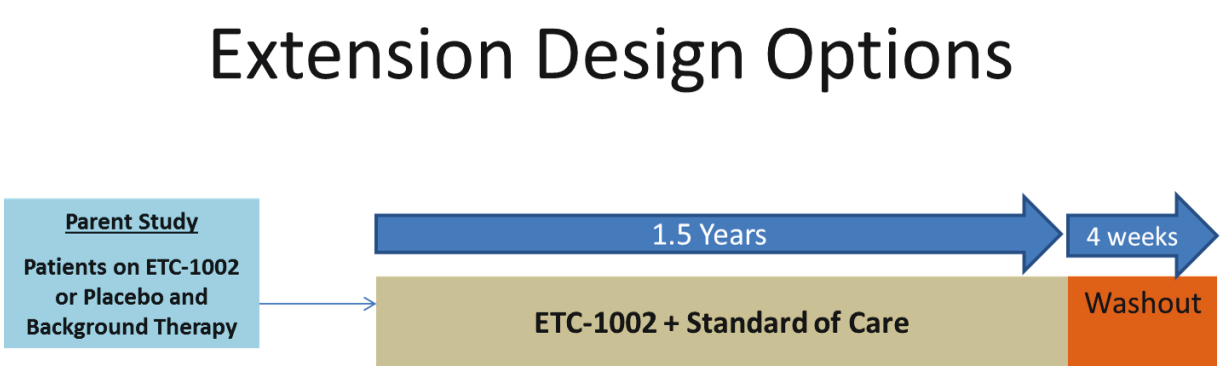
2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.
Name of Investigational Product: Bempedoic acid (ETC-1002) film-coated tablets
Name of Active Ingredient: Bempedoic acid
Title of Study: A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg
Study Number: 1002-050
Phase of Development: 3
Clinical Sites: Approximately 125 sites located in the United States, Canada, Germany, Netherlands, Poland, and United Kingdom
Objectives: **Primary:** • To characterize the safety and tolerability of long-term administration of bempedoic acid (ETC-1002) 180 mg **Secondary:** • To characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), triglycerides (TG), and high-sensitivity C-reactive protein (hs-CRP) in patients with hyperlipidemia
Methodology: **1002-050 Study Design**  This is a multicenter OLE study designed to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from the parent study (Study 1002-040) followed by a follow-up period off study drug for 4 weeks. Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available.

[redacted]

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

Primary Endpoint:

Patient incidence of adverse events (AEs)

Secondary Endpoints:

- Percent change from baseline in LDL-C at Weeks 52 and 78
- Change from baseline in LDL-C at Weeks 52 and 78
- Percent change from baseline in non-HDL-C at Weeks 52 and 78
- Percent change from baseline in TC at Weeks 52 and 78
- Percent change from baseline in ApoB at Weeks 52 and 78
- Percent change from baseline in hs-CRP at Weeks 52 and 78
- Percent change from baseline in TG at Weeks 52 and 78
- Percent change from baseline in HDL-C at Weeks 52 and 78

Number of patients (planned): The number of patients entering this study will depend on the number of patients completing Study 1002-040 and their willingness to enroll and continue taking investigational product. Approximately 1300 patients of the 1950 eligible from parent study 1002-040 are expected to participate in this study.

Diagnosis and Criteria for Inclusion:

Key inclusion criteria

1. Successfully completed the parent study (1002-040) and meet both of the following criteria:
   - The patient was compliant with the parent study requirements including study visits, procedures, and investigational medicinal product (IMP) in the opinion of the principal investigator;
   - The patient was able to tolerate IMP through the end of the parent study.

Key exclusion criteria

1. Female patient is not willing to use at least 1 acceptable method of birth control during treatment and for an additional 30 days after the end of treatment unless patient is sterilized or postmenopausal;
   - Menopause is defined as greater than 55 years and ≥1 year without menses, less than 55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L, or surgically sterile (including hysterectomy and/or bilateral oophorectomy);
   - Acceptable methods of birth control include: oral birth control medications; placement of an intrauterine device (IUD) with or without hormones; barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly; vasectomized male partner who is the sole partner for this patient; or true abstinence where it is the preferred and usual lifestyle of the patient (not including periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, or withdrawal).

2. Patient is pregnant or breast feeding, or might become pregnant during treatment and/or within 30 days after the end of treatment
3. Unreliability as a study participant based on the investigator's (or designee's) knowledge of the patient (eg, inability or unwillingness to adhere to the protocol)
4. Experienced a treatment-related SAE that led to study drug discontinuation in the parent study
5. Disorder that would interfere with understanding and giving informed consent or compliance with protocol requirements
6. Have any medical condition that in the opinion of the investigator may affect patient safety or ability to complete scheduled assessments
7. Patient's medical condition requires lipid measurement and/or adjustment of background lipid-regulating therapy during the first 12 weeks of study participation
8. Known sensitivity to any of the products to be administered during dosing
9. Currently enrolled in another investigational device or drug study (excluding ETC-1002-040), or less than 30 days since ending another investigational device or drug study(s), or receiving or planning to receive other investigational agent(s) during this study

Test product, dose, and mode of administration:

- Bempedoic acid 180-mg tablets

All study drug (bempedoic acid) will be ingested once daily with or without food. On clinic days patients will come to the clinic in the fasted state and study drug will be administered after laboratories are obtained.

Duration of treatment:

The total duration of treatment for an individual subject will be 1.5 years (18 months). The total duration in the study will be 19 months.

Criteria for evaluation:

Efficacy:

Lipid and Cardiometabolic Assessments:

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

Safety:

Safety Assessments:

- Adverse events and SAEs will be collected and reported. Clinical endpoints will be collected and adjudicated by an independent CEC. Clinical endpoints will also be reported as SAEs as appropriate. Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, glycosylated hemoglobin, Type A_{1C} (HbA_{1C}), fasting glucose, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram (ECG) readings, and weight.

Clinical Laboratory Assessments:

- Hematology: Hematocrit (Hct), hemoglobin (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), alanine aminotransferase (ALT; or serum glutamic pyruvic transaminase [SGPT]), aspartate aminotransferase (AST; or serum glutamic oxaloacetic transaminase [SGOT]), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO_2), chloride (Cl), creatinine, creatine kinase (CK), glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid
- HbA_{1C}

Safety and Monitoring:

Lipid results will be masked in order to maintain the blind from the parent study (1002-040) for the first 12 weeks of trial and unmasked after the Week 12 visit. See Section 10.1.4.4.1 for additional details.

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

Potential AEs:

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

Musculoskeletal Safety:

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

Hepatic:

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

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

Statistical methods:

Sample Size

[redacted]

General Considerations

Statistical analyses in this open-label, multicenter single arm study will be descriptive in nature. No statistical inference is planned.

Patient disposition, demographics and baseline characteristics will be summarized.

Summary statistics for continuous variables will include the number of patients, mean, median, standard deviation or standard error, first and third quartiles minimum, and maximum. For categorical variables, the frequency and percentage will be given. Ninety-five percent (95%) confidence intervals will be calculated for select continuous and categorical endpoint estimates.

All patients will be summarized together as well as by their prior treatment in the parent study.

For all efficacy endpoints, the percent changes in lipid parameters are calculated from baseline of the parent study. The full analysis set (FAS) will include all patients enrolled in this study that had at least 1 dose of bempedoic acid 180 mg in this study. All analyses will be performed using the FAS. There will be no imputation for missing data.

Clinical endpoints from this and other Phase 3 studies will be monitored and adjudicated by an independent CEC to facilitate aggregated analyses across the bempedoic acid program.

Analyses of the Primary Endpoint

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Patient incidences of treatment-emergent adverse events (TEAEs), treatment-related AEs, SAEs, and AEs leading to withdrawal of study medication will be tabulated by system organ class and preferred term.

Analysis of Secondary Endpoints

Secondary endpoints will be summarized at Weeks 52 and 78. Descriptive statistics will be presented.

Other Safety Analyses

Measurements of laboratory parameters and vital signs will be summarized at each scheduled visit. Lab shift tables will be provided. Summaries of vital signs will also be provided.

Safety Monitoring

The study includes adjudication of events by an independent CEC and formal review of ongoing data by an independent DMC. The DMC will formally review the accumulating data from this ongoing study in conjunction with other bempedoic acid studies to ensure there is no avoidable increased risk or harm to patients.

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[redacted]

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACL	Adenosine triphosphate-citrate lyase
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular diseases
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
C_{max}	Time to peak maximum concentrations
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
CV	Cardiovascular

Abbreviation or Specialist Term	Explanation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ETC-1002	Bempedoic acid
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A_{1C}
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product

[redacted]

Abbreviation or Specialist Term	Explanation
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LPLV	Last patient last visit
LS	Least square
MACE	Major adverse cardiac event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
N/A	Not available
N/D	Not done
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension (study)
Parent study	Study 1002-040
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)

Abbreviation or Specialist Term	Explanation
PO	By mouth
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SP	Safety population
SUSARS	Suspected and unexpected serious adverse reactions
$t_{½}$	Terminal elimination half-live
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TQT	Thorough QT/QTc
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

4.1. Lipid-Regulating Drugs and Cardiovascular Disease

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

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

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

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

Familial hypercholesterolemia refers to individuals with extremely elevated LDL-C due to underlying genetic mutations of the LDL receptor (LDLR), apolipoprotein B (ApoB), and proprotein convertase subtilisin/kexin type 9 (PCSK9) (FH Foundation 2015). In adult HeFH patients, LDL-C usually exceeds 190 mg/dL (4.9 mmol/L) and can be as high as 400 mg/dL (10.4 mmol/L). HeFH is the most common form of the disease with a prevalence of approximately 1 in 300 to 500 persons worldwide and as high as 1 in 100 persons in some populations (NORD 2015). Patients with HeFH inherit a genetic mutation from 1 parent. Inheritance is generally via an autosomal-dominant mechanism (Robinson 2013). HeFH increases the risk of atherosclerosis leading to CV events. The mean age for the onset of CV disease is relatively young, at 42 to 46 years in men and 51 to 52 years in women (Robinson 2013). The cumulative risk of experiencing a coronary event by the age of 60 years without

effective treatment is at least 50% in men and approximately 30% in women with a marked increase in postmenopausal women. Before effective treatment with statins became available, mortality from coronary disease was increased by nearly 100-fold in young adults 20 to 39 years of age, and approximately 4-fold for patients aged 40 to 59 years (Neil 2008). The National Lipid Association (NLA) recommends achievement of ≥50% reduction in LDL-C in adult patients using statins. HeFH patients at even higher risk for CV disease (such as those with established ASCVD, diabetes, smoking, family history, and other risk factors) have a treatment goal of ≤70 mg/dL (1.8 mmol/L). Those unable to achieve these treatment goals with maximally tolerated statin therapy require additional lipid-lowering therapy and still may be unable to reach LDL-C treatment goals.

