



ETC-1002

1002-040

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED,
MULTICENTER LONG-TERM SAFETY AND TOLERABILITY STUDY
OF ETC-1002 IN PATIENTS WITH HYPERLIPIDEMIA AT HIGH
CARDIOVASCULAR RISK WHO ARE NOT ADEQUATELY
CONTROLLED BY THEIR LIPID-MODIFYING THERAPY**

Study Phase: 3
IND Number: 106,654
EudraCT Number: 2015-004136-36
Indication: Treatment of hyperlipidemia
Investigators: Approximately 125 sites located in the United States, Canada, Germany, Netherlands, Poland, United Kingdom
Sponsor: Esperion Therapeutics, Inc.
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Sponsor Contact:

Medical Monitor:

Version	Date
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Amendment 5	10 May 2017

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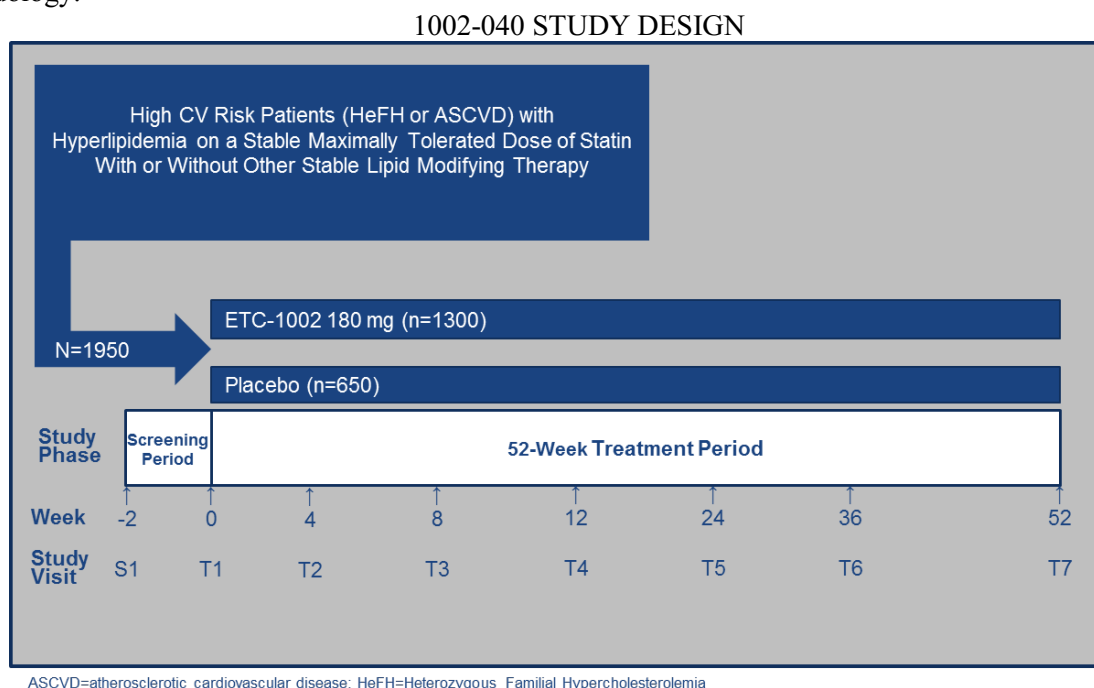
NCT number: NCT02666664

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2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.
Name of Investigational Product: ETC-1002 film-coated tablets
Name of Active Ingredient: ETC-1002 (bempedoic acid)
Title of Study: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy
Study Number: 1002-040
Phase of Development: 3
Clinical Sites: Approximately 125 sites located in the United States, Canada, Germany, Netherlands, Poland, United Kingdom
Objectives: Primary <i>Safety</i> : <ul style="list-style-type: none"> To evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular diseases [ASCVD]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy Secondary <i>Efficacy</i> : <ul style="list-style-type: none"> To assess percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL-C) Tertiary <i>Efficacy</i> : <ul style="list-style-type: none"> To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and triglycerides (TG) values at Week 12, 24, and 52 To assess apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hs-CRP) values at Week 12, 24, and 52
Study Hypothesis: The primary clinical hypothesis is that long-term exposure of ETC-1002 will be safe and well tolerated in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy, including a maximally tolerated statin. The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = 1950) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option.

Methodology:



Study Design:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil]). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, patients *who are currently taking simvastatin at average daily doses that are greater than 40 mg per day or who are currently taking a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from enrolling in this study. PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in [Section 11.1.6.3.5](#).*

Screening (Visit S1) will occur approximately 2 weeks prior to Day 1 (Visit T1). Patients on maximally tolerated lipid-lowering therapy, as determined by the investigator, will be stratified based on the patient's CV risk and baseline statin dose. There will be no cap placed on randomization into any particular stratum. Approximately 1950 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either ETC-1002 180 mg (n = 1300), or placebo (n = 650) once daily for 52 weeks. Randomized patients will continue in the study until they have completed Week 52 (Visit T7). Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), Week 12 (Visit T4), Week 24 (Visit T5), Week 36 (Visit T6), and Week 52 (Visit T7). 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 *and procedures*. 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 ETC-1002. *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), non-coronary 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.
Number of patients (planned): Approximately 1950 adult male and female patients
Duration of treatment: Fifty-two weeks
End of Study: The study will end when the last randomized patient completes <i>their last study visit</i> . The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 28 months.
<p>Diagnosis and criteria for patient eligibility:</p> <p>The study will enroll adult male and female patients with hyperlipidemia</p> <p><i>Each patient must meet the following criteria to be eligible for this study:</i></p> <p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> • Provision of written informed consent prior to any study-specific procedure • Age ≥ 18 years or legal age of majority depending on regional law, whichever is greater at Week -2 (Visit S1) • Men and nonpregnant, nonlactating women. Women must be either: <ul style="list-style-type: none"> - Naturally postmenopausal (as reported by the patient, 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, bilateral oophorectomy, or tubal ligation or; - Women of childbearing potential must be willing to use 1 acceptable method of birth control. The minimal requirement for adequate contraception is that it should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include: 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). - There are no protocol-specific birth control requirements for men with partners who are able to become pregnant. • Fasting LDL-C value at Week -2 (Visit S1) ≥ 70 mg/dL (1.8 mmol/L) <i>Note: LDL-C may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat LDL-C, the mean of the first value and the repeat value will be used to determine eligibility.</i> • Have high cardiovascular risk that is defined as either: <ul style="list-style-type: none"> - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not have established coronary heart disease (CHD) or CHD risk equivalents. <p>OR</p>

- Have ASCVD (with established CHD or CHD risk equivalents)
Documented history of CHD (includes 1 or more of the following):
 - Acute MI
 - Silent MI
 - Unstable angina
 - Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)
 - Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging)Documented CHD risk equivalents (includes 1 or more of the following criteria):
 - Peripheral arterial disease
 - Previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease
 - Be on maximally tolerated lipid-modifying therapy, including a *maximally tolerated statin either alone or in combination with other lipid-lowering therapies*, at stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; *however, gemfibrozil is not allowed*). Regimens other than daily dosing, including those at very low doses, are acceptable.
A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.
Patients currently taking an average daily dose of simvastatin that is greater than 40 mg will be excluded from this study.
Patients who are currently taking a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.
- Exclusion Criteria:
- Total fasting triglyceride ≥ 500 mg/dL (5.6 mmol/L) at Week -2 (Visit S1)
Note: TG may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG, the mean of the first value and the repeat value will be used to determine eligibility.
 - Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) < 30 mL/min/1.73 m² at Week -2 (Visit S1) [1].
Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.
Note: Also excluded are renally impaired patients receiving an average daily dose of simvastatin 40 mg with eGFR below < 45 mL/min/1.73 m².
 - Body mass index (BMI) ≥ 50 kg/m²
 - Concomitant use of simvastatin at average daily doses greater than 40 mg.
 - Concomitant use of a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) at Week -2 (Visit S1) or prior use of a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.
Note: Patients are allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the

LDL-C threshold criteria have been met as described in [Section 11.1.6.3.5](#).

- *Recent (within 3 months prior to the screening visit [Week -2 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.*
- *Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥ 160 mmHg and diastolic blood pressure (DBP) ≥ 100 mmHg after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the Investigator, the screening period may be extended up to 2 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria*
- *Hemoglobin A_{1C} (HbA_{1C}) $\geq 10\%$ at Week -2 (Visit S1)*
- *Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $> 1.5 \times$ the upper limit of normal (ULN) at Week -2 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.*
- *Liver disease or dysfunction, including:*
 - *Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or*
 - *Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 2 \times$ ULN, and/or total bilirubin (TB) $\geq 1.2 \times$ ULN at Week -2 (Visit S1).*

Note: If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease. Patients without active disease may be enrolled in the study.

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.

If TB $\geq 1.2 \times$ ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if the results are consistent with Gilbert's disease, the patient may be enrolled in the study.
- *Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption*
- *Hematologic or coagulation disorders or a hemoglobin (Hgb) level < 10.0 g/dL (100 g/L) at Week -2 (Visit S1)*
- *Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Patients with a history of nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed.*
- *Unexplained creatine kinase (CK) $> 3 \times$ ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK $\leq 3 \times$ ULN prior to randomization.*
- *History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care*

<p><i>practitioner can be enrolled after evaluation by the Investigator.</i></p> <ul style="list-style-type: none"> • <i>Blood donation, blood transfusion for any reason, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization</i> • <i>Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer</i> • <i>Prior participation in a previous ETC-1002 clinical study. Prior participation in a clinical study with ETC-1002 is defined as having been enrolled in an ETC-1002 study.</i> • <i>Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study;</i> • <i>New or planned dose changes of systemic corticosteroids</i> • <i>Requirement for mipomersen or lomitapide or apheresis therapy</i> • <i>Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:</i> <ul style="list-style-type: none"> - <i>Hormone replacement (6 weeks prior to randomization)</i> - <i>Thyroid replacement (6 weeks prior to randomization)</i> - <i>Diabetes medications (4 weeks prior to randomization)</i> - <i>Obesity medication (3 months prior to randomization)</i> • <i>An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.</i>
<p>IMP, dosage and mode of administration:</p> <ul style="list-style-type: none"> • ETC-1002 180-mg tablets. • Matching placebo tablets • All IMP will be ingested once daily (<i>once every 24 hours, at approximately the same time each day</i>) with or without food. <p>Non-investigational medicinal product(s) (NIMP), dosage and mode of administration:</p> <ul style="list-style-type: none"> • Background lipid-lowering therapy including maximally tolerated statins • All background lipid-lowering therapy will be ingested as prescribed by a physician
<p>Criteria for evaluation:</p> <p><u>Safety Assessments:</u></p> <p>Adverse events (AEs) and SAEs will be collected and reported. <i>Clinical endpoints</i> will be collected and adjudicated by an independent CEC. <i>Clinical endpoints will also be reported as SAEs.</i> Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, coagulation, HbA_{1C}, glucose, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram [ECG] readings, and weight.</p> <p><u>Clinical Laboratory Assessments:</u></p> <ul style="list-style-type: none"> • Hematology: Hematocrit (Hct), Hgb, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute values only) • Urinalysis (Dipstick): Clarity, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen • Urinalysis (Microscopic): Obtain centrally only if positive urine dipstick; bacteria, casts, crystals, epithelial cells, RBC, and WBC • Coagulation: Prothrombin time (PT),