Lowering LDL-C is the primary therapeutic lipid target in ASCVD and HeFH patients (Goldberg 2011). LDL-C is largely accepted as a valid surrogate endpoint of CV events by clinicians and regulatory authorities (Stone 2014). Long-term elevations in LDL-C lead to progressive accumulation of atherosclerotic lesions in the walls of arteries that require long-term management. While lifestyle changes are the primary intervention, these measures rarely reduce plasma LDL-C by >15%. Particularly in ASCVD and HeFH patients, pharmacologic treatments are required to adequately treat hyperlipidemia (Pollex 2008). Evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes comes from interventional studies with LDL-C-lowering therapies, epidemiological studies, genetic variants (both gain of function and loss of function). Large randomized clinical studies aimed at lowering LDL-C show a consistent, log-linear relationship between LDL-C reduction and CV risk reduction, independent of the way LDL-C lowering was achieved based on mechanism of action (Kathiresan 2008; Baigent 2010; Robinson 2005; Stamler 1986). A published patient-level meta-analysis including 26 trials and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and CV outcomes (Baigent 2010). This analysis showed that with a 1 mmol/L reduction in LDL-C associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. Intensive statin therapy relative to low/moderate intensity statin treatment produces greater benefit in patients at high CV risk (Cannon 2004). Unfortunately, some patients are unable to take high intensity statins due to dosing limits based on co-morbidities, contraindications, and/or tolerance (Jacobson 2014). Nonstatin therapies may provide additional lowering of CV risk as demonstrated in the IMPROVE-IT trial, which added ezetimibe to statin therapy (Cannon 2015).

Patients with ASCVD and HeFH on maximally tolerated lipid-lowering therapy including maximally tolerated doses of statins who require additional lipid-lowering therapy have an unmet medical need. Bempedoic acid may offer a once daily option for these patients. The oral route of administration may be preferable to injectable biologic therapy for some patients. Bempedoic acid has been well tolerated to date, and Phase 2 data demonstrate significant LDL-C lowering, prompting further evaluation in Phase 3 clinical studies.

4.2. Background on Bempedoic Acid

4.2.1. Mechanism of Action

Bempedoic acid is a first-in-class small molecule inhibitor of ACL, an enzyme upstream of HMG-CoA in the cholesterol biosynthesis pathway. Bempedoic acid is a prodrug that requires

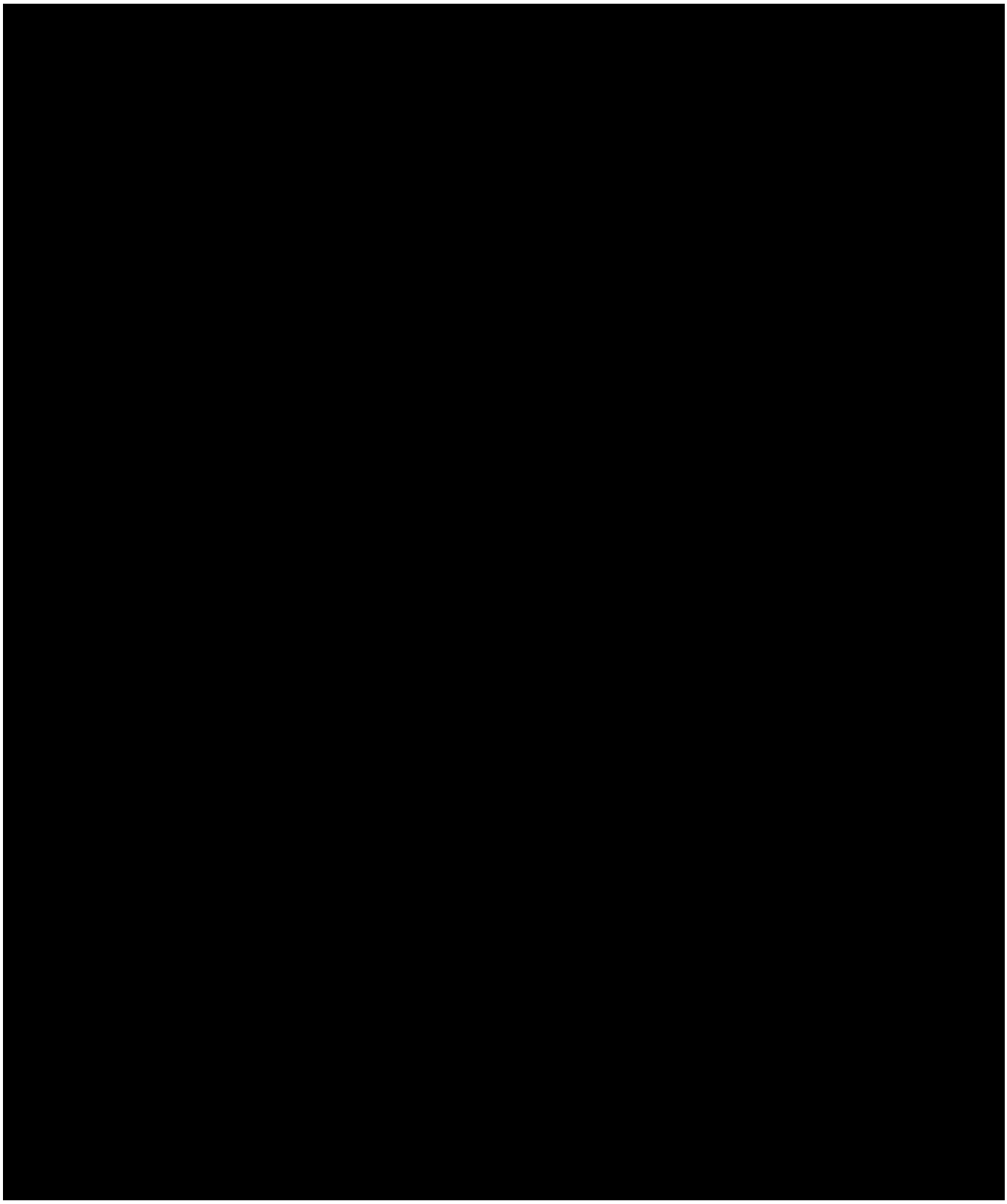
activation in liver to ETC-1002-co-enzyme A (ETC-1002-CoA), which mediates competitive inhibition of ACL. Inhibition of ACL by ETC-1002-CoA decreases cholesterol synthesis in liver leading to increased LDLR expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC-1002-CoA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

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

4.2.2. Nonclinical Experience

[redacted]

4.2.3. Previous Human Experience



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4.2.4. Dose Selection

[redacted]

4.2.5. Background Therapy

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

4.2.6. Risk Benefit Summary

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

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

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Study Objectives

5.1.1. Primary Objective

- To characterize the safety and tolerability of long-term administration of bempedoic acid (ETC-1002) 180 mg

5.1.2. Secondary Objectives

- To characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in LDL-C, HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), ApoB, total cholesterol (TC), TG and high-sensitivity C-reactive protein (hs-CRP) in patients with hyperlipidemia

5.2. Study Endpoints

5.2.1. Primary Endpoint

- The primary efficacy endpoint for this study is patient incidence of AEs

5.2.2. Secondary Endpoints

- Percent change from baseline in LDL-C at Weeks 52 and 78
- Change from baseline in LDL-C at Weeks 52 and 78
- Percent change from baseline in non-HDL-C at Weeks 52 and 78
- Percent change from baseline in TC at Weeks 52 and 78
- Percent change from baseline in ApoB at Weeks 52 and 78
- Percent change from baseline in hs-CRP at Weeks 52 and 78
- Percent change from baseline in TG at Weeks 52 and 78
- Percent change from baseline in HDL-C at Weeks 52 and 78

6. INVESTIGATIONAL PLAN

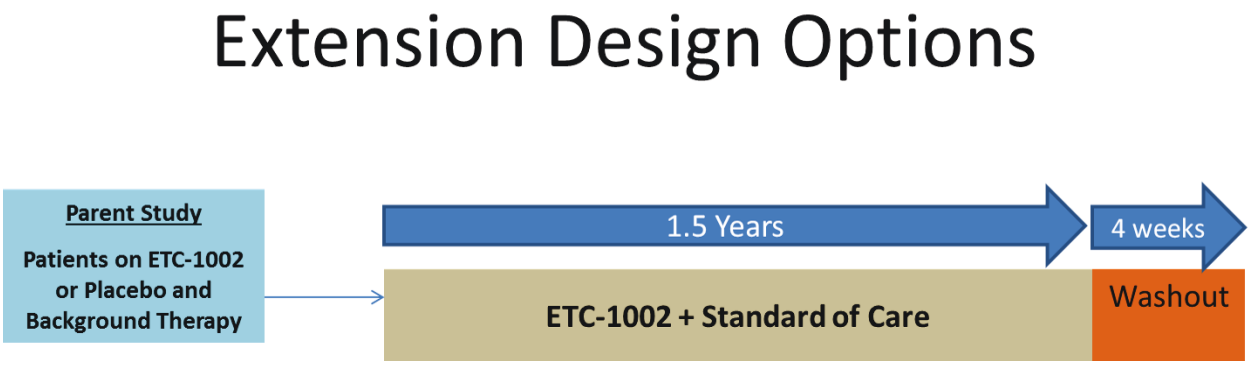
6.1. Overall Study Design

This is a multicenter open-label extension (OLE) study designed to assess the long-term safety and efficacy of bempedoic acid 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from Study 1002-040 (parent study) followed by a period off study drug for 4 weeks. Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available to sites. The study will be conducted at approximately 125 clinical sites in the US, Canada, Germany, Netherlands, Poland, and United Kingdom. It's anticipated that approximately 1300 patients will elect to enroll into this study. Patients will have visits every 3 months. Patients will be required to visit the site at baseline (end of study [EOS] parent), Week 12, Week 52, Week 78, and Week 82. Phone visits will occur at Weeks 24, 36, and 64.

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

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

Figure 1. Study 1002-050 Study Design



6.2. Study Hypothesis

The primary clinical hypothesis is that long-term exposure of bempedoic acid (ETC-1002) 180 mg will be safe and well tolerated.

6.3. Study Duration

Patients will be enrolled after successfully completing study ETC-1002-040. The total study duration for an individual subject is 82 weeks (1 year and 7 months).

6.4. End of Study

The study will end when the last patient completes their Week 82 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 2.5 years.

6.5. Number of Patients

The study will enroll approximately 1300 patients with hyperlipidemia from approximately 125 clinical sites.

6.6. Patient Identification Numbers

All patients who enter the study will retain the same unique patient identification number from the parent study (ETC-1002-040).

6.6.1. Enrollment

Patients that successfully complete parent study and satisfy all entry criteria will be enrolled.

6.7. Patient Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Successfully completed the parent study (1002-040) and meet both of the following criteria:
    - The patient was compliant with the parent study requirements including study visits, procedures, and IMP in the opinion of the principal investigator.
    - The patient was able to tolerate IMP through the end of the parent study.

6.8. Patient Exclusion Criteria

1. Female patient is not willing to use at least 1 acceptable method of birth control during treatment and for an additional 30 days after the end of treatment unless patient is sterilized or postmenopausal;
    - Menopause is defined as greater than 55 years and ≥1 year without menses, less than 55 years and ≥1 year without menses with follicle-stimulating hormone (FSH)

≥40.0 IU/L, or surgically sterile (including hysterectomy and/or bilateral oophorectomy);

- Acceptable methods of birth control include: oral birth control medications; placement of an intrauterine device (IUD) with or without hormones; barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly; vasectomized male partner who is the sole partner for this patient; or true abstinence where it is the preferred and usual lifestyle of the patient (not including periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, or withdrawal).

2. Patient is pregnant or breastfeeding, or might become pregnant during treatment and/ or within 30 days after the end of treatment
3. Unreliability as a study participant based on the investigator's (or designee's) knowledge of the patient (eg, inability or unwillingness to adhere to the protocol)
4. Experienced a treatment-related SAE that led to study drug discontinuation in the parent study
5. Disorder that would interfere with understanding and giving informed consent or compliance with protocol requirements
6. Have any medical condition that in the opinion of the investigator may affect patient safety or ability to complete scheduled assessments
7. Patient's medical condition requires lipid measurement and/or adjustment of background lipid-regulating therapy during the first 12 weeks of study participation
8. Known sensitivity to any of the products to be administered during dosing
9. Currently enrolled in another investigational device or drug study (excluding ETC-1002-040), or less than 30 days since ending another investigational device or drug study(s), or receiving or planning to receive other investigational agent(s) during this study.

6.9. Investigator/Sponsor Suspension or Termination of Patient Enrollment

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

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

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

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection on a chronic basis

[redacted]

- Falsification of records
- Failure to adhere to the protocol
- Lack of study oversight by the Principal Investigator and/or designee

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

7. TREATMENT OF PATIENTS

7.1. Description of IMP

Table 2: Investigational Medicinal Products

Product Name:	Bempedoic acid
Dosage Form:	Film-coated tablets
Unit Dose:	180 mg
Container/Closure[a]	100-count bottle with screw on, childproof cap
Route of Administration:	Oral, daily, with or without food
Physical Description:	[redacted]
Manufacturer (Fill/Finish):	

Study drug should be taken once a day (once every 24 hours) at approximately the same time every day and may be taken with or without food. Patients will fast (no food or drink, other than water) for a minimum of 10 hours prior to collection of all laboratory samples.

Please see Pharmacy Manual for detailed storage requirements and instructions.

7.2. Concomitant Medications

During the study investigators may prescribe any necessary concomitant medication. However, lipid-altering therapies cannot be adjusted during the first 12 weeks of the study. In addition, during the 4-week period after last dose, every effort should be made to maintain the patients' background lipid-modifying therapy unless it is medically necessary to safely manage the patient. Patients will be questioned about their concomitant medication use at each clinic visit. All concomitant medication taken chronically or intermittently during the study must be recorded with indication, total daily dose, and start and stop dates of administration. Prior and concomitant medications will be collected using an electronic case report form (eCRF).

7.2.1. Prohibited Medications and supplements

All medications deemed medically necessary may be prescribed during this study, with the following exceptions:

- Mipomersen
- Lomitapide or apheresis therapy
- Red yeast rice containing products
- Uptitration of simvastatin to a dose that is greater than or equal to 40 mg/day
- Gemfibrozil
- Ezetimibe/simvastatin (Zocor®) where simvastatin doses are ≥40 mg/day (Vytorin® 10/40 and 10/80 and Inegy® 10 mg/40 mg and 10 mg/80 mg are prohibitory)

7.3. Blinding

Laboratory results for lipid panel and hs-CRP will be masked to investigators, patients, and the study team until the Week 12 visit is completed. All site staff involved with this trial should refrain from obtaining lipid panels between date of last ETC-1002-040 dose at end of parent study Week 52 (Visit T7) and Week 12 in this OLE trial.

While this is an open-label study where all patients will receive active treatment with bempedoic acid (180 mg by mouth [PO] once daily [QD]), blinding of the treatment that patients received during the parent study must be maintained for all patients unless, in the opinion of the Investigator, the safety of the patient may be at risk. Only under the rarest of circumstances should the Investigator consider breaking the parent study blind and only when medical/supportive care cannot be provided without determining if the patient was previously receiving active drug treatment. In the event that the parent study blind needs to be broken prior to completion of the parent study, the Investigator should contact the appropriate Medical Monitor by telephone. If the parent study 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 interactive web response system (IWRS) utilized in the parent study. In all cases of breaking the parent study blind, the Investigator must document in the patient's medical record the date, time, and reason for breaking the blind, and the names of personnel involved.

7.4. Overdose

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

8. INVESTIGATIONAL MEDICINAL PRODUCT

8.1. Investigational Medicinal Product Supply and Control

The Sponsor will supply bempedoic acid (180-mg film-coated tablets) for this study. Study drug will be distributed and released in accordance with regional and local requirements during the conduct of the study.

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

9. STUDY PROCEDURES

9.1. Informed Consent

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

9.2. Procedures and Schedule of Assessments

Patients who provide informed consent and sign the ICD will be eligible to enroll in the study.

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

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

9.2.1. Enrollment (EOS/Day 1 OLE)

Day 1 for this study should occur on the same day as the end of study visit for the parent study (1002-040). All efforts should be made to avoid delays in rolling over. The study procedures below, from the parent study EOS visit, will be used to qualify for this study. If Day 1 of the OLE study occurs >30 days from the end of study visit from the parent study, all procedures will need to be repeated including taking a new medical history.

- Review of inclusion/exclusion criteria
- Concomitant medication review
- Assess AE/SAEs
- Physical exam
- Weight (kg)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, coagulation (only in patients receiving anticoagulant therapy), and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - ApoB
  - Hs-CRP
  - Glycosylated hemoglobin, Type A_{1C} (HbA_{1C})
- Urine pregnancy test
- Contact IWRS to register the patient

- Dispense study drug

Please note the following for patients enrolling into Study 1002-050 within 30 days of completing the EOS visit in the parent study:

- If the patient is not receiving anticoagulant therapy and/or is a woman who is not of childbearing potential, clinical laboratory samples do not need to be collected as the results from the parent study EOS visit will be used for this visit.
- If the patient is receiving anticoagulant therapy, then a coagulation laboratory sample is required at this visit using a Study 1002-050 unscheduled laboratory kit.
- If the patient is a woman of childbearing potential, then a urine pregnancy test is required at this visit.

Please note the following for patients enrolling into Study 1002-050 greater than 30 days after completing the EOS visit in the parent study:

- Clinical laboratory samples should be collected using a Study 1002-050 Day 1 kit. Supplies for collecting the coagulation sample are included in this kit.
- If the patient is a woman of childbearing potential, then a urine pregnancy test is required at this visit.

9.2.2. Month 3 (Week 12 ±7 days)

If the patient is withdrawing early from the study at this visit, proceed to Section 9.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 9.3.2 for the list of the required assessments. The patient will be asked to continue to be followed for safety using the protocol-specified visit schedule. If the patient consents for follow-up, schedule the next protocol-specified visit.

Patients who do not provide consent to continue to return to the clinic for safety assessments after withdrawing from IMP treatment will be asked to participate in phone calls from the site at protocol-specified visits, or at a minimum at 78 weeks, to inquire about the patient's current health status and collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If the patient consents for telephone contacts, schedule the next protocol-specified visit.

Patients will undergo the following assessments and procedures:

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis

  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB and hsCRP
- Return of IMP; assessment and recording of IMP compliance
- Dispense IMP containers to patient for continued dosing and provide dosing instruction
- Schedule next visit

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments, including basic fasting lipids, after withdrawing from IMP treatment, all assessments except for those procedures pertaining to IMP management (IMP dispensing, IMP compliance, IMP accountability) should be completed.

Note: If this visit is being conducted by telephone contact for patients who have consented to be followed by phone for safety assessments after withdrawing from IMP treatment, collect information as reported by the patient regarding AEs, concomitant medication, and current health status.