- Serum Chemistry (fasting): Albumin (ALB), alkaline phosphatase (ALK-P), ALT (or serum glutamic pyruvic transaminase [SGPT]), AST (or serum glutamic oxaloacetic transaminase [SGOT]), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO₂), chloride (Cl), creatinine, CK, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid
- HbA_{1c}

Other Screening Laboratories:

- Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) (*if HCV is positive, a reflex HCV RNA will be performed to rule out active disease*), serum pregnancy test (only for females who are of childbearing potential), FSH (*only for females who are <55 years old and >1 year without menses*), urine pregnancy test Day 1 prior to randomization (*only for females who are of childbearing potential*), TSH

Lipid Assessments:

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

Other Biomarkers:

- hs-CRP
- Reserve 10 mL blood samples for potential future measurement of ETC-1002 biomarkers. *Based upon Sponsor assessment and decision, reserve sample collection will be discontinued after a sufficient number of samples have been collected.*

Other Assessments:

- Trough plasma concentrations of ETC-1002 and its metabolite ESP15228 will be collected at Weeks 12, 24, and 52.
- All patients will be invited to provide a blood sample for potential future genetic testing, but participation in this portion of the study is optional and where approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and by local law.

Safety and Monitoring:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin at doses of ≥ 40 mg/day and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits ([Appendix 1](#)).
 - The initiation of any new or dose changes of any lipid-lowering treatment will be

documented on the electronic case report form (eCRF) as a concomitant medication with the associated start date

- *Patients who have their lipid-lowering treatments modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine safety laboratory assessment. Additional safety laboratory assessments may be conducted at the investigator's discretion. Patients receiving an average daily dose of simvastatin 40 mg based on lipid-lowering treatment modification, should adhere to the additional safety visits as described in [Sections 10.2.5 and 10.2.6](#).*
- Adjunctive therapy medications will not be provided by the sponsor
- Patients continuing to exceed the LDL-C threshold after maximizing the standard-of-care LDL-C-lowering therapy and, in the opinion of the investigator, require therapies that are prohibited by the protocol will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

Elevated Triglycerides:

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds 1000 mg/dL (11.3 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >1000 mg/dL (11.3 mmol/L), will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value meets the threshold criteria
- Any patient with a confirmed TG >1000 mg/dL (11.3 mmol/L) may initiate standard-of-care therapy (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.
- Patients continuing to exceed the TG threshold after maximizing the standard-of-care triglyceride-lowering therapy will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

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

Adverse Events Associated with Experience with ETC-1002 to Date:

Small group mean increases in uric acid and homocysteine, and decreases in hemoglobin have been observed, but in general, these shifts have not been associated with clinical symptoms. Clinical labs and hematology will be monitored throughout the study.

Potential AEs:

Based on findings in nonclinical models, potential AEs include reversible hypoglycemia and metabolic acidosis. *Patients will be educated on the signs and symptoms of hypoglycemia and instructed to report the signs and symptoms they experienced to the investigator. Investigator confirmed occurrences of hypoglycemia will be reported as AEs.* 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.

Diabetes and Hyperglycemia:

Cases of new onset of diabetes will be recorded as AEs. Clinical laboratories, including HbA_{1C}, and glucose will also be evaluated across treatment groups during this study and all ongoing studies to identify potential cases of new onset of diabetes.

Clinical Endpoints:

Clinical endpoints will be monitored and adjudicated by an independent expert CEC for this study and other ongoing studies in the ETC-1002 program.

Routine cardiovascular monitoring will include review of cardiovascular AEs, SAEs, (both as adjudicated by the CEC), standard vital signs, and ECGs

Neurocognitive Events:

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs.

Additional details regarding safety monitoring are included in [Section 11.1.6.3.1](#) through [Section 11.1.6.4](#).

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

Statistical methods:

Sample Size

A total of 1950 patients will be enrolled in this study with 1300 patients randomized to ETC-1002 and 650 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥6 Months</i>	<i>Patients ≥12 Months</i>
<i>ETC-1002</i>	<i>1,202</i>	<i>1,170</i>
<i>Placebo</i>	<i>601</i>	<i>585</i>

*Absolute risk will be addressed by 1300 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled *Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events* [2]. In this study, adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.*

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of 1300 patients randomized to ETC-1002 and 650 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits:

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
<i>0.5%</i>	<i>0.5%</i>	<i>1.0</i>	<i>(0.3, 3.8)</i>
<i>0.5%</i>	<i>1.0%</i>	<i>2.0</i>	<i>(0.6, 6.7)</i>
<i>13.6%</i>	<i>13.6%</i>	<i>1.0</i>	<i>(0.8, 1.3)</i>
<i>13.6%</i>	<i>27.2%</i>	<i>2.0</i>	<i>(1.6, 2.5)</i>

Analysis Populations

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

The Full Analysis Set (FAS), used for *the LDL-C analyses and the* lipid and cardiometabolic summaries, is defined as all randomized patients and is also known as the intention-to-treat (ITT) set of patients.

Disposition and Baseline Characteristics

Disposition, including reason for withdrawal from the study, will be summarized by treatment group.

Demographic information and patient characteristics including, but not limited to, gender, race, age, and baseline vital signs will also be summarized by treatment group.

Primary Safety Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

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

Hepatic Safety

Liver-associated enzymes and TB will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST, and TB. Hy's law criteria ($\geq 3 \times \text{ULN}$ for either ALT or AST, with accompanying TB $> 2 \times \text{ULN}$) 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 $2 \times \text{ULN}$ will be based upon direct (conjugated) bilirubin.*

Musculoskeletal Safety

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

Diabetes and Glycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group. Glucose and HbA_{1C} will be monitored at baseline and at Weeks 12, 24, and 52, and be summarized.

Renal Safety

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

Clinical Endpoints

Clinical endpoints will be monitored and adjudicated by an independent blinded expert CEC for ongoing studies the ETC-1002 program. Adjudicated *clinical endpoints* will be summarized by event type and treatment group. Additional details regarding *clinical endpoints* and *clinical endpoint* definitions will be included in CEC charter.

Neurocognitive Events

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

Key Efficacy Endpoints

Percent change from baseline to Week 12 or Week 24 in LDL-C, non-HDL-C, TC, apoB, and hs-CRP will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors and respective baseline value as a covariate. The FAS will be used. Missing data for these endpoints will be imputed using multiple imputation taking account for treatment adherence.

Other Efficacy Endpoints

LDL-C, HDL-C, TG, TC, non-HDL-C, hs-CRP, and apoB values at other time points will be summarized and analyzed similarly to the key lipid endpoints. In addition, a summary using the FAS, excluding patients who received additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 time point; by Week 52 for the Week 52 time point), will be provided. For both summaries, only observed case data will be used (no imputation for missing data).

Additional post-randomization adjunctive lipid-modifying therapy

The number and percent of patients in each treatment group requiring additional (post-randomization) adjunctive lipid-modifying therapy will be summarized. Medications and the reasons for their additional treatment (hyperlipidemia vs. hypertriglyceridemia) will be summarized separately.

PK and Other biomarkers

Trough plasma concentrations will be collected at Weeks 12, 24, and 52 from patients randomized into the study prior to the implementation of Protocol Amendment 3 for use in further developing the population pharmacokinetic (PK) model. Trough plasma concentrations will not be collected from patients randomized into the study after the implementation of Protocol Amendment 3.

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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
ACS	Acyl-CoA synthetase
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
<i>ANCOVA</i>	<i>Analysis of covariance</i>
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
CABG	Coronary artery bypass graft
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Coronary heart disease
<i>CI</i>	<i>Confidence interval</i>
CK	Creatine kinase
Cl	Chloride
C _{max}	Time to peak maximum concentrations
CMV	Cytomegalovirus
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO ₂	Carbon dioxide

Abbreviation or Specialist Term	Explanation
CPK	<i>creatine phosphokinase</i>
CT	Computed tomography
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
eGFR	Estimated glomerular filtration rate
EOS	<i>End of Study</i>
EU	European Union
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA _{1c}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-AB	Hepatitis C antibodies
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
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
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
<i>LSM</i>	<i>Least square mean</i>
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
MED ID	Medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
NIMP	Non-investigational medicinal product(s)
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
<i>PMM</i>	<i>Pattern mixed model</i>
PT	Prothrombin time
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
<i>SE</i>	<i>Standard error</i>

Abbreviation or Specialist Term	Explanation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SOP	Standard operating procedures
SP	Safety population
<i>SUSARS</i>	<i>Suspected and unexpected serious adverse reactions</i>
$t_{1/2}$	Terminal elimination half-life
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
TQT	Thorough QT/QTc
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

4.1. Lipid-Regulating Drugs and Cardiovascular Disease

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

Hyperlipidemic patients at high cardiovascular 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 [3]. Despite aggressive interventional and pharmacologic therapies, cardiovascular disease is the number 1 cause of death globally [4]. An estimated 17.5 million people died from cardiovascular diseases in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke [4]. 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 (15 616.1 million deaths) were caused by cardiovascular disease in 2010, more than all communicable, maternal, neonatal and nutritional disorders combined, and double the number of deaths caused by cancers [5]. In the United States, based on 2011 death rate data, more than 2150 Americans die from cardiovascular diseases daily, an average of 1 death every 40 seconds. Approximately 155, 000 Americans dying from cardiovascular disease are less than 65 years of age. In 2011, 34% of deaths due to cardiovascular disease occurred prior to the age of 75 years, less than the current 78.7-year average life expectancy [6].

Patients with documented ASCVD are at very high risk for events and require intensive pharmacologic intervention [7]. 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 [8].

Familial hypercholesterolemia refers to individuals with extremely elevated LDL-C due to underlying genetic mutations of the LDL receptor, apolipoprotein B (apoB), and proprotein convertase subtilisin/kexin type 9 (PCSK9) [9]. 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 [10]. Patients with HeFH inherit a genetic mutation from 1 parent. Inheritance is generally via an autosomal-dominant mechanism [11]. HeFH increases the risk of atherosclerosis leading to cardiovascular events. The mean age for the onset of cardiovascular disease is relatively young, at 42 to 46 years in men and 51 to 52 years in women [11]. 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 [12]. The National Lipid Association (NLA) recommends achievement of $\geq 50\%$ reduction in LDL-C in *adult patients* using statins. HeFH patients at even higher risk for cardiovascular 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 [13]. LDL-C is largely accepted as a valid surrogate endpoint of cardiovascular events by clinicians and regulatory authorities [7]. 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 [14]. Evidence supporting LDL-C as a therapeutic target and surrogate for cardiovascular 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 cardiovascular risk reduction, independent of the way LDL-C lowering was achieved based on mechanism of action [15,16,17,18]. A published patient-level meta-analysis including 26 trials and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and cardiovascular outcomes [16]. 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 cardiovascular risk [19]. Unfortunately, some patients are unable to take high intensity statins due to dosing limits based on co-morbidities, contraindications, and/or tolerance [8]. Nonstatin therapies may provide additional lowering of cardiovascular risk as demonstrated in the IMPROVE-IT trial *which added* ezetimibe to statin therapy [20].

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. ETC-1002 may offer a once daily option for these patients. The oral route of administration may be preferable to injectable biologic therapy for some patients. ETC-1002 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 ETC-1002

4.2.1. Mechanism of Action

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

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

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.2.4. Dose Selection

[REDACTED]

4.2.5. Background Therapy

ETC-1002 in this study is currently being evaluated as an add-on to statin therapy in high-risk patients (ie, those with HeFH *and/or* ASCVD) who have not achieved their LDL-C goal despite maximally tolerated statin therapy.

4.2.6. Risk Benefit Summary

To date, the nonclinical and clinical data indicate that ETC-1002 has a favorable risk-benefit profile. The ability of ETC-1002 to achieve clinically meaningful LDL-C-lowering responses while demonstrating a favorable tolerability profile in a variety of patient populations supports continued development of ETC-1002, 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. Primary *Safety* Objective

The primary objective is to evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

5.2. Secondary *Efficacy* Objectives

- *To assess percent change from baseline to Week 12 in LDL-C*

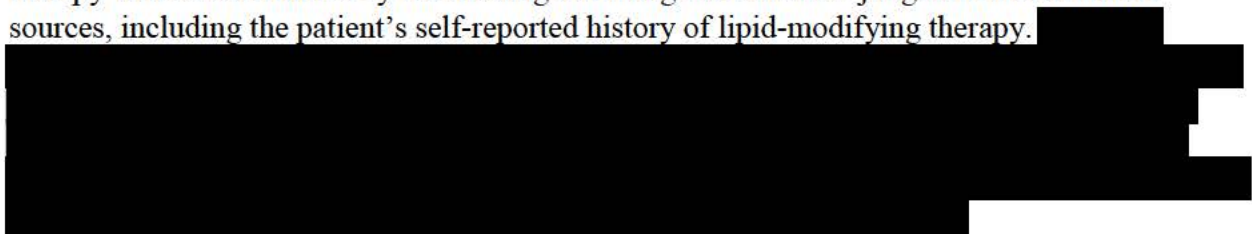
5.3. Tertiary *Efficacy* Objectives

- *To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy*
- *To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and TG at Weeks 12, 24, and 52*
- *To assess apoB and high-sensitivity C-reactive protein (hs-CRP) at Weeks 12, 24, and 52*

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil]). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.



The study will be conducted at approximately 125 clinical sites in United States, Canada, Germany, Netherlands, Poland, and United Kingdom.

Screening (Visit S1) will occur approximately 2 weeks prior to Day 1 (Visit T1). Patients on maximally tolerated lipid-lowering therapy, as determined by the investigator, will be stratified based on CV risk (HeFH and ASCVD diagnosis) and baseline statin dose category (see [Table 2](#)). Patients will be randomized into 1 of the 6 strata (see [Table 3](#)).

Statin dose categories, *based on average daily dose*, and randomization strata are defined in the [Table 2](#) and [Table 3](#) below, respectively:

Table 2: Baseline Statin Dose Categories

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins ^a
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 ^b mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

^a Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)




Table 3: Randomization Strata

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH+ Low Intensity Statins	ASCVD + Low Intensity Statins
HeFH+ Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH+ High Intensity Statins ^a	ASCVD + High Intensity Statins ^a

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

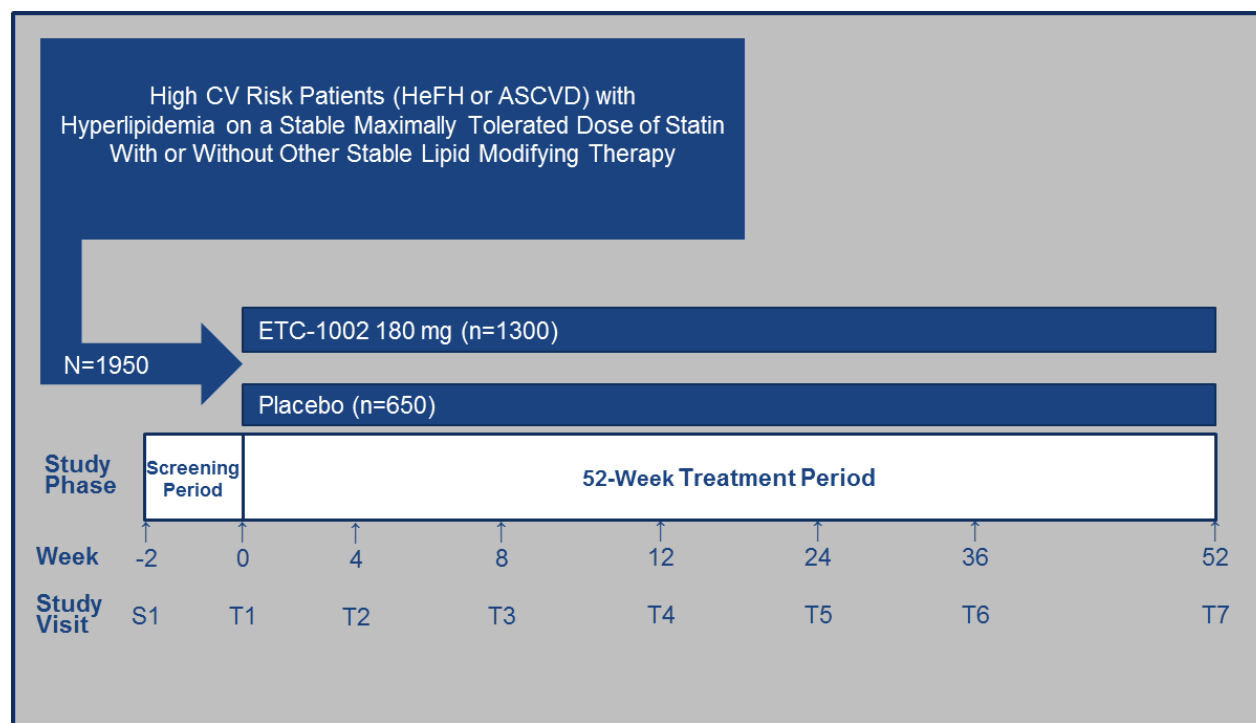
^a Simvastatin *with doses* ≥ 40 mg/day are not allowed in this study.

There will be no cap placed on randomization into any particular stratum. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), Week 12 (Visit T4), Week 24 (Visit T5), Week 36 (Visit T6), and Week 52 (Visit T7). 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 ETC-1002. All *clinical endpoints*, including *all major 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), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE)*, will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions. *Any clinical endpoints that meet SAE criteria* will be reported as SAEs

Figure 1. Study 1002-040 Study Design



ASCVD=atherosclerotic cardiovascular disease; HeFH=Heterozygous Familial Hypercholesterolemia

6.2. Study Hypothesis

The primary clinical hypothesis is that long-term exposure of ETC-1002 will be safe and well tolerated in high CV risk patients with hyperlipidemia (patients with underlying HeFH *and/or* ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy, including a maximally tolerated statin.

The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin *alone or in combination with other lipid-lowering therapies*, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number ($n = 1950$) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option.

6.3. Study Duration and Period

The expected total duration of study participation for each randomized patient is approximately 54 weeks. This duration includes a 2-week screening period and a 52-week treatment period.

6.4. End of Study

The study will end when the last randomized patient completes *their last study visit* (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 28 months.

6.5. Number of Patients

The study will enroll approximately 1950 adult male and female HeFH and/or ASCVD patients with hyperlipidemia from approximately 125 clinical sites.

6.6. Patient Identification Numbers

A unique patient identification number will be assigned to each patient to identify each patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, their patient identification number cannot be assigned to another patient.

Patient identification numbers will be assigned sequentially by interactive web response system (IWRS) at the time of informed consent during the screening module transaction. The patient numbers will be an 8-digit patient unique number that is comprised of protocol, site, and patient-specific numbers (ie, 40-001-001 identifies Protocol 40, Site 001, Patient 001).

6.6.1. Screening

Screening will occur approximately 2 weeks prior to Day 1 (Visit T1) where the patient's eligibility will be evaluated. Eligible patients who are taking concomitant medications must be on stable regimens as defined in [Section 8.2](#). At the investigator's discretion, screening may be extended by 2 weeks to allow for re-evaluation of LDL-C, TG, blood pressure, liver enzymes, and estimated glomerular filtration rate (eGFR) eligibility criteria (see [Section 7.1](#) and [Section 7.2](#)).

6.6.2. Randomization and Treatment Period

For patients who satisfy all entry criteria and complete the 2-week screening period, randomization will occur and their randomization number will be assigned via IWRS at Week 0 (Visit T1). Patients will be stratified on CV risk (HeFH and ASCVD diagnosis) and baseline statin dose and randomized in a ratio of 2:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- ETC-1002 180-mg tablet
- Matching placebo tablet
- For details regarding the randomization strata see [Table 3](#).

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Subject Inclusion Criteria

Each patient with hyperlipidemia must meet the following criteria to be randomized in this study:

1. Age ≥ 18 years or legal age of majority based on regional law, whichever is greater at Week -2 (Visit S1)
2. Men and nonpregnant, nonlactating women. Women must be either:
 - Naturally postmenopausal (as reported by the patient, 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, bilateral oophorectomy, or tubal ligation or;
 - Women of childbearing potential must be willing to use 1 acceptable method of birth control. *The minimal requirement for adequate contraception it is that it should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug.* Acceptable methods of birth control include: 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).
 - There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
3. Fasting LDL-C value at Week -2 (Visit S1) ≥ 70 mg/dL (1.8 mmol/L).

Note: LDL-C may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat LDL-C, the mean of the first value and the repeat value will be used to determine eligibility.

4. Have high cardiovascular risk that is defined as either:
 - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see [Appendix 4](#)) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see [Appendix 5](#)). Patients with a diagnosis of HeFH may or may not have established CHD or CHD risk equivalents.

OR

- Have ASCVD (with established CHD or CHD risk equivalents)
Documented history of CHD (includes 1 or more of the following):
 - Acute MI
 - Silent MI
 - Unstable angina
 - Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)
 - Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

Documented CHD risk equivalents (includes 1 or more of the following criteria):

- Peripheral arterial disease
- Previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease

Note: Patients with T2DM are allowed in this study; however, for this study T2DM is not considered a CHD risk equivalent

5. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin *either alone or in combination with other lipid-lowering therapies*, at stable doses for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed). Regimens other than daily dosing, including those at very low doses, are acceptable.