9.2.3. Month 6 (Week 24) and Month 9 (Week 36) / Telephone Visit (±7 days)

Patients will undergo the following assessments via telephone:

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

Note: If the patient discontinues at or between study visits, please proceed to Section 9.3.2 for detailed instructions.

9.2.4. Month 12 (Week 52 ±7 days)

If the patient is withdrawing early from the study at this visit, proceed to Section 9.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 9.3.2 for the list of the required assessments. The patient will be asked to continue to be followed for safety using the protocol-specified visit schedule. If the patient consents for follow-up, schedule the next protocol-specified visit.

Patients who do not provide consent to continue to return to the clinic for safety assessments after withdrawing from IMP treatment will be asked to participate in phone calls from the site at protocol-specified visits, or at a minimum at 78 weeks, to inquire about the patient's current health status and collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If the patient consents for telephone contacts, schedule the next protocol-specified visit.

Patients will undergo the following assessments and procedures:

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs
- Physical Exam
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
  - ApoB and hs-CRP
  - HbA_{1C}
- Return of IMP; assessment and recording of IMP compliance
- Dispense IMP containers to patient for continued dosing and provide dosing instruction
- Schedule next visit

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments, including basic fasting lipids, after withdrawing from IMP treatment, all assessments except for those procedures pertaining to IMP management (IMP dispensing, IMP compliance, IMP accountability) should be completed.

Note: If this visit is being conducted by telephone contact for patients who have consented to be followed by phone for safety assessments after withdrawing from IMP treatment, collect information as reported by the patient regarding AEs, concomitant medication, and current health status.

9.2.5. Month 15 Telephone Visit (Week 64 ±7 days)

Patients will undergo the following assessments via telephone:

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

Note: If the patient discontinues at or between study visits, please proceed to Section 9.3.2 for detailed instructions.

9.2.6. Treatment Month 18/EOT (Week 78 ±7days)

Patients will undergo the following assessments and procedures when completing the End of Treatment (EOT) visit, withdrawing from study prior to Week 78 (early withdrawal), or withdrawing from IMP treatment:

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs
- Physical exam
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
  - ApoB and hs-CRP
  - HbA_{1C}
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study).

9.2.7. Off Study Drug Period Month 19/EOS (Week 82 +14 days)

Patients will return for a final EOS visit 4 weeks after IMP treatment has been completed (including patients who withdraw from IMP treatment prior to Week 78) to undergo the following assessments and procedures.

- Concomitant medication review
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
  - ApoB and hs-CRP
  - HbA_{1C}

9.3. Patient Withdrawal Criteria

9.3.1. Early Withdrawal from the Study

Patients must remain in the study until the last scheduled visit at Month 19 (Week 82) to be considered as having completed participation in the study. Patients must remain in the study through Month 18 (Week 78) to be considered as having completed participation in the treatment portion of the study.

Patients who withdraw from IMP prior to Month 18 (Week 78) for any reason will be asked to continue to be followed for safety assessments, including basic fasting lipids, at clinic visit following the protocol-specified visit schedule (see Appendix 1). The patient must provide consent to be followed in the study after withdrawing from IMP treatment. Protocol procedures to be completed for patients who consent will include those specified at each visit as noted in Schedule of Events (see Appendix 1).

Patients who temporarily withdraw from IMP prior to Month 18 (Week 78) for any reason may restart IMP providing that 1) the patient and the investigator are in agreement regarding this course of action, and 2) IMP can be started as soon as possible. For cases where the patient has been off of IMP for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting IMP.

Patients who do not provide consent to continue to return to the clinic for safety assessments will be asked to participate in phone calls from the site at protocol-specified visits (see Appendix 1), or at a minimum at 78 weeks, to collect information on AEs, concomitant medications, and current health status. The patient must provide consent to be contacted by phone by site personnel for the purposes of assessing current AEs and current health status.

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

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

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

- Unacceptable AE
- Patient's withdrawal of consent
- Failure to comply with the protocol
- Lost to follow-up
- Illness, condition, or procedural complication affecting the patient's ability to participate or requiring prohibited medication
- The Sponsor or Investigator terminates the study

- In the Investigator's judgment, it is deemed in the best interest of the patient to discontinue his/her participation in the study
- Any other reason

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

9.3.2. Procedures for Early Withdrawal

If a patient withdraws or is removed from the study for any reason prior to Week 78, all EOT procedures should be completed. In addition, the patient should return 4 weeks after last dose of IMP for the Week 82/EOS procedures. Reason for withdrawal, date of the discontinuation, and date of the last dose of study drug should be recorded in the appropriate section of the eCRF. Additionally, the discontinuation visit date must be registered in IWRS. Study drug assigned to the withdrawn patient may not be assigned to another patient.

All effort should be made to have each patient complete all study visits on schedule according to the protocol. Accommodations for early or late visits in special circumstances will be considered by the Sponsor to prevent early withdrawal. Written notice (regardless of cause) is to be provided within 48 hours of the withdrawal to the Sponsor personnel or the Medical Monitor. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed. Except in the case of a medical emergency, the procedures and assessments detailed in Section 9.2.6 will be performed upon the discontinuation of the study.

Patients choosing to withdraw from the study early should be encouraged to return for all study scheduled clinic visit even if they are no longer taking IMP. Patients who withdraw from all aspects of the study will be asked to consent to clinical visits or phone calls for safety assessments, including AEs, concomitant medication, and current health status through Month 19 (Week 82).

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

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

10.1.1. Demographic/Medical History

Demographic and medical history collected from the parent study will be used for this study. If a patient is entering the study beyond the 30-day rollover window, changes to medical history and AEs that occur during that period will be collected.

10.1.2 Vital Signs

Vital signs will include diastolic blood pressure (DBP) and systolic blood pressure (SBP) as well as heart rate.

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

10.1.2. Weight and Body Mass Index

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

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

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

10.1.3. Physical Examination

Physical exam (PE) will include an assessment of the following:

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

- Musculoskeletal examination
- Respiratory examination
- Cardiovascular assessment, including rhythm and presence of cardiac abnormalities
- Abdominal examination
- Neurologic examination including documentation of the presence of abnormalities in mental status and motor and sensory function
- Any additional assessments deemed necessary by the investigator

Documentation of the PE findings will be included in the source documentation at the clinical site. Only changes from baseline PE findings that meet the definition of an AE will be recorded on the AE page of the eCRF.

Note: Additional information will be collected regarding muscle-related AEs. See Section 12.6.

10.1.4. Clinical Laboratory Tests

10.1.4.1. Laboratory Parameters (Safety)

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

Table 3: Clinical Laboratory Parameters (Safety)

<table>
<tr><th>Clinical Laboratory Test</th><th>Clinical Laboratory Test</th></tr>
<tr><td>• Hematology
• Hematocrit (Hct)
• Hemoglobin (Hgb)
• Mean corpuscular hemoglobin (MCH)
• Mean corpuscular hemoglobin concentration (MCHC)
• Mean corpuscular volume (MCV)
• Platelet count
• Red blood (RBC) cell count
• White blood (WBC) cell count with differential (absolute and %)</td><td rowspan="2">Blood Chemistry (serum, fasting)
• Albumin (Alb)
• Alkaline phosphatase (ALK-P)
• Alanine aminotransferase (ALT; SGPT)
• Aspartate aminotransferase (AST; SGOT)
• Blood urea nitrogen (BUN)
• Calcium (Ca)
• Carbon dioxide (CO_2)
• Chloride (Cl)
• Creatinine
• Creatine kinase (CK)
• Glucose
• Lactate dehydrogenase (LDH)
• Phosphorus
• Potassium (K)
• Sodium (Na)
• Total and direct bilirubin (TB)[a]
• Total protein
• Uric acid
Coagulation—only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0
• Prothrombin time (PT)
• International normalized ration (INR)</td></tr>
<tr><td>Urinalysis (Dipstick)
• Clarity
• Bilirubin
• Color
• Glucose
• Ketones
• Leukocyte esterase
• Nitrate
• Occult blood
• pH
• Protein
• Specific gravity
• Urobilinogen</td></tr>
<tr><td>Urinalysis (Microscopic)-only if urine dipstick abnormal
• Bacteria
• Casts
• Crystals
• Epithelial cells
• RBC
• WBC</td><td>Other Labs:
• Urine pregnancy test
• Hemoglobin A_{1C} (HbA_{1C})</td></tr>
</table>

[a] If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained.

[redacted]

10.1.4.2. Sample Collection, Storage, and Shipping

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

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

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

10.1.4.3. General Monitoring and Management of Abnormal Clinical Labs

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

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

10.1.4.3.1. Monitoring and Management of Elevated Liver Function Tests

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

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

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN, consideration should be given to withdrawing the patient and administering no further doses of study drug.

At the investigator's discretion, study drug may be interrupted and the patient rechallenged with study drug after LFTs have returned to baseline levels.

- If repeat LFT assessment confirms ALT and/or AST >5 × ULN, patient should be withdrawn from IMP treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1).
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following, the patient should be given no further IMP treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1):
  - TB >2 × ULN

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

10.1.4.3.2. Monitoring and Management of Elevated Serum Creatinine

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

10.1.4.3.3. Monitoring and Management of Elevated Creatine Kinase

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

Repeat CK assessment will include query for related symptoms.

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

  - Review possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology)
  - Evaluation for additional diagnoses or other conditions which can cause myopathy including muscle tenderness (by PE), weakness, rash, measurement of serum creatinine, dipstick urinalysis with microscopy if indicated
  - Obtain clinical chemistries to assess the possibility of lactic acidosis
  - Follow symptoms and CK until the abnormality has resolved
  - If based on the above evaluation an alternative explanation is suspected, consideration can be given to resuming IMP once CK returns to baseline levels
  - If no alternative explanation exists, consideration should be given to withdrawing the patient from IMP treatment.
- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality as listed below, the patient should be withdrawn and given no further doses of study drug:
  - >10 × ULN, even in the absence of symptoms.
  - In all cases, evaluate the signs/symptoms and laboratory evaluations as outlined above.
- If the patient is withdrawn from IMP treatment, the patient should be asked to continue being followed for safety using the protocol-specified visit schedule (see Appendix 1).

10.1.4.4. Monitoring and Management of Potential Hypoglycemia and Metabolic Acidosis

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

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

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

10.1.4.4.1. Lipid Measurements

Investigators, site staff, patients, and the study team will be masked to study lipid levels as well as ApoB and hs-CRP until the Week 12 study visit, after which time lipid values will be made available and concomitant medications may be adjusted as necessary.

- The initiation of any new or dose changes of any existing lipid-lowering treatment will be documented on the eCRF as a concomitant medication with the associated start date. Uptitration of simvastatin to an average daily dose that is greater than or equal to 40 mg is not permitted.

10.1.4.5. Total Blood Volume of Clinical Laboratory Samples

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

11. ADVERSE AND SERIOUS ADVERSE EVENTS

11.1. Adverse Events

11.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, including control, and which does not necessarily have a causal relationship with treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the patient are recorded in the patient's medical record.

An AE can be:

- Any unfavorable and unintended sign/symptom, including an abnormal laboratory finding, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease
- Laboratory abnormality or diagnostic test abnormalities (eg, electrocardiogram [ECG] or X-ray) should be reported as an AE if one of the following occurs
  - Treatment required due to the abnormality
  - Discontinuation of IMP
  - Per Investigator judgement

11.1.2. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction (ADR). "Responses" to a medicinal product means that a causal relationship between the medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

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

11.1.3. Reporting for Adverse Events

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

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. A cluster of signs and symptoms that results from a single cause should be reported as a single AE (eg, fever,

elevated white blood cells [WBC], cough, abnormal chest X-ray, etc, can all be reported as "pneumonia" if that is the final diagnosis). However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure should be recorded as the AE, not the procedure itself.

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

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs. 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 IMP. For each AE, the following information will be recorded:

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

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

11.1.4. Severity

It is the investigator's responsibility to assess the intensity (severity) of an AE.

The severity of the AE will be characterized as mild, moderate, or severe according to the following definitions:

- Mild: Events are usually transient and do not interfere with the patient's daily activities
- Moderate: Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities

- Severe: Events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

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

11.1.5. Relationship

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

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

11.1.6. Monitoring and Follow-up of Adverse Events

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

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

Patients with AEs related to IMP that are ongoing at study discontinuation or completion must be followed until resolution or for 30 days after study completion, whichever comes first, with the exception of patients reporting SAEs (see Section 11.2.2).

11.1.7. Treatment-Emergent Adverse Events

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

11.2. Serious Adverse Events

11.2.1. Definition of Serious Adverse Event

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

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

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

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

11.2.2. Reporting Serious Adverse Events

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

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

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

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

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

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

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

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

11.2.3. Reporting of Serious Adverse Events to Regulatory Authorities

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

SAEs that are anticipated to occur in this patient population will be collected and reported by the Investigator as described in Section 11.2.2. However, these events will not be submitted to the regulatory authorities as expedited reports unless they meet SUSAR criteria. These events that are considered to be exempt from expedited reporting include the following clinical endpoints:

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

11.2.4. Reporting of Patient Death

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

11.2.5. Reports of Pregnancy and Lactation

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

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

11.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) are included in this protocol for reasons either associated with other lipid lowering therapies or where deemed important based on nonclinical data. AESI for this protocol include: metabolic acidosis (clinical laboratories), hypoglycemia, muscular (AE and CK evaluation), hepatic, and neurocognitive/neurologic events.

Hypoglycemia and Metabolic Acidosis: [redacted]

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

Hepatic: Hepatic function will be monitored throughout with the clinical safety labs. More detailed investigation will occur if the safety clinical laboratory results are >3 × ULN.

Neurocognitive Events: Theoretically, it is possible that lipid-lowering agents that disrupt cholesterol homeostasis in the brain could impact neurological function, and there have been reports of cognitive impairment (eg, memory loss) associated with the use of statin drugs

(FDA 2012). Summarization of events will occur using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms outlined in the statistical analysis plan (SAP).

11.4. Data Monitoring Committee

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

11.5. Clinical Event Committee (CEC)

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

11.6. Assessment of Lipid Endpoints

11.6.1. Lipid Parameters

After enrollment, patients will return to clinic at Weeks 12, 52, and 78. Clinical laboratory samples will be collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers including non-HDL-C, HDL-C, TC, ApoB, and TG at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters.

11.6.2. Clinical Laboratory Tests (Lipids)

Clinical laboratory samples will be collected at all clinic visits. All efforts should be made to collect these samples within the visit window.

Patients are encouraged to be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in Table 4. Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping as well as monitoring and management of abnormal laboratories are described in Section 10.1.4.

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

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

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

[redacted]

12. STATISTICS

12.1. General Considerations

Statistical analyses in this open label, multicenter single arm study will be descriptive in nature. No statistical inference is planned. Patient disposition, demographics and baseline characteristics will be summarized. Summary statistics for continuous variables will include the number of patients, mean, median, standard deviation or standard error, first and third quartiles minimum, and maximum. For categorical variables, the frequency and percentage will be given. Ninety-five percent (95%) confidence intervals (CIs) will be calculated for select continuous and categorical endpoint estimates. All patients will be summarized together as well as by their prior treatment group in the parent study.

12.2. Determination of Sample Size

The number of patients entering this study will depend on the number of patients completing Study 1002-040 and their willingness to enroll. [redacted]

12.3. Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy summaries and analyses, is defined as all enrolled patients. The FAS is also known as the intention-to-treat (ITT) set of patients.

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

12.4. Primary Endpoint

All safety endpoints will be summarized using the SP.

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

The patient incidence of all TEAE, SAEs, related AEs, AEs leading to withdrawal of IMP, fatal AEs, and AESI will be tabulated by system organ class and preferred term in descending order of frequency. If appropriate, exposure-adjusted patient incidence rate will also be provided.

Adverse events occurred in the parent study and continued into the OLE study without change in severity will be captured in the parent study only.

12.5. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be summarized descriptively using FAS. The change or percent change in lipid parameters will be calculated at each scheduled visit from the baseline of the parent study. No imputation is planned for missing data. Ninety-five percent (95%) CI will be provided for the estimates at each scheduled visit during the treatment period..

12.6. Other Safety Endpoints

Laboratory Results

Actual value or change from baseline (where appropriate) in clinical safety laboratories, including hematology, blood chemistry, HbA_{1C}, glucose, and urinalysis will be summarized at each scheduled visit.

Shift tables for selected safety laboratory parameters will be provided.

Physical Measurements

Height and weight will be summarized at each scheduled visit.

Vital Signs

Hear rate, SBP and DBP will be summarized at each scheduled visit.

Hepatic Safety

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

Musculoskeletal Safety

Adverse events of muscle-related symptoms will be summarized. Creatine kinase levels will be summarized by the value and change from baseline in the value, by visit. In addition, the number and percent of patients with normal vs. abnormal CK values will be summarized by their baseline and post-baseline status.

Diabetes and Hyperglycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug. Glucose and HbA_{1C} will be monitored at baseline and at Weeks 12, 52 and 78, and be summarized by history of diabetes.

Renal Safety

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

Neurocognitive Events

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

Clinical Endpoints

Clinical endpoints using standardized definitions will be adjudicated by an independent blinded expert CEC for all ongoing Phase 3 studies in the bempedoic acid program. Investigator-reported clinical endpoints and adjudicated clinical endpoints will be summarized by event type. Additional details regarding the clinical endpoints and their definitions will be included in CEC Charter.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

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

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

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

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

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

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

13.2. Audits and Inspections

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

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

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

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor / designee may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

15. ETHICS

15.1. Institutional Review Board/Independent Ethics Committee Approval

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

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

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

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

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

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

15.2. Ethical Conduct of the Study

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

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

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

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

15.3. Written Informed Consent

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

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

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

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

15.4. Patient Confidentiality

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

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

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

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

16.2. Retention of Records

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

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

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

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

16.3. Case Report Forms and Study Records

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

Study records are comprised of source documents, eCRFs, and all other administrative documents (eg, IRB or IEC correspondence, clinical study materials and supplies shipment

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

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

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

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

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

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

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

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

17. ADMINISTRATIVE CONSIDERATIONS

17.1. Investigators

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

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

Refer also to:

- FDA Regulations Related to GCP and Clinical Trials: http://www.fda.gov/oc/gcp/regulations.html
- Guidance and Information Sheets on GCP in FDA-Regulated Clinical Trials: http://www.fda.gov/oc/gcp/guidance.html
- Guidance for IRBs and Clinical Investigators: http://www.fda.gov/oc/ohrt/irbs/default.htm
- DIRECTIVE 2001/20/EC: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
- Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance: http://www.fda.gov/cder/guidance/959fnl.pdf

17.2. Amendments

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

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

17.3. Financial Disclosure

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

18. PUBLICATION AND DISCLOSURE POLICY

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

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

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

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

19. LIST OF REFERENCES

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

20. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS (PATIENT VISIT SCHEDULE)

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOT[1]**	**19/EOS[2]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**	**Wk 82**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+14 days**
In-clinic Visit	**X**	**X**			**X**		**X**	**X**
Phone Visit			**X**	**X**		**X**		
Procedure								
Informed Consent	X							
Enrollment Criteria	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X	X
Physical Exam	X				X		X	
Weight[3]	X	X			X		X	X
Vital Signs[4]	X	X			X		X	X
Urine Pregnancy Test[5]	X							
Clinical Safety Labs[6]	X	X			X		X	X
Basic Fasting Lipids[7]	X	X			X		X	X
Coagulation[8]	X							
ApoB and hsCRP	X	X			X		X	X
HbA_{1C}	X				X		X	X
IWRS Contact[9]	X	X			X		X	
Drug Dispensing	X	X			X			
Drug Return/ Compliance		X			X		X	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), and vital signs. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit Week 78/End of Treatment (EOT) will be scheduled as soon as possible and the patient will be asked to come back 4 weeks after last investigational medicinal product (IMP) dose for Visit Week 82/End of Study (EOS). No further visits will be scheduled.