A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

7.2. Subject Exclusion Criteria

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

1. Total fasting triglyceride ≥ 500 mg/dL (5.6 mmol/L) at Week -2 (Visit S1)

Note: TG may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG, the mean of the first value and the repeat value will be used to determine eligibility.

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) $<30 \text{ mL/min/1.73 m}^2$ at Week -2 (Visit S1) [1].

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

Note: Also excluded are renally impaired patients receiving an average daily dose of simvastatin 40 mg with eGFR below $<45 \text{ mL/min/1.73 m}^2$.

3. Body mass index (BMI) $\geq 50 \text{ kg/m}^2$
4. Concomitant use of simvastatin at average daily doses greater than 40 mg.
5. Concomitant use of a PCSK9 inhibitor (Praluent[®] [alirocumab] or Repatha[®] [evolocumab]) at Week -2 (Visit S1) or prior use of a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.

Note: Patients are allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in [Section 11.1.6.3.5](#).

6. Recent (within 3 months prior to the screening visit [Week -2 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.
7. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) $\geq 160 \text{ mmHg}$ and diastolic blood pressure (DBP) $\geq 100 \text{ mmHg}$ after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the Investigator, the screening period may be extended up to 2 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria
8. Hemoglobin A_{1C} (HbA_{1C}) $\geq 10\%$ at Week -2 (Visit S1)
9. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $>1.5 \times$ the upper limit of normal (ULN) at Week -2 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.

10. Liver disease or dysfunction, including:

- Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 2 \times$ ULN, and/or total bilirubin (TB) $\geq 1.2 \times$ ULN at Week -2 (Visit S1).

Note: If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease. Patients without active disease may be enrolled the study.

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.

If TB $\geq 1.2 \times$ ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease, the patient may be enrolled in the study.

11. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band[®] or gastric bypass) that may affect drug absorption
12. Hematologic or coagulation disorders or a hemoglobin (Hgb) level < 10.0 g/dL (100 g/L) at Week -2 (Visit S1)
13. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. *Patients with a history of nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed*
14. Unexplained creatine kinase (CK) $> 3 \times$ ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK $\leq 3 \times$ ULN prior to randomization.
15. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
16. Blood donation, *blood transfusion for any reason*, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization
17. Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer
18. Prior participation in a previous ETC-1002 clinical study. Prior participation in a clinical study with ETC-1002 is defined as having been enrolled in an ETC-1002 study.
19. Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study;
 - New or planned dose changes of systemic corticosteroids
 - Requirement for mipomersen or lomitapide or apheresis therapy

20. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
- Hormone replacement (6 weeks prior to randomization)
 - Thyroid replacement (6 weeks prior to randomization)
 - Diabetes medications (4 weeks prior to randomization)
 - Obesity medication (3 months prior to randomization)
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

7.3. Patient Lifestyle and Dietary Guidelines

Each dose of study drug is comprised of 1 tablet from 1 bottle that will be dispensed at each scheduled clinic visit. 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. If a patient forgets to take study drug in the morning, it may be taken up to 12 hours later the same day. If study drug has not been ingested by that time, the patient should not take study drug that day and should resume ingestion of study drug the following morning.

Patients will fast for a minimum of 10 hours prior to collection of all laboratory samples.

Patients will be counseled to follow a lipid-lowering diet as per local or regional guidelines and should be encouraged (as able) to participate in a regular exercise program throughout the study.

7.4. Investigator/Sponsor Suspension or Termination of Patient Enrollment

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

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

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

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

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

8. TREATMENT OF PATIENTS

8.1. Description of IMP

Table 4: Investigational Medicinal Products

	Investigational Medicinal Product	
Product Name:	ETC-1002	Placebo
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure^a	35- and/or 100-count bottle (depending upon visit) with screw on, non-child proof cap	35- and/or 100-count bottle (depending upon visit) with screw on, non-child proof cap
Route of Administration:	Oral, daily in the morning, with or without food	Oral, daily in the morning, with or without food
Physical Description:	[REDACTED]	[REDACTED]
Manufacturer (Fill/Finish):	[REDACTED]	[REDACTED]

^a A 100-day supply of IMP will be included in the 100-count bottle and a 35-day supply of IMP will be included in the 35-count bottle.

Please see Pharmacy Manual for detailed storage requirements and instructions.

8.2. Concomitant Medications

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

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

8.2.1. Lipid-Regulating Medications and Supplements

Patients will be required to be on stable lipid-modifying therapy(s), including a maximally tolerated statin for at least 4 weeks prior to screening. Use of fibrates must be stable at least 6 weeks prior to screening. Gemfibrozil, a fibrate, is prohibited. *Patients may not currently be taking or have taken a PCSK9 inhibitor within 4 weeks prior to Screening (Week -2, Visit S1); however, they may be allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in [Section 11.1.6.3.5](#).* Stable lipid-modifying therapy(s) includes, but is not limited to, monotherapies or combination therapies containing the compounds below:

Statins

- Atorvastatin (Lipitor[®], Sortis[®])
- Fluvastatin (Lescol[®])
- Lovastatin (Mevacor[®], Altoprev[™])
- Pravastatin (Pravachol[®])
- Pitavastatin (Livalo[®], Lipostat[®])
- Rosuvastatin (Crestor[®])
- Simvastatin (Zocor[®]), with *daily* doses *less than* 40 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestyramine (Questran[®], Questran Light[®], Prevalite[®], Locholest[®], Locholest[®] Light)
- Colestipol (Colestid[®])
- Colesevelam hydrochloride (Welchol[®], Cholestagel[®])
- Ezetimibe (Zetia[®], Ezetrol[®])

Fibrates

- Fenofibrate (Antara[®], Lofibra[®], Tricor[®], Triglide[™], Lipantil[®], Supralip[®])
- Bezafibrate (Bezalip[®])
- Ciprofibrate (Modalim[®])

PCSK9 inhibitors (*allowed as adjunctive therapy beginning at Week 24 [Visit T5]; see [Section 11.1.6.3.5](#)*)

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

Other

- Ezetimibe/simvastatin where simvastatin is less than 40 mg/day (Vytorin[®] 10 mg/10 mg and 10 mg/20 mg, Inegy[®] 10 mg/20 mg are allowed)

- Atorvastatin/ezetimibe (Atozet[®])

8.2.2. Prohibited Medications

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥ 4 weeks). Short-term intermittent use (< 14 days) of pulse steroids are allowed.
- Gemfibrozil (Lopid[®])
- Cholestin (red yeast rice, also known as monascus purpureus extract)
- Simvastatin (Zocor[®]), *greater than or equal to 40 mg/day*
- *Ezetimibe/simvastatin where simvastatin doses are greater than or equal to 40 mg/day (Vytorin[®] 10 mg/40 mg and 10 mg/80 mg per day and Inegy[®] 10 mg/40 mg and 10 mg/80 mg per day are prohibited)*

Patients will not have used the medications listed below within 4 weeks prior to screening:

- Alirocumab (Praluent[®])
- Evolocumab (Repatha[®])
- *Note: Patients may be allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the LDL-C threshold has been met as described in [Section 11.1.6.3.5](#).*

8.2.3. Allowable Medications

Other concomitant medication must be stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety.

The following must be stable for a minimum of 6 weeks prior to randomization:

- Postmenopausal hormone therapy
- Thyroid hormone supplements
- Fibrates (excluding gemfibrozil)

The following must be stable for: a minimum of 4 weeks prior to screening:

- Hypertriglyceridemia therapy
- Lipid-lowering therapy, including dietary supplements and herbal remedies used for the purposes of lipid lowering
- Diabetes medications

The following must be stable for a minimum of 3 months prior to screening and, if possible not be adjusted during the study except for reasons of safety:

- Antiobesity medications

The following may not be taken within 4 weeks of Screening (Week -2, Visit S1), but may be initiated beginning at Week 24 if LDL-C threshold criteria have been met and it is needed as adjunctive LDL-C-lowering therapy.

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

8.3. Treatment Compliance

Screening Compliance

No study medication treatment will be given during the Screening period; therefore, compliance will not be assessed.

Treatment Period Compliance

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

8.4. Blinding

At Week 0 (Visit T1), patients who satisfy all entry criteria during the screening period will be randomized to a treatment group. The Investigator or designee will contact IWRS at this visit to randomize the patient into the study. The IWRS will determine the randomized treatment assignment based on their HeFH status and baseline statin dose and assign a randomization number and the appropriate study drug container via medication identification numbers (MED ID). A patient is considered to be randomized when they have been assigned a randomization number by IWRS.

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

Blinding of treatment must be maintained for all patients unless, in the opinion of the Investigator, the safety of the patient may be at risk. Only under the rarest of circumstances

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

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

Postrandomization values for individual laboratory measures for LDL-C, TG, TC, HDL-C, non-HDL, apoB, and hs-CRP, including any plasma concentration of ETC-1002 and its metabolite, that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, [REDACTED].

An independent blinded expert CEC will adjudicate all *clinical endpoints*, including death, using standardized definitions. *Clinical endpoints will also be reported as SAEs*. Additional details and definitions will be provided in a CEC Charter.

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

8.5. Overdose

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

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Investigational Medicinal Product Supply and Control

The Sponsor will supply the IMP for this study. The IMP for this study includes ETC-1002 (180-mg film-coated tablets) and matching placebo (film-coated tablets). IMP will be distributed and released in accordance with regional and local requirements during the conduct of the study.

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

Double-blind IMP will be dispensed in 100 day supply increments (one 100-day supply bottle) to patients by appropriate clinical site personnel at Week 0 (Visit T1), Week 12 (Visit T4), and Week 24 (Visit T5). Double-blind IMP will be dispensed in 35-day supply increments (2 bottles; one 100-day supply bottle and one 35-day supply bottle) to patients at Week 36 (Visit T6).

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

9.2. Administration of Investigational Medicinal Product

Patients will be instructed to ingest IMP orally once daily (*once every 24 hours*) at *approximately the same time each day* with water. *IMP may be taken* with or without food. On clinic visit days, patients will be instructed to delay ingestion of IMP until all study procedures have been completed. If a patient arrive at clinic on Visits T4, T5, or T7 without having fasted or having taken IMP before arriving at the clinic, reschedule the visit (the next day or as soon as possible) so that the fasting and dosing requirements have been met. Patients will be instructed to return all packaging and unused IMP at each clinic visit.

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

9.3. Investigational Medicinal Product Accountability

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

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

- Amount received/placed in storage area
- Amount currently in storage area
- MED ID number for all IMP

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

9.4. Investigational Medicinal Product Handling and Disposal

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

10. STUDY PROCEDURES

10.1. Informed Consent

The patient must be adequately informed of the nature and risks of the study and understand the informed consent document (ICD). No study-related procedure will be performed until the patient has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICD approved by the Sponsor (or designee) and the IRB or IEC. Participation in banking of samples for genetic analysis is optional for all patients, and consent for this must be documented in the patient's written informed consent.