[1] All procedures will be completed for all patients at either EOT or early withdrawal.

[2] All procedures will be completed for all patients 4 weeks after last IMP dose if completing the study or early withdrawal.

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

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

[5] Urine pregnancy test in women of childbearing potential only

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

[7] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).

[8] Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0

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

APPENDIX 2. SPONSOR'S SIGNATURE

Study Title: A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg

Study Number: 1002-050

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

Signed: [redacted]

Esperion Therapeutics, Inc.

Date: [redacted]

[redacted]

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title:	A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg
Study Number:	1002-050

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

Signed: _____ Date: _____

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

APPENDIX 4. SUMMARY OF CHANGES IN AMENDMENT 1

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002-050
Study Title:	A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg
Protocol Version Incorporating Current Summary of Changes:	Amendment 1: 09 May 2017
Preceding Protocol Version:	Original Protocol: 01 November 2016
Investigational Product Name:	ETC-1002

Conventions used in this Summary of Changes Document

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

Summary and Justification of Changes

The protocol was amended for the following:

- Added a line for Amendment 1 version and date to reflect amendment version details.
- Updated the design schematic to represent patients could receive ETC-1002 or matching placebo in the parent study.
- Revised inclusion criteria to specify the requirements pertaining to the parent study
- Updated exclusion criteria with regards to contraception to be consistent with European Medicines Agency (EMA) requirements
- Based upon the recommendation of the Data Monitoring Committee and Esperion's decision, doses of simvastatin 40 mg/day or greater have been added as a prohibited medication.
- The instructions around maintaining study blind have been expanded.

- Procedures have been clarified for patients enrolling into the study after the last visit for the parent study.
- The monitoring and management of CK values for asymptomatic patients was modified to be consistent with other protocols across the program.
- The Schedule of Events was updated to reflect changes or correct errors.
- Typographical errors and formatting were corrected or revised based on these changes or to improve clarity and consistency.

CHANGE 1 REVISION OF TITLE PAGE VERSION INFORMATION

Location:

Title Page

Original Text:

	Version	Date
	Original Protocol:	01 November 2016

New Text:

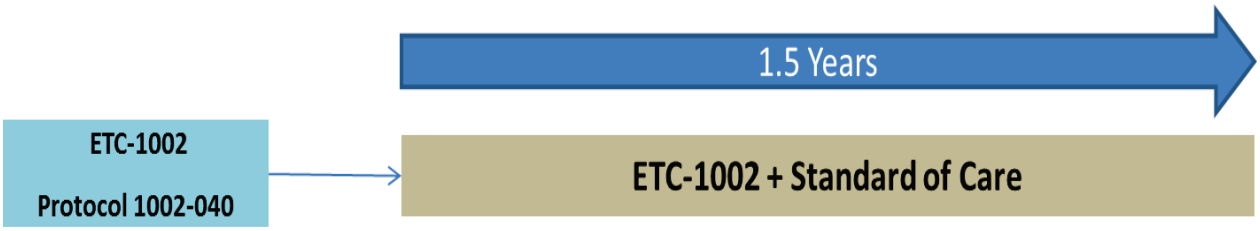
	Version	Date
	Original Protocol:	01 November 2017
	Amendment 1:	***09 May 2017***

CHANGE 2 REVISION TO THE DESIGN SCHEMATIC

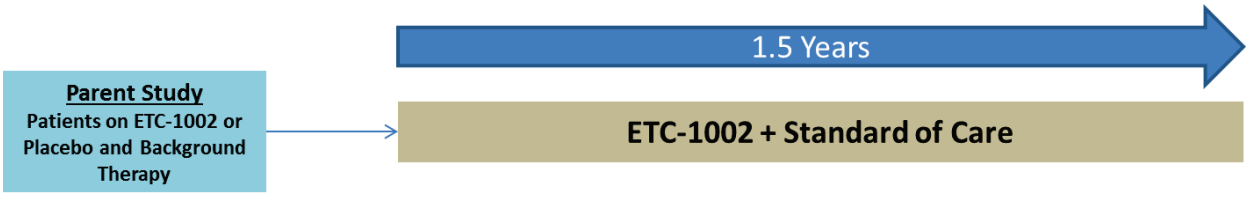
Location:

Section 2, Synopsis; Section 6.1, Overall Study Design

Original Text:



New Text:



CHANGE 3 REVISION OF INCLUSION CRITERIA

Location:

Section 2, Synopsis: Key inclusion criteria; Section 6.7, Patient Inclusion Criteria

Original Text:

1. Successfully completed study ETC-1002-040 (at least 80% investigational medicinal product [IMP]-compliant and able to tolerate IMP at the end of parent study)

New Text:

1. Successfully completed ***the parent study (1002-040) and meet both of the following criteria:***~~ETC-1002-040 (at least 80% investigational medicinal product [IMP]-compliant and able to tolerate IMP at the end of parent study)~~

   - ***The patient was compliant with the parent study requirements including study visits, procedures, and investigational medicinal product (IMP) in the opinion of the principal investigator.***
   - ***The patient was able to tolerate IMP through the end of the parent study.***

CHANGE 4 REVISION OF EXCLUSION CRITERIA

Location:

Section 2, Synopsis: Key exclusion criteria; Section 6.8, Patient Exclusion Criteria

Original Text:

1. Female patient is not willing to use at least 1 highly effective method of birth control during treatment and for an additional 30 days after the end of treatment unless patient is sterilized or postmenopausal;

   - Menopause is defined as greater than 55 years and ≥1 year without menses, less than 55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L, or surgically sterile (including hysterectomy and/or bilateral oophorectomy);
   - Acceptable methods of birth control include: oral birth control medications; placement of an intrauterine device (IUD) with or without hormones; barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly; vasectomized male partner who is the sole partner for this patient; or true abstinence (not including periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, or withdrawal).

New Text:

1. Female patient is not willing to use at least 1 ~~highly effective~~***acceptable*** method of birth control during treatment and for an additional 30 days after the end of treatment unless patient is sterilized or postmenopausal;

   - Menopause is defined as greater than 55 years and ≥1 year without menses, less than 55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L, or surgically sterile (including hysterectomy and/or bilateral oophorectomy);
   - Acceptable methods of birth control include: oral birth control medications; placement of an intrauterine device (IUD) with or without hormones; barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly; vasectomized male partner who is the sole partner for this patient; or true abstinence

where it is the preferred and usual lifestyle of the patient (not including periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, or withdrawal).

Original Text:

5. Renally impaired patients receiving an average daily dose of simvastatin 40 mg with estimated glomerular filtration rate (eGFR) below <45 mL/min/1.73 m^2.

New Text:

~~5. Renally impaired patients receiving an average daily dose of simvastatin 40 mg with estimated glomerular filtration rate (eGFR) below <45 mL/min/1.73 m^2.~~

CHANGE 5 REVISION TO PROHIBITED MEDICATIONS

Location:

Section 7.2.1, Prohibited Medications and Supplements

Original Text:

All medications deemed medically necessary may be prescribed during this study, with the following exceptions:

- Mipomersen
- Lomitapide or apheresis therapy
- Red yeast rice containing products
- Uptitration of simvastatin to an average daily dose that is greater than 40 mg
- Gemfibrozil

New Text:

All medications deemed medically necessary may be prescribed during this study, with the following exceptions:

- Mipomersen
- Lomitapide or apheresis therapy
- Red yeast rice containing products
- Uptitration of simvastatin to ~~an average daily~~***a*** dose that is greater than ***or equal to*** 40 mg***/day***
- Gemfibrozil
- ***Ezetimibe/simvastatin (Zocor®) where simvastatin doses are ≥40 mg/day (Vytorin® 10/40 and 10/80 and Inegy® 10 mg/40 mg and 10 mg/80 mg are prohibited)***

[redacted]

CHANGE 6 REVISION TO BLINDING INSTRUCTIONS

Location:

Section 7.3, Blinding

Original Text:

Laboratory results for lipid panel and hs-CRP will be masked to investigators, patients, and the study team until the Week 12 visit is completed. All site staff involved with this trial should refrain from obtaining lipid panels between date of last ETC-1002-040 dose at end of parent study Week 52 (Visit T7) and Week 12 in this OLE trial.

New Text:

Laboratory results for lipid panel and hs-CRP will be masked to investigators, patients, and the study team until the Week 12 visit is completed. All site staff involved with this trial should refrain from obtaining lipid panels between date of last ETC-1002-040 dose at end of parent study Week 52 (Visit T7) and Week 12 in this OLE trial.

While this is an open-label study where all patients will receive active treatment with bempedoic acid (180 mg by mouth [PO] once daily [QD]), blinding of the treatment that patients received during the parent study must be maintained for all patients unless, in the opinion of the Investigator, the safety of the patient may be at risk. Only under the rarest of circumstances should the Investigator consider breaking the parent study blind and only when medical/supportive care cannot be provided without determining if the patient was previously receiving active drug treatment. In the event that the parent study blind needs to be broken prior to completion of the parent study, the Investigator should contact the appropriate Medical Monitor by telephone. If the parent study 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 interactive web response system (IWRS) utilized in the parent study. In all cases of breaking the parent study blind, the Investigator must document in the patient's medical record the date, time, and reason for breaking the blind, and the names of personnel involved.

CHANGE 7 REVISION TO PROCEDURES AT ENROLLMENT, EOS/DAY 1 OLE

Location:

Section 9.2.1, Enrollment (EOS/Day 1 OLE)

Original Text:

Day 1 for this study should occur on the same day as the end of study visit for the parent study (1002-040). All efforts should be made to avoid delays in rolling over. The study procedures below, from the parent study EOS visit, will be used to qualify for this study. If Day 1 of the OLE study occurs >30 days from the end of study visit from the parent study, all procedures will need to be repeated including taking a new medical history.