10.2. Procedures and Schedule of Assessments

Patients who provide informed consent and sign the ICD will be eligible to begin screening for the study. The study is comprised of 2 distinct periods: screening and double-blind treatment.

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

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

10.2.1. Screening Week -2 (Visit S1; Days -16 to -4)

The screening period will begin with a screening visit that will occur 2 weeks prior to randomization. Visit S1 will allow the Investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Demographics
- Clinically relevant medical history, including assessment of HeFH status and ASCVD
- Concomitant and prohibited medication review
- Height (cm), weight (kg), BMI
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - HbA_{1C}
 - TSH
 - FSH (*in appropriate female patients*)
 - Serum pregnancy test (*on appropriate female patients*)

- Serology (including HBsAg, HCV)
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Conduct diet and exercise counseling
- Contact IWRS to register the patient

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their therapy(s) for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. Patients who fail to meet any entry criterion that can be assessed at Visit S1 are considered to be screen failures and are not required to return for additional visits (although a patient can be seen at any time for safety reasons).

Note:

- An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- *An optional visit between Visits S1 and T1 may be scheduled to collect screening fasting labs in the event that the patient arrives at Visit S1 in a nonfasted state.*
- An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, they have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) no longer meet exclusionary values.
- An optional visit between Visits S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- Patients who are considered to be screen failures due to not meeting stability requirements for a condition or concurrent medication may be considered for rescreening after consultation with the Sponsor (or designee). These patients must be re-consented, re-registered in the IWRS, and will have a new patient ID number assigned.

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

Prior to scheduling Visit T1, review the screening clinical results to evaluate whether the patient continues to meet eligibility criteria.

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

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

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing *of* the informed consent document)
- Physical examination (PE)
- Weight
- 12-Lead electrocardiogram (ECG)
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, and urinalysis
Note: Urine pregnancy test (for females of childbearing potential)
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - Reserve sample
 - *Genetic sample (if the patient has consented to provide a genetic sample)*
- Review inclusion/exclusion criteria to establish patient eligibility
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions
- Schedule next visit

10.2.3. Treatment Week 4 (Visit T2; ± 3 days)

If the patient is withdrawing early from the study at this visit, proceed to [Section 10.2.8](#) for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.2.8 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 52 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 at Week 4 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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)
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- Return IMP container from Visit T1 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.

10.2.4. Treatment Week 8 (Visit T3; \pm 3 days)

If the patient is withdrawing early from the study at this visit, proceed to [Section 10.2.8](#) for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.2.8 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 52 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 at Week 8 (Visit T3):
- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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)
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- Return IMP container from Visit T1 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 medications*, and current health status.

10.2.5. Treatment Week 12 (Visit T4; \pm 3 days)

If the patient is withdrawing early from the study at this visit, proceed to [Section 10.2.8](#) for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.2.8 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 52 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 at Week 12 (Visit T4):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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
 - HbA_{1C}
 - hs-CRP
 - PK sample (*patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling*)
 - Reserve sample
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP
- 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 apoB, hs-CRP, PK samples, reserve samples, and 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 medications*, and current health status.

10.2.5.1. Treatment Week 16 (Visit T4.1; ± 3 days)

Patients on simvastatin 40 mg/day will be scheduled for the additional Visit T4.1 for clinical safety laboratory evaluations specifically to monitor changes in creatine phosphokinase (CPK)

and liver function tests (LFTs). Should changes be noted, the procedures described in [Section 11.1.6.3.1](#) will apply.

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Clinical laboratory evaluations:*
 - *Hematology, blood chemistry, and urinalysis*
- *Conduct diet and exercise counseling*

10.2.5.2. Treatment Week 20 (Visit T4.2; ± 3 days)

Patients on simvastatin 40 mg/day will be contacted by telephone for the additional Visit T4.2

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*

10.2.6. Treatment Week 24 (Visit T5; ± 7 days)

If the patient is withdrawing early from the study at this visit, proceed to [Section 10.2.8](#) for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.2.8 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 52 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 at Week 24 (Visit T5):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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
 - hs-CRP

- PK sample (*patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling*)
- Reserve sample
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP
- 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 apoB, hs-CRP, PK samples, reserve samples, and IMP (IMP dispensing, IMP compliance, IMP accountability) management 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 medications*, and current health status.

10.2.6.1. Treatment Week 28 (Visit T5.1; ± 7 days)

Patients on simvastatin 40 mg/day will be scheduled for the additional Visit T5.1 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs. Should changes be noted, the procedures described in [Section 11.1.6.3.1](#) will apply.

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Clinical laboratory evaluations:*
 - *Hematology, blood chemistry, and urinalysis*
- *Conduct diet and exercise counseling*

10.2.6.2. Treatment Week 32 (Visit T5.2; ± 7 days)

Patients on simvastatin 40 mg/day will be contacted by telephone for the additional Visit T5.2

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*

10.2.7. Treatment Week 36 (Visit T6; ± 7 days)

If the patient is withdrawing early from the study at this visit, proceed to [Section 10.2.8](#) for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to [Section 10.2.8](#) 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 52 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 at Week 36 (Visit T6):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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)
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP
- 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 medications*, and current health status.

10.2.8. Treatment Week 52 (Visit T7; \pm 7 days)

Patients will undergo the following assessments and procedures at Week 52 (Visit T7), when completing an End of Study (EOS) visit, withdrawing from study (early withdrawal), or withdrawing from IMP treatment:

Patients will undergo the following assessments and procedures at Week 52 (Visit T7):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- PE
- Weight
- 12-Lead ECG
- 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
 - HbA_{1C}
 - hs-CRP
 - PK sample (*patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling*)
 - Reserve sample
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study)
- *Review and offer the open-label extension study (Study 1002-050) to the patient*

Note: For patients who withdraw from IMP treatment:

- *Capture the reason for withdrawing from IMP treatment and record on the eCRF*
- Determine whether the patient will or will not consent for follow-up visits through study completion
- If the patient provides consent to continue to be followed for safety assessments per the protocol visit schedule, schedule follow-up visits as they would have occurred if the patient were continuing in the study and complete the visit required procedures listed in the appropriate visit specific section within [Section 10](#) and [Appendix 1](#). No further IMP will be dispensed for patients who withdraw from IMP treatment.
- If the patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), this visit (Visit T7) will be considered the EOS/Early Withdrawal from study visit and no further visits will be scheduled.

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 apoB, hs-CRP, PK samples, reserve samples, and IMP (IMP dispensing, IMP compliance, IMP accountability) management 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 medications*, and current health status.

10.3. Subject Withdrawal Criteria

10.3.1. Early Withdrawal from the Study

Patients must remain in the study until the last scheduled visit at Week 52 (Visit T7) to be considered as having completed participation in the study.

Patients who withdraw from IMP prior to Week 52 (Visit T7) 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 Week 52 (Visit T7) for any reason may restart IMP providing that 1) the patient and the investigator are in agreement regarding this course of action, 2) the patient has been off of IMP for 4 weeks or less; and 3) IMP can be started as soon as possible. For cases where the patient has been off of IMP for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting IMP.

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 52 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:

- Patient's withdrawal of consent
- Failure to comply with the protocol
- Lost to follow-up

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

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

10.3.2. Procedures for Early Withdrawal

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

All effort should be made to have each patient complete all study visits on schedule according to the protocol. Accommodations for early or late visits in special circumstances will be considered by the Sponsor to prevent early withdrawal. Written notice (regardless of cause) is to be provided within 48 hours of the withdrawal to the Sponsor personnel or the Medical Monitor. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed. Except in the case of a medical emergency, the procedures and assessments detailed in [Section 10.2.8](#) 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 Week 52 (Visit T7)

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

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

11.1.1. Demographic/Medical History

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

11.1.2. Vital Signs

Vital signs will include diastolic and systolic blood pressure 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 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, blood pressure may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study. The patient should be in a seated position with feet touching the floor. Patients should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on the ground, and their arms bared and supported at heart level.

11.1.3. Weight, Height, and Body Mass Index

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

Height will be measured using standard clinic procedures.

BMI will be calculated using the formula:

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

11.1.4. Physical Examination

PEs will include an assessment of the following:

- General appearance
- Skin

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

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

Note: Additional information will be collected regarding muscle-related AEs. See [Section 11.2.3](#).

11.1.5. Electrocardiogram

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

11.1.5.1. Monitoring and Management of Abnormal Electrocardiograms

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

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

11.1.6. Clinical Laboratory Tests

11.1.6.1. 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 5](#). Collection schedule, schedule of laboratory

parameters by visit, and instructions are in the Clinical Laboratory Manual provided by Central Laboratory.

Table 5: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
<ul style="list-style-type: none"> 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 <i>and</i> %) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> Albumin (Alb) Alkaline phosphatase (Alk-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO₂) Chloride (Cl) Creatinine Creatine kinase (CK) Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium (K) Sodium (Na) Total and direct bilirubin (TB)^a Total protein Uric acid
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> Clarity Bilirubin Color Glucose Ketones Leukocyte esterase Nitrate Occult blood pH Protein Specific gravity Urobilinogen 	

Table 5: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> Bacteria Casts Crystals Epithelial cells Red blood cell (RBC) WBC 	<u>Coagulation—In all patients at screening, then only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Visit T1 and 3 to 5 days post Visit T1</u> <ul style="list-style-type: none"> Prothrombin time (PT) International normalized ration (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV)^b Serum pregnancy test (only for females of childbearing potential) <i>Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses)</i> <i>Urine pregnancy test prior to randomization (for females of childbearing potential)</i> Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> Hemoglobin A_{1C} (HbA_{1C}) Reserve blood samples for potential future measurement of ETC-1002 safety or pharmacodynamic biomarkers PK sample (<i>patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling</i>) Reserve genetic blood sample (optional)

^a If TB $\geq 1.2 \times$ ULN, a reflex indirect (unconjugated) bilirubin will be obtained.

^b If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease.

11.1.6.2. 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. For collection and processing of PK samples, please see [Section 11.1.6.4](#) and [Section 11.1.6.6](#). Samples will be processed by the Central Laboratory, and PK samples will be forwarded to the Bioanalytical Laboratory for analysis. Reserve samples will be stored frozen for potential future measurement of additional ETC-1002 safety and efficacy biomarkers. A reserve genetic blood sample (optional) will also be stored frozen for potential future ETC-1002 genetic analyses.

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)

11.1.6.3. 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.

11.1.6.3.1. Monitoring and Management of Elevated Liver Function Tests

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

Repeat LFT assessment will include: 1) measurement of ALT, AST, alkaline phosphatase, total and direct bilirubin, prothrombin time (PT)/international normalized ratio (INR), eosinophil count, CK, antihepatitis A virus (total), HBsAg (confirmation of screening measurement), HCV (confirmation of screening measurement), and 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 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 $>3 \times$ 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 $>5 \times$ 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 $>3 \times \text{ULN}$ 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 $>2 \times \text{ULN}$

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

11.1.6.3.2. Monitoring and Management of Elevated Serum Creatinine

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

11.1.6.3.3. Monitoring and Management of Hemoglobin Change

If at any time after randomization a patient experiences a decrease $>2.0 \text{ g/dL}$ (20 g/L) from baseline (Week 0 [Visit T1]), the patient will undergo repeat confirmatory hematology testing as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat hematology assessment will include: 1) measurement of Hgb, hematocrit (Hct), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, reticulocyte count (percent and absolute), red blood cell count (RBC), and white blood cell count (WBC) with differential (absolute values only); 2) history of concomitant medication use; and 3) query for related symptoms. Additionally, further testing may be warranted to rule out additional pathology depending on clinical presentation, and should be discussed with Esperion Therapeutics personnel or the authorized [REDACTED] Medical Monitor.

- If repeat Hgb assessment confirms a decrease $>2.0 \text{ g/dL}$ (20 g/L) from baseline, the patient should be monitored carefully during the study and return at 2 week intervals after study completion for additional Hgb measurement until the level returns to baseline or reaches a stable level.
- If repeat Hgb assessment confirms Hgb $<8 \text{ g/dL}$ (80 g/L), the patient should be withdrawn from IMP treatment. The patient will return at 1-week intervals after withdrawing from IMP treatment for additional Hgb measurement until the level returns to baseline or reaches a satisfactory conclusion.
- 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](#)).

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

11.1.6.3.4. Monitoring and Management of Elevated Creatine Kinase

If at any time after randomization a patient experiences a marked CK elevation $>5 \times$ 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 $>5 \times$ 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:
 - $>10 \times$ ULN, even in the absence of symptoms.
 - In all cases, evaluate the signs/symptoms and laboratory evaluations as outlined above.
- If the patient is withdrawn from IMP treatment, the patient should be asked to continue being followed for safety using the protocol-specified visit schedule (see [Appendix 1](#)).

11.1.6.3.5. Monitoring and Management of Elevated LDL-C

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0, (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin at doses ≥ 40 mg/day and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits ([Appendix 1](#)).
 - 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
 - *Patients who have their lipid-lowering medications modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine safety laboratory assessment. Additional safety laboratory assessments may be conducted at the investigator's discretion. Patients receiving an average daily dose of simvastatin 40 mg based on lipid-lowering treatment modification, should adhere to the additional safety visits as described in [Sections 10.2.5](#) and [10.2.6](#).*
 - Adjunctive therapy medications will not be provided by the sponsor
 - Patients continuing to exceed the LDL-C threshold after maximizing the standard-of-care LCL-C-lowering therapy and, in the opinion of the investigator, require therapies that are prohibited by the protocol will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule (see [Appendix 1](#)).
 - Please see the Clinical Laboratory Manual and [Section 11.7](#) for sample collection and instructions.

11.1.6.3.6. Monitoring and Management of Elevated Triglycerides

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds 1000 mg/dL (11.3 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >1000 mg/dL (11.3 mmol/L), will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value meets the threshold criteria
- Any patient with a confirmed TG >1000 mg/dL (11.3 mmol/L) may initiate standard-of-care therapy (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.
- Patients continuing to exceed the TG threshold after maximizing the standard-of-care triglyceride-lowering therapy will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule (see [Appendix 1](#)).
- Please see the Clinical Laboratory Manual and [Section 11.7](#) for sample collection and instructions.

11.1.6.4. 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.

11.1.6.5. Pharmacokinetic Assessments

Plasma concentrations of ETC-1002 and its metabolite ESP15228 will be determined from 6 mL whole blood samples collected from patients at Weeks 12, 24, and 52. At the time of sample collection, the date and time of blood draw and the last 2 doses of study medication will be collected.

11.1.6.6. Collection and Assessment of Pharmacokinetic Samples

Pharmacokinetic samples will be collected from patients who were randomized into the study prior to the implementation of Protocol Amendment 3.

Pharmacokinetic samples will not be collected for patients randomized into the study after initiation of Protocol Amendment 3.

Plasma concentrations of ETC-1002 and its metabolite (ESP15228) will be determined using validated methods. Plasma PK samples will be labeled with preprinted information, including study number, patient identification number, study day, nominal time of sample collection, matrix, and a text identification (ie, "Plasma PK"). See the study laboratory manual for further instructions.

11.1.6.7. Exploratory Biomarker Measurement

Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from reserve samples. *Based upon Sponsor assessment and decision, reserve sample collection will be discontinued after a sufficient number of samples have been collected. Study centers will be notified in writing informing them that sufficient samples have been collected and that further collection may be discontinued.*

11.1.6.8. Shipment of Pharmacokinetic Samples

Plasma PK samples will be shipped frozen on dry ice according to instructions provided in the laboratory manual.

11.1.6.9. Genetic Testing

As part of this study, all patients will be invited to provide a blood sample to be banked for potential future genetic analyses, but participation in this portion of the study is optional. Those who choose not to provide a sample for genetic analysis may still participate in the main portion of the study. Samples will be anonymized before testing to assure that the results cannot be traced back to an individual patient. Signing a separate informed consent document is required to obtain this sample.

11.1.6.10. Total Blood Volume of Clinical Laboratory and Pharmacokinetic 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, PK, efficacy, biomarker assessment, and genetic analysis. Total whole blood volume collected over the study duration is not to exceed approximately 250 mL for each patient.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

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

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- TEAEs are defined as AEs that begin or worsen after the first dose of study drug
- Adverse Drug Reaction (see Section 11.2.2)

11.2.2. 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 a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

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

11.2.3. Reporting

All AEs occurring during the course of the study (starting from signing informed consent to study completion) will be collected on the AE eCRF. Patients should be instructed to report any AE that they experience to the Investigator. Beginning with Visit S1 (Week -2), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

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

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

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

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

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

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

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

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

11.2.4. 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.

11.2.5. Relationship

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

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

11.2.6. Monitoring and Follow-up of Adverse Events

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

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

Patients with AEs that are ongoing at study completion or study withdrawal must be followed until resolution or for 30 days after the last study *visit*, whichever comes first (see [Section 11.3](#)).

11.2.7. Treatment-Emergent Adverse Events

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

11.2.7.1. 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: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for an elective or outpatient procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective or outpatient surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the 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.

Any clinical endpoints that meet SAE criteria will be reported as SAEs. The CEC will adjudicate *clinical endpoints* in a blinded fashion, but the DMC will review *clinical endpoints* and SAEs in an unblinded fashion.

11.3. Reporting Serious Adverse Events

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following study completion or study discontinuation, must be reported by the Principal Investigator or designee to [REDACTED] Medical and Safety Services within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. For most patients this will be 30 days following their Week 52 (Visit T7) visit. All SAEs that the Investigator considers related to study drug that occur after the 30-day follow-up of the study period must be reported to the Sponsor.

To report the SAE, complete the provided SAE form and fax it to [REDACTED] Medical and Safety Services within 24 hours of becoming aware of the occurrence. Regional fax numbers will be listed on the bottom the provided SAE form. If you are unable to fax the SAE form or if you have questions, please call [REDACTED] Medical and Safety Services for assistance. [REDACTED] Safety personnel are available for SAE reporting on a 24-hour basis. Incoming reports are reviewed during normal business hours.

Safety Contact Information:

[REDACTED] Medical and Safety Services
[REDACTED] 24-Hour SAE hotline: [REDACTED]

Detailed instructions and contact information for the Global and Regional Medical Monitor(s) will be provided by [REDACTED] in the SAE Completion Guidelines.

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

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

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

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to [REDACTED] Medical and Safety Services personnel via fax.

11.3.1. Reporting of Serious Adverse Events to Regulatory Authorities

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

SAEs that are anticipated to occur in this patient population will be collected and reported by the Investigator as described in Section 11.3. 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*

11.3.2. Reporting of Patient Death

The death of any patient during the study, or within *the 30-day follow-up period after they have completed the study* (regardless of the cause), must be reported to [REDACTED] Medical and Safety Services as detailed in [Section 11.3](#).

11.3.3. Reports of Pregnancy

Although not considered an SAE (unless an event occurs with a serious outcome), pregnancy information on female patients will be collected by [REDACTED] Medical and Safety Services. If a female patient should become pregnant during the course of the study, the Principal Investigator or designee must contact [REDACTED] Medical and Safety Services within 24 hours of the Principal Investigator or designee first becoming aware of the pregnancy. [REDACTED] Medical and Clinical Safety Services will then forward the Exposure In Utero form to the Investigator for completion.

Patients who become pregnant will discontinue study medication immediately and complete the Early Withdrawal evaluations.

11.4. Adverse Events of Special Interest

[REDACTED]

The protocol procedures included in the ETC-1002 clinical studies are part of standard clinical care for patients with primary hyperlipidemia and mixed dyslipidemia and also address the potential and theoretic risks of ETC-1002.

All ETC-1002 studies will include standard pharmacovigilance including evaluation of AEs, PE findings, vital signs, and laboratory assessments. Cardiovascular events will be adjudicated by an independent CEC in accordance with a pre-specified charter. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

11.5. 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 ETC-1002 will be provided to the DMC by an independent unblinded [REDACTED] statistician and programmer. Additional details will be provided in a DMC Charter.

11.6. Clinical Event Committee (CEC)

A blinded independent expert CEC will adjudicate *clinical endpoints*. 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 ETC-1002 Phase 3 development program will be aggregated to allow for a safety assessment across the entire development program.

11.7. Assessment of Lipid Endpoints

11.7.1. Lipid Parameters

After randomization, patients will return to clinic every 4 weeks for the first 12 weeks, then approximately every 12-16 weeks through Week 52 (Visit T7). 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 ETC-1002 effects on lipids and cardiometabolic parameters*.

11.7.2. Clinical Laboratory Tests (Lipids)

Clinical laboratory samples will be collected at all clinic visits.

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

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

Patients are encouraged to be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in [Table 6](#). Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping as well as monitoring and management of abnormal laboratories are described in [Section 11.1.6](#).