- Review of inclusion/exclusion criteria

- Concomitant medication review
- Assess AE/SAEs
- Physical exam
- Weight (kg)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, coagulation (only in patients receiving anticoagulant therapy), and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - ApoB
  - Hs-CRP
  - Glycosylated hemoglobin, Type A_{1C} (HbA_{1C})
- Urine pregnancy test
- Contact IWRS to register the patient
- Dispense study drug

New Text:

Day 1 for this study should occur on the same day as the end of study visit for the parent study (1002-040). All efforts should be made to avoid delays in rolling over. The study procedures below, from the parent study EOS visit, will be used to qualify for this study. If Day 1 of the OLE study occurs >30 days from the end of study visit from the parent study, all procedures will need to be repeated including taking a new medical history.

- Review of inclusion/exclusion criteria
- Concomitant medication review
- Assess AE/SAEs
- Physical exam
- Weight (kg)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, coagulation (only in patients receiving anticoagulant therapy), and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - ApoB

  - Hs-CRP
  - Glycosylated hemoglobin, Type A_{1C} (HbA_{1C})
- Urine pregnancy test
- Contact IWRS to register the patient
- Dispense study drug

Please note the following for patients enrolling into Study 1002-050 within 30 days of completing the EOS visit in the parent study:

- ***If the patient is not receiving anticoagulant therapy and/or is a woman who is not of childbearing potential, clinical laboratory samples do not need to be collected as the results from the parent study EOS visit will be used for this visit.***
- ***If the patient is receiving anticoagulant therapy, then a coagulation laboratory sample is required at this visit using a Study 1002-050 unscheduled laboratory kit.***
- ***If the patient is a woman of childbearing potential, then a urine pregnancy test is required at this visit.***

Please note the following for patients enrolling into Study 1002-050 greater than 30 days after completing the EOS visit in the parent study:

- ***Clinical laboratory samples should be collected using a Study 1002-050 Day 1 kit. Supplies for collecting the coagulation sample are included in this kit.***
- ***If the patient is a woman of childbearing potential, then a urine pregnancy test is required at this visit.***

CHANGE 8 REVISION TO MONITORING AND MANAGEMENT OF ELEVATED CREATINE KINASE

Location:

Section 10.1.4.3.3, Monitoring and Management of Elevated Creatine Kinase

Original Text:

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

Repeat CK assessment will include query for related symptoms.

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

[redacted]

New Text:

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

Repeat CK assessment will include query for related symptoms.

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

CHANGE 9 REVISION TO LIPID MEASUREMENTS

Location:

Section 10.1.4.4.1, Lipid Measurements

Original Text:

Investigators, site staff, patients, and the study team will be masked to study lipid levels as well as ApoB and hs-CRP until the Week 12 study visit, after which time lipid values will be made available and concomitant medications may be adjusted as necessary.

- The initiation of any new or dose changes of any existing lipid-lowering treatment will be documented on the eCRF as a concomitant medication with the associated start date. Uptitration of simvastatin to an average daily dose that is greater than 40 mg is not permitted.

New Text:

Investigators, site staff, patients, and the study team will be masked to study lipid levels as well as ApoB and hs-CRP until the Week 12 study visit, after which time lipid values will be made available and concomitant medications may be adjusted as necessary.

- The initiation of any new or dose changes of any existing lipid-lowering treatment will be documented on the eCRF as a concomitant medication with the associated start date. Uptitration of simvastatin to an average daily dose that is greater than ***or equal to*** 40 mg is not permitted.

CHANGE 10 REVISION TO APPENDIX 1

Location:

Appendix 1: Schedule of Events (Patient Visit Schedule)

Original Text:

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOS[1]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
In-clinic Visit	**X**	**X**			**X**		**X**
Phone Visit			**X**	**X**		**X**	
Procedure							
Informed Consent	X						
Enrollment Criteria	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X
Physical Exam	X				X		X
Weight[2]	X	X			X		X
Vital Signs[3]	X	X			X		X
Urine Pregnancy Test	X						
Clinical Safety Labs[4]	X	X			X		X
Basic Fasting Lipids[5]	X	X			X		X
Coagulation[6]	X						
ApoB and hsCRP	X	X			X		X
HbA_{1C}	X				X		X
IWRS Contact[7]	X	X			X		X
Drug Dispensing	X	X			X		
Drug Return/Compliance		X			X		X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs). For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the

patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit week 78 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

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

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

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

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

[5] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).

[6] Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0

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

New Text:

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOS[1]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
In-clinic Visit	**X**	**X**			**X**		**X**
Phone Visit			**X**	**X**		**X**	
Procedure							
Informed Consent	X						
Enrollment Criteria	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X
Physical Exam	X				X		X
Weight[2]	X	X			X		X
Vital Signs[3]	X	X			X		X
Urine Pregnancy Test[4]	X						
Clinical Safety Labs[4,5]	X	X			X		X
Basic Fasting Lipids[5,6]	X	X			X		X
Coagulation[6,7]	X						
ApoB and hsCRP	X	X			X		X
HbA_{1C}	X				X		X

[redacted]

IWRS Contact[7~~8~~]	X	X			X		X
Drug Dispensing	X	X			X		
Drug Return/ Compliance		X			X		X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), ***and*** vital signs~~, and electrocardiograms (ECGs)~~. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit week 78 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

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

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

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

[4] ***Urine pregnancy test in women of childbearing potential only***

[4~~5~~]Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Please refer to laboratory manual for detailed schedule of tests.

[5~~6~~]Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).

[6~~7~~]Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0

[7~~8~~]Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date

CHANGE 11 REMOVED FINAL DATE

Location:

Appendix 2: Final Date, all pages within Appendix 2 and Appendix 3

Original text:

Final Date: 01 November 2016

New text:

~~Final Date:~~ ~~01 November 2016~~

CHANGE 12 CHANGE IN SPONSOR REPRESENTATIVES PROVIDING PROTOCOL SIGNAGE

Location:

Appendix 2: Sponsor Signatures

Original text:

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

Signed: [redacted] Date: _____

Esperion Therapeutics, Inc.

New Text:

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

Signed: [redacted] Date: _____

Esperion Therapeutics, Inc.

~~**Study Title:**~~ ~~A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg~~

~~**Study Number:**~~ ~~1002-050~~

~~**Final Date:**~~ ~~01 November 2016~~

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

~~Signed:~~ _____ ~~Date:~~ _____

[redacted]

~~Esperion Therapeutics, Inc.~~

APPENDIX 5. SUMMARY OF CHANGES IN AMENDMENT 2

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002-050
Study Title:	A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg
Protocol Version Incorporating Current Summary of Changes:	Amendment 2: 15 Jan 2018
Preceding Protocol Version:	Amendment 1: 09 May 2017
Investigational Product Name:	ETC-1002

Conventions used in this Summary of Changes Document

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

Summary and Justification of Changes

The protocol was amended for the following:

- Updated contact details for Sponsor Contact and Medical Monitor
- Added a line for Amendment 2 version and date to reflect amendment version details.
- Revised the study design to include an assessment at Week 82, 4 weeks after patients have completed their last dose of bempedoic acid. This assessment was added to have safety and efficacy data off study drug to help interpret any potential findings during the treatment period.
- Updated the design schematic to include the 4-week follow-up period from Week 78 to Week 82.
- Week 78 is now called the End of Treatment (EOT) visit and Week 82 is described as the Off Study Drug Period/End of Study (EOS) visit.
- The section on Background of Bempedoic Acid has been updated to reflect the current version of the Investigator's Brochure.

- The section on Concomitant Medications has been revised to avoid changes in lipid-lowering medications during the 4-week washout period to limit the introduction of medications that may affect endpoints of interest measured at Week 82.
- The statistical analysis plan for renal events was updated to remove text that indicated muscle related events would be analyzed based on baseline eGFR. There is no data or clinical justification to justify assessment of muscle related events by eGFR.
- Text throughout the protocol was updated to reflect the addition of the 4-week follow-up period.
- Typographical errors and formatting were corrected or revised based on these changes or to improve clarity and consistency.

CHANGE 1 REVISION OF TITLE PAGE VERSION INFORMATION

Location:

Title Page

Original Text:

Sponsor Contact: [redacted]

Medical Monitor:

New Text:

Sponsor Contact: [redacted]

Medical Monitor:

Original Text:

	Version	Date
	Original Protocol:	01 November 2017
	Amendment 1:	9 May 2017

New Text:

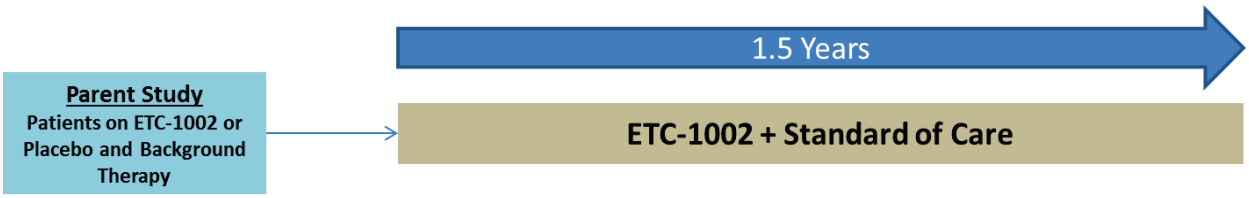
	Version	Date
	Original Protocol:	01 November 2017
	Amendment 1:	09 May 2017
	Amendment 2:	***15 January 2018***

CHANGE 2 REVISION TO THE STUDY DESIGN TO INCLUDE A 4 WEEK FOLLOW UP PERIOD AFTER WEEK 78

Location:

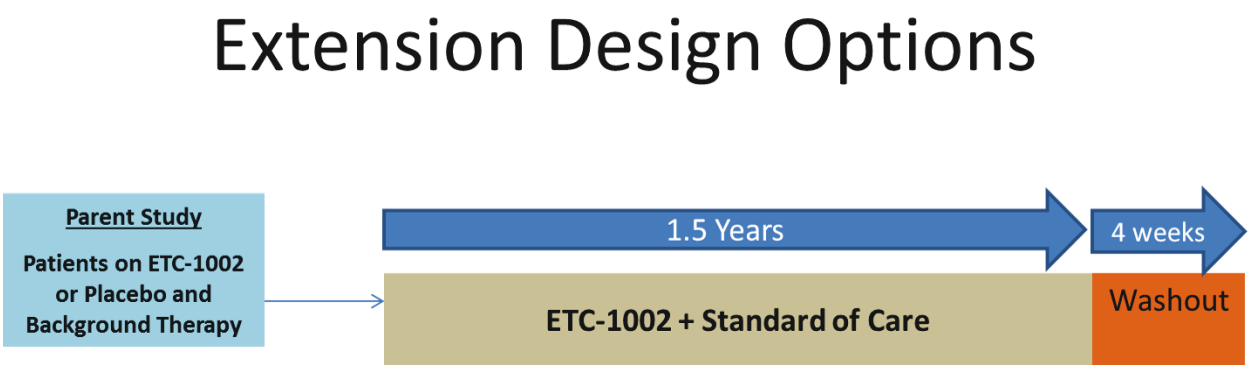
Section 2, Synopsis; Section 6.1, Overall Study Design; Section 6.3, Study Duration; Section 6.4, End of Study; Section 9.2.6, Treatment Month 18; Section 9.2.7, Washout Month 19; Section 9.3.1, Early Withdrawal from the Study; Section 9.3.2, Procedures for Early Withdrawal

Original Text:



This is a multicenter OLE study designed to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from the parent study (Study 1002-040). Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available.