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

Table 6: Clinical Laboratory Parameters (Lipids) and Cardiometabolic Biomarkers

Clinical Laboratory Test	Clinical Laboratory Test
<u>Basic Lipid Parameters</u> <ul style="list-style-type: none">• Total cholesterol (TC)• low-density lipoprotein cholesterol (LDL-C) and non-HDL-C• High-density lipoprotein cholesterol (HDL-C)• Triglycerides (TG)	<u>Other Parameters</u> <ul style="list-style-type: none">• High-sensitivity C-reactive protein (hs-CRP)• apoB

12. STATISTICS

12.1. General Considerations

The statistical analyses described in this section will be performed as further outlined in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the first DMC assessment of safety. The SAP will supersede the protocol in the event of any differences between the 2 documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

12.2. Determination of Sample Size

A total of 1950 patients will be enrolled in this study with 1300 patients randomized to ETC-1002 and 650 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥6 Months</i>	<i>Patients ≥12 Months</i>
<i>ETC-1002</i>	<i>1,202</i>	<i>1,170</i>
<i>Placebo</i>	<i>601</i>	<i>585</i>

*Absolute risk will be addressed by 1300 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled *Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events*[2]. In this study adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.*

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of 1300 patients randomized to ETC-1002 and 650 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits:

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
<i>0.5%</i>	<i>0.5%</i>	<i>1.0</i>	<i>(0.3, 3.8)</i>
<i>0.5%</i>	<i>1.0%</i>	<i>2.0</i>	<i>(0.6, 6.7)</i>
<i>13.6%</i>	<i>13.6%</i>	<i>1.0</i>	<i>(0.8, 1.3)</i>
<i>13.6%</i>	<i>27.2%</i>	<i>2.0</i>	<i>(1.6, 2.5)</i>

12.3. Analysis Populations

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

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

12.4. Disposition, Demographics, and Baseline Characteristics

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

12.5. Primary Safety Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

The summarization of AEs will include only TEAEs, defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. *These AE summaries* will be provided overall and for subgroups such as gender, age, and HeFH status. *If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates.* Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group. Potential AEs based on findings in non-clinical models include reversible hypoglycemia and metabolic acidosis. Further details on occurrence and monitoring are available in [Section 11.1.6.4](#) and the IB. AESI will be summarized as follows:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

screening and the predose Day 1/Week 0 value. When only one assessment or value is available, that single assessment/value will be used as baseline.

The FAS will be used for efficacy endpoints, with patients included in their randomized group, regardless of the treatment they actually received. Missing data for key lipid endpoints will be imputed using a multiple imputation method that accounts for treatment adherence. A pattern mixture model (PMM) will be used to specify different imputation strategies depending on whether the patient is still on study treatment. The ANCOVA output will include the least squares mean (LSM) and standard error (SE) for each treatment group, along with the placebo-correct LSM and its 95% confidence interval (CI) and p-value. Specific details on how the PMM will be implemented will be included in the SAP.

Additional sensitivity analyses based on subsets of the FAS or alternative missing data handling will be performed and the details will be provided in the SAP.

12.6.2. Other Efficacy Endpoints

Percent change or change in LDL-C, HDL-C, TG, TC, non-HDL-C, hs-CRP, and apoB values at other protocol-scheduled time points will be analyzed similarly using the ANCOVA model. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. No imputation for missing data will be performed.

For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group.

In addition, percent change from baseline to Week 24 and to Week 52 LDL-C will be analyzed with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI and p-value.

12.7. PK and Other Biomarkers

The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).

Trough plasma concentrations of ETC-1002 and ESP15228 will be collected from patients randomized before the implementation of Protocol Amendment 3 at Weeks 12, 24, and 52 for use in further developing the population PK model. Trough plasma concentrations will not be collected from patients randomized after the implementation of Protocol Amendment 3.

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 Good Clinical Practice (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 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 hand-written or computer-generated document that contains medical information or test results that have been collected for or in support of the protocol specifications (eg, laboratory reports, clinic notes, 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. Study Administrative Structure

Fill/Finish Manufacturing:

[REDACTED]

[REDACTED]

[REDACTED]

Secondary Packaging/Depot for Clinical Site Drug Shipments:

[REDACTED]

[REDACTED]

Central Laboratory:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Randomization, IWRS, Statistical Analysis, Study Management and Monitoring, Data Management, Medical and Safety Services including Medical Monitoring (see Medical and Safety Services below), Programming, and Medical Writing:

[REDACTED]

Medical and Safety Services:

[REDACTED]

17.3. Amendments

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

17.4. Financial Disclosure

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

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

[Appendix 1: Schedule of Assessments](#)

[Appendix 2: Sponsor's Signature](#)

[Appendix 3: Investigator's Signature](#)

[Appendix 4: Dutch Lipid Clinic Network Criteria for Familial Hypercholesterolemia](#)

[Appendix 5: Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia](#)

[Appendix 6: Summary of Changes in Amendment 1](#)

[Appendix 7: Summary of Changes in Amendment 2](#)

[Appendix 8: Summary of Changes in Amendment 3](#)

[Appendix 9: Summary of Changes in Amendment 4](#)

[Appendix 10: Summary of Changes in Amendment 5](#)

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
Informed Consent	X											
Enrollment Criteria	X											
Demographics	X											
Medical History	X											
HeFH Status Determination	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X										X
Weight ⁴	X	X	X	X	X			X			X	X
Height/BMI	X											
12-Lead ECG ⁵		X										X
Vital Signs ⁶	X	X	X	X	X			X			X	X
Serology ⁷	X											
Serum Pregnancy and/or FSH ⁸	X											
Urine Pregnancy Test ⁸		X										
TSH	X											
Clinical Safety Labs ⁹	X	X	X	X	X			X			X	X
Additional Clinical Safety Labs ¹⁰						X			X			
Basic Fasting Lipids ¹¹	X	X	X	X	X			X			X	X
HbA _{1c}	X	X			X							X
10 mL reserve sample ¹²		X			X			X				X
Genetic sample		X										
apoB		X			X			X				X
hs-CRP		X			X			X				X
Diet and exercise counseling ¹³	X	X	X	X	X	X		X	X		X	
Plasma PK ¹⁴					X			X				X
Establish Patient Eligibility		X										
Randomization		X										

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
IWRS Contact	X	X			X			X			X	X ¹⁵
Double-blind Drug Dispensing ¹⁶		X			X			X			X	
Drug Return/Compliance			X	X	X			X			X	X
Offer Study 1002-050												X ¹⁷
Schedule next visit	X	X	X	X	X			X			X	X ¹⁸

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCV
- ⁸ Serum pregnancy test completed in premenopausal women only. Urine pregnancy test is completed in premenopausal women who are able to become pregnant. FSH test is completed in women <55 years old and >1 year without menses
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. These will also be conducted 4 weeks after any changes in the patient's lipid-modifying treatment. Coagulation is included at Screening (Visit S1) for all patients, and then only in patients receiving anticoagulant therapy that in the investigator's judgement requires monitoring at Baseline (Visit T1) and 3 to 5 days post Visit T1. Please refer to [REDACTED] laboratory manual for detailed schedule of tests.

¹⁰ [REDACTED]

¹¹ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.

¹² Based upon Sponsor assessment and decision, reserve sample collection will be discontinued after a sufficient number of samples have been collected.

¹³ Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

¹⁴ Patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling.

¹⁵ IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

¹⁶ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.

¹⁷ *Review and offer the open-label extension study (Study 1002-050) to the patient. If the patient was not offered Study 1002-050, record the reason why in the eCRF*

¹⁸ If patient is discontinuing treatment, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

APPENDIX 2. SPONSOR'S SIGNATURE

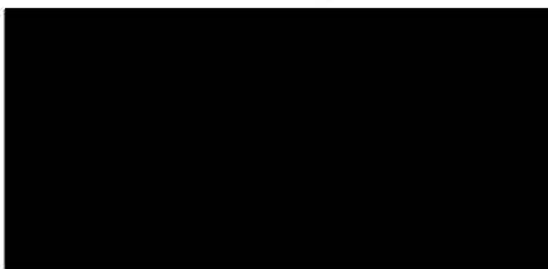
Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-040

Final Date: 10 May 2017

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

Signed: _____



Date: 12 May 2017

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-040

Final Date: 10 May 2017

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

Signed: _____

Date: May 12, 2017

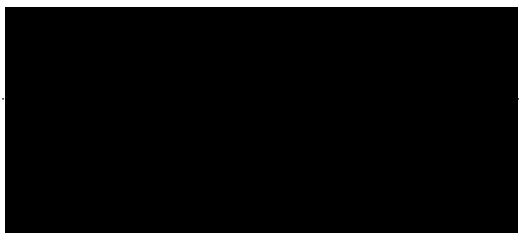
Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-040

Final Date: 10 May 2017

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

Signed: _____



Date: _____

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-040

Final Date: 10 May 2017

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

Signed: _____

Date: _____

12 May 2017

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-040

Final Date: 10 May 2017

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

Signed: _____ Date: _____

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

APPENDIX 4. DUTCH LIPID CLINIC NETWORK CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia ^{1,2,3}

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

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

^a Premature ≤55 years in men; ≤60 years in women

Scoring:

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

References:

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

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

Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia ¹

Definite Familial Hypercholesterolemia:

- Required laboratory = high cholesterol levels:
 - Adult = Total cholesterol levels >290 mg/dL (7.5 mmol/L) or LDL-C >190 mg/dL (4.9 mmol/L)
 - Child less than 16 years of age = Total cholesterol levels >260 mg/dL (6.7 mmol/L) or LDL-C >155 mg/dL (4.0 mmol/L)
 - Plus at least one of the two:
 - Plus physical finding = tend xanthomas, or tendon xanthomas in first or second degree relative
- OR***
- DNA-based evidence of an LDL-receptor mutation, familial defective apoB-100, or PCSK9 mutation

Possible Familial Hypercholesterolemia:

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

References:

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

APPENDIX 6. SUMMARY OF CHANGES IN AMENDMENT 1

SUMMARY OF CHANGES CLINICAL STUDY PROTOCOL

Study Number: 1002-040

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Protocol Version Incorporating Current Summary of Changes: Amendment 1: Amended Protocol 28 January 2016

Preceding Protocol Version: Original Protocol: 02 October 2015

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:

- Addition of secondary and tertiary study objectives to evaluate lipid and cardiometabolic parameters at specific time points throughout the study
- Addition of protocol requirements to address the recent marketing of PCSK9 inhibitors resulting in the addition of exclusion criteria, prohibited medications instructions, and allowable medication instructions to reflect the protocol requirements
- Defined clinical endpoints to provide clarity regarding the events that will be adjudicated by the CEC
- Clarified the definition for duration of treatment and end of study
- Revised the reporting requirements for clinical endpoints
- Revised inclusion/exclusion criteria by aligning the medical history and concurrent conditions of the study population with those commonly observed in patients with hyperlipidemia and high cardiovascular risk
- Clarified that the IMP would be provided in 100-count or 35-counts bottles with either 100 or 35 pills included in each respective container
- Updated clinical laboratory parameters (safety, lipid, and/cardiometabolic biomarker), the laboratory sample collection schedule, and laboratory result reporting to ensure consistency across sections within this protocol.
 - Removal of insulin and aPTT from list of clinical laboratory samples
 - Clarified that glucose will be a fasting value evaluated from collected serum
 - Clarified that FSH will be tested in the appropriate female patients
 - Clarified that WBC with differential will be reported in both absolute and percent values
 - Updated to include all lipid values will not be available to investigators and site staff, sponsor, [REDACTED]
- Updated the Study Procedures and the Schedule of Events (Appendix 1) to reflect the procedures and instructions required for each visit
- Addition of instructions for subject withdrawal criteria and restarting IMP for patients who have had a temporary withdrawal from IMP
- Revised safety monitoring and management instructions to ensure patient safety for the following:
 - Elevated serum creatinine
 - Hemoglobin
 - Elevated creatine kinase

- LDL-C threshold criteria for the addition of adjunctive therapy beginning at Week 24 (Visit T5)
- Hypoglycemia
- Clarified the reporting requirements for AEs, SAEs, and pregnancies
- Updated the lipid endpoint assessments for consistency with study objectives
- Revised the statistical section to include:
 - Updated sample size justification
 - Clarification of the analysis population
 - Updated analysis and summarization description for primary endpoints
 - Addition of analysis and summarization description for secondary and tertiary endpoints
 - Updated analysis and summarization description for PK and biomarkers
- Typographical errors and formatting were corrected or revised to improve clarity and consistency. These included, but were not limited to:
 - Updating the synopsis to include a complete list of inclusion and exclusion criteria
 - Consistently clarifying that a maximally tolerated statin is either alone or in combination with other lipid-lowering therapies
 - Updating the list of abbreviations and definition of terms
 - Revising the reference list and in text reference numbers to accommodate the addition of a reference

This amendment represents cumulative changes to the original protocol.