New Text:



This is a multicenter OLE study designed to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from the parent study (Study 1002-040) ***followed by a follow-up period off study drug for 4 weeks***. Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available.

Original Text:

Duration of treatment:

The total duration of treatment for an individual subject will be 1.5 years.

[redacted]

New Text:

Duration of treatment:

The total duration of treatment for an individual subject will be 1.5 years ***(18 months). The total duration in the study will be 19 months.***

Original Text:

This is a multicenter open-label extension (OLE) study designed to assess the long-term safety and efficacy of bempedoic acid 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from Study 1002-040 (parent study). Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available to sites. The study will be conducted at approximately 125 clinical sites in the US, Canada, Germany, Netherlands, Poland, and United Kingdom. It's anticipated that approximately 1300 patients will elect to enroll into this study. Patients will have visits every 3 months. Patients will be required to visit the site at baseline (end of study [EOS] parent), Week 12, Week 52, and Week 78. Phone visits will occur at Weeks 24, 36, and 64.

New Text:

This is a multicenter open-label extension (OLE) study designed to assess the long-term safety and efficacy of bempedoic acid 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from Study 1002-040 (parent study) ***followed by a period off study drug for 4 weeks.*** Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available to sites. The study will be conducted at approximately 125 clinical sites in the US, Canada, Germany, Netherlands, Poland, and United Kingdom. It's anticipated that approximately 1300 patients will elect to enroll into this study. Patients will have visits every 3 months. Patients will be required to visit the site at baseline (end of study [EOS] parent), Week 12, Week 52, ***Week 78,*** and Week ~~78~~***82***. Phone visits will occur at Weeks 24, 36, and 64.

Original Text:

Patients will be enrolled after successfully completing study ETC-1002-040. The total study duration for an individual subject is 1.5 years.

New Text:

Patients will be enrolled after successfully completing study ETC-1002-040. The total study duration for an individual subject is ~~1.5 years~~ ***82 weeks (1 year and 7 months).***

[redacted]

Original Text:

The study will end when the last patient completes their Week 78 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 2.5 years.

New Text:

The study will end when the last patient completes their Week ~~78~~***82*** visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 2.5 years.

Original Text:

9.2.6 Treatment Month 18/EOS (Week 78 ±7days)

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

- Concomitant and medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
  - ApoB and hs-CRP
  - HbA_{1C}
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study).

New Text:

9.2.6 Treatment Month 18/EO~~S~~***T*** (Week 78 ±7days)

Patients will undergo the following assessments and procedures when completing the End of ~~Study (EOS)~~ ***End of Treatment (EOT)*** visit, withdrawing from study ***prior to Week 78*** (early withdrawal), or withdrawing from IMP treatment:

- Concomitant ~~and~~ medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight

[redacted]

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

New Section/Text:

9.2.7 Off Study Drug Period Month 19/EOS (Week 82 +14 days)

Patients will return for a final EOS visit 4 weeks after IMP treatment has been completed (including patients who withdraw from IMP treatment prior to Week 78) to undergo the following assessments and procedures.

- ***Concomitant medication review***
- ***Assess AEs, SAEs, and potential clinical endpoints***
- ***Weight***
- ***Vital signs***
- ***Clinical laboratory evaluations:***
  - ***hematology, blood chemistry, and urinalysis***
  - ***Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)***
  - ***ApoB and hs-CRP***
  - ***HbA_{1C}***

Original Text:

Patients must remain in the study until the last scheduled visit at Month 18 (Week 78) to be considered as having completed participation of the study.

New Text:

Patients must remain in the study until the last scheduled visit at Month ***19 (Week 82) to be considered as having completed participation in the study. Patients must remain in the study***

through Month 18 (Week 78) to be considered as having completed participation ***in the treatment portion*** of the study.

Original Text:

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

Patients choosing to withdraw from the study early should be encouraged to return for all study scheduled clinic visit even if they are no longer taking IMP. Patients who withdraw from all aspects of the study will be asked to consent to clinical visits or phone calls for safety assessments, including AEs, concomitant medication, and current health status through Month 18 (Week 78).

New Text:

If a patient withdraws or is removed from the study for any reason ***prior to Week 78***, all ***EOT***~~EOS~~ procedures should be completed. ***In addition, the patient should return 4 weeks after last dose of IMP for the Week 82/EOS procedures.*** Reason for withdrawal, date of the discontinuation, and date of the last dose of study drug should be recorded in the appropriate section of the eCRF. Additionally, the discontinuation visit date must be registered in IWRS. Study drug assigned to the withdrawn patient may not be assigned to another patient.

…

Patients choosing to withdraw from the study early should be encouraged to return for all study scheduled clinic visit even if they are no longer taking IMP. Patients who withdraw from all aspects of the study will be asked to consent to clinical visits or phone calls for safety assessments, including AEs, concomitant medication, and current health status through Month ~~18~~***19 (Week 82)***.

[redacted]

Original Text:

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOS[1]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
In-clinic Visit	**X**	**X**			**X**		**X**
Phone Visit			**X**	**X**		**X**	
Procedure							
Informed Consent	X						
Enrollment Criteria	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X
Physical Exam	X				X		X
Weight[2]	X	X			X		X
Vital Signs[3]	X	X			X		X
Urine Pregnancy Test[4]	X						
Clinical Safety Labs[4,5]	X	X			X		X
Basic Fasting Lipids[5,6]	X	X			X		X
Coagulation[6,7]	X						
ApoB and hsCRP	X	X			X		X
HbA_{1C}	X				X		X
IWRS Contact[7,8]	X	X			X		X
Drug Dispensing	X	X			X		
Drug Return/ Compliance		X			X		X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), and vital signs. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit week 78 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

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

[redacted]

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

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

[4] Urine pregnancy test in women of childbearing potential only

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

[6] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).

[7] Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0

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

[redacted]

New Text:

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOT~~S~~[1]**	***20/EOS[2]***
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**	***Wk 82***
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	***+14 days***
In-clinic Visit	**X**	**X**			**X**		**X**	***X***
Phone Visit			**X**	**X**		**X**		
Procedure								
Informed Consent	X							
Enrollment Criteria	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	***X***
Adverse Event Recording	X	X	X	X	X	X	X	***X***
Physical Exam	X				X		X	
Weight[2~~3~~]	X	X			X		X	***X***
Vital Signs[3~~4~~]	X	X			X		X	***X***
Urine Pregnancy Test[4~~5~~]	X							
Clinical Safety Labs[5~~6~~]	X	X			X		X	***X***
Basic Fasting Lipids[6~~7~~]	X	X			X		X	***X***
Coagulation[7~~8~~]	X							
ApoB and hsCRP	X	X			X		X	***X***
HbA_{1C}	X				X		X	***X***
IWRS Contact[8~~9~~]	X	X			X		X	
Drug Dispensing	X	X			X			
Drug Return/ Compliance		X			X		X	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), and vital signs. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit Week 78***/End of Treatment (EOT)*** will be ~~considered the End of Study (EOS)/Early Withdrawal from study~~ ***scheduled as soon as possible and the patient will be asked to come back 4 weeks after last investigational medicinal product (IMP) dose for Visit Week 82/End of Study (EOS).*** ~~And no~~***No*** further visits will be scheduled.

[1] All procedures will be completed for all-patients at either ***EOT*** ~~EOS if completing the study~~ or early withdrawal

[redacted]

[2] ***All procedures will be completed for all patients 4 weeks after last IMP dose if completing the study or early withdrawal.***

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

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

[45] Urine pregnancy test in women of childbearing potential only

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

[67] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).

[78] Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0

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

CHANGE 3 REVISION OF BACKGROUND OF BEMPEDOIC ACID

Location:

Section 4.2.3, Previous Human Experience

[redacted]

…

[redacted]

[redacted]

CHANGE 4 REVISION OF CONCOMITANT MEDICATIONS

Location:

Section 7.2, Concomitant Medications

Original Text:

During the study investigators may prescribe any necessary concomitant medication. However, lipid-altering therapies cannot be adjusted during the first 12 weeks of the study.

New Text:

During the study investigators may prescribe any necessary concomitant medication. However, lipid-altering therapies cannot be adjusted during the first 12 weeks of the study. ***In addition, during the 4-week period after last dose, every effort should be made to maintain the patients' lipid-modifying therapy unless it is medically necessary to safely manage the patient.***

CHANGE 5 REMOVAL OF TEXT AROUND ANALYSIS OF MUSCLE EVENTS BY eGFR

Location:

Section 12.6 Other Endpoints, Renal Events

Original Text:

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

New Text:

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

summarized by baseline eGFR category. ~~Finally, muscle-related AEs will be summarized by baseline eGFR category.~~