CHANGE 1 ADDITION OF SECONDARY AND TERTIARY STUDY OBJECTIVES

Location:

Synopsis; Secondary Objectives

Original Text:

Secondary:

- To assess lipid values (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], non-HDL-C, total cholesterol [TC], and triglycerides [TG]) at 12, 24, and 52 weeks
- To assess apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hs-CRP) at 12, 24, and 52 weeks

New Text:

Secondary:

- To assess percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL-C)
- ~~To assess lipid values (low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], non-HDL-C, total cholesterol [TC], and triglycerides [TG]) at 12, 24, and 52 weeks~~
- ~~To assess apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hs-CRP) at 12, 24, and 52 weeks~~

CHANGE 2 ADDITION OF SECONDARY AND TERTIARY STUDY OBJECTIVES

Location:

- Synopsis; Tertiary Objectives

Original Text:

Original protocol did not have tertiary objectives; therefore, there is no original text to be displayed.

New Text:

Tertiary:

- To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy
- To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and triglycerides (TG) values at Week 12, 24, and 52
- To assess apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hs-CRP) values at Week 12, 24, and 52

CHANGE 3 ADDITION OF PROTOCOL REQUIREMENTS TO ADDRESS THE AVAILABILITY OF PCSK9 INHIBITORS

Location:

Synopsis; Study Design

Original Text

Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil], evolocumab, and alirocumab). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day will be excluded from this study.

New Text

Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil], ~~evolocumab, and alirocumab~~). A patient's maximally tolerated lipid-modifying therapy will be determined by the

investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day, *or who are currently taking a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks* will be excluded from enrolling in this study. *PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.*

CHANGE 4 TYPOGRAPHICAL AND FORMATTING

Location:

Synopsis; Study Design

Original Text:

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.

New Text:

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

CHANGE 5 DEFINITION OF CLINICAL ENDPOINTS

Location:

Synopsis; Study Design

Original Text:

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety data from this and other ongoing studies of ETC-1002. All CV events, including death, will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions. Until the CEC has been established, CV events will be reported as both serious adverse events (SAEs) and major adverse cardiovascular events and mortality (MACE).

New Text:

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety *and efficacy* data from this and other ongoing studies of ETC-1002. ~~All CV events, including death, will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions.~~ *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), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Until the CEC has been established, CV events will be reported as both serious adverse events (SAEs) and major adverse cardiovascular events and mortality (MACE). Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs.*

CHANGE 6 CLARIFICATION OF DURATION OF TREATMENT AND END OF STUDY

Location:

Synopsis; Duration of treatment

Original Text:

Fifty-two weeks for all randomized patients who complete the study

New Text:

Fifty-two weeks for all randomized patients who complete the study

CHANGE 7 CLARIFICATION OF DURATION OF TREATMENT AND END OF STUDY

Location:

Synopsis; End of Study

Original Text:

The study will end when the last randomized patient completes 52 weeks of treatment. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 22 months.

New Text:

The study will end when the last randomized patient completes *their last study visit* ~~52 weeks of treatment~~. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 22 months.

CHANGE 8 TYPOGRAPHICAL AND FORMATTING

Location:

Synopsis; Diagnosis and criteria for patient eligibility

Original Text:

Diagnosis and key criteria for patient eligibility:

The study will enroll adult male and female patients with hyperlipidemia

Key eligibility criteria include the following:

- Provision of written informed consent prior to any study-specific procedure
- Men and nonpregnant, nonlactating women
- Age ≥ 18 years or legal age of majority depending on regional law, whichever is greater at Week -2 (Visit S1)
- Qualifying fasting LDL-C value at Week -2 (Visit S1) ≥ 70 mg/dL (1.8 mmol/L)
- Qualifying fasting TG value at Week -2 (Visit S1) ≤ 400 mg/dL (4.5 mmol/L)
- Body mass index (BMI) < 50 kg/m²
- Have high cardiovascular risk that is defined as either:
 - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid

Clinical Network Criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not have established coronary heart disease (CHD) or CHD risk equivalents.

OR

- Have ASCVD (with established CHD or CHD risk equivalents)
Documented history of CHD (includes 1 or more of the following):
 - Acute myocardial infarction (MI)
 - Silent MI
 - Unstable angina
 - Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)
 - Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging)
- Documented CHD risk equivalents (includes 1 or more of the following criteria):
 - Peripheral arterial disease
 - Previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease
- Be on maximally tolerated lipid-modifying therapy, including a statin, at a stable dose and regimen for at least 4 weeks prior to screening (6 weeks for fibrates). Regimens other than daily dosing, including those at very low doses, are acceptable.
A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.
Patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day will be excluded from this study.

For the complete list of inclusion and exclusion criteria, please refer to Section 7 of the protocol.

New Text:

Diagnosis and key criteria for patient eligibility:

The study will enroll adult male and female patients with hyperlipidemia

~~Key-Each patient must meet the following eligibility criteria include the following to be eligible for this study:~~

Inclusion Criteria

- Provision of written informed consent prior to any study-specific procedure
- *Age ≥ 18 years or legal age of majority depending on regional law, whichever is greater at Week -2 (Visit S1)*
- Men and nonpregnant, nonlactating women. *Women must be either:*
 - *Naturally postmenopausal (as reported by the patient, 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, but not tubal ligation alone) or;*

- *Women of childbearing potential must be willing to use 1 acceptable method of birth control. 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).*
 - *There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.*
 - ~~Age ≥ 18 years or legal age of majority depending on regional law, whichever is greater at Week -2 (Visit S1)~~ Qualifying fasting LDL-C value at Week -2 (Visit S1) ≥ 70 mg/dL (1.8 mmol/L)
Note: LDL-C may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat LDL-C, the mean of the first value and the repeat value will be used to determine eligibility.
 - ~~Qualifying fasting TG value at Week -2 (Visit S1) ≤ 400 mg/dL (4.5 mmol/L)~~
 - ~~Body mass index (BMI) < 50 kg/m²~~
 - Have high cardiovascular risk that is defined as either:
 - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is > 8 points (see Appendix 4) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not have established coronary heart disease (CHD) or CHD risk equivalents.
- OR**
- Have ASCVD (with established CHD or CHD risk equivalents)
Documented history of CHD (includes 1 or more of the following):
 - Acute myocardial infarction (MI)
 - Silent MI
 - Unstable angina
 - Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)
 - Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging)Documented CHD risk equivalents (includes 1 or more of the following criteria):
 - Peripheral arterial disease
 - Previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease
- Be on maximally tolerated lipid-modifying therapy, including a *maximally tolerated* statin *either alone or in combination with other lipid-lowering therapies*, at ~~a~~ stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; *however, gemfibrozil is not allowed*). Regimens other than daily dosing, including those at very low doses, are acceptable.

A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

Patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day will be excluded from this study.

Patients who are currently taking a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.

Exclusion Criteria:

- *Total fasting triglyceride >400 mg/dL (4.5 mmol/L) at Week -2 (Visit S1)*

Note: TG may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG, the mean of the first value and the repeat value will be used to determine eligibility.

- *Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <45 mL/min/1.73 m² at Week -2 (Visit S1) [1].*

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

- *Body mass index (BMI) ≥50 kg/m²*
- *Concomitant use of high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg daily.*
- *Concomitant use of a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) at Week -2 (Visit S1) or prior use of a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.*

Note: Patients are allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.

- *Recent (within 3 months prior to the screening visit [Week -2 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.*
- *Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the Investigator, the screening period may be extended up to 2 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria*
- *Hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -2 (Visit S1)*

- *Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $>1.5 \times$ the upper limit of normal (ULN) at Week -2 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.*
- *Liver disease or dysfunction, including:*
- *Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or*
- *Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 1.5 \times$ ULN, and/or total bilirubin (TB) $\geq 1.2 \times$ ULN at Week -2 (Visit S1).*

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.
- *Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption*
- *Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL (100 g/L) at Week -2 (Visit S1)*
- *Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed)*
- *Unexplained creatine kinase (CK) $>3 \times$ ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK $\leq 3 \times$ ULN prior to randomization.*
- *History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.*
- *Blood donation, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization*
- *Blood transfusion for any reason within 90 days prior to randomization*
- *Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer*
- *Prior participation in a previous ETC-1002 clinical study. Prior participation in a clinical study with ETC-1002 is defined as having been enrolled in an ETC-1002 study.*
- *Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study;*
- *New or planned dose changes of systemic corticosteroids*
- *Requirement for mipomersen or lomitapide or apheresis therapy*
- *Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:*
 - *Hormone replacement (6 weeks prior to randomization)*
 - *Thyroid replacement (6 weeks prior to randomization)*
 - *Diabetes medications (4 weeks prior to randomization)*
 - *Obesity medication (6 months prior to randomization)*
- *An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.*

For the complete list of inclusion and exclusion criteria, please refer to [Section 7](#) of the protocol.

CHANGE 9 DEFINITION OF CLINICAL ENDPOINTS

Location:

Synopsis; Criteria for evaluation

Original Text:

Safety Assessments:

Adverse events (AEs) and SAEs will be collected and reported. MACE will be collected and adjudicated by an independent CEC. Until the CEC has been established, MACE that also meets the definition of an SAE will be reported both as MACE and as SAEs.

New Text:

Safety Assessments:

Adverse events (AEs) and SAEs will be collected and reported. ~~MACE~~ *Clinical endpoints* will be collected and adjudicated by an independent CEC. ~~Until the CEC has been established, MACE that also meets the definition of an SAE will be reported both as MACE and as SAEs~~ *Clinical endpoints will also be reported as SAEs.*

CHANGE 10 UPDATE CLINICAL LABORATORY PARAMETERS

Location:

Synopsis; Criteria for evaluation

Original Text:

Safety Assessments:

Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, coagulation, glycosylated hemoglobin type A_{1c} [HbA_{1c}], fasting glucose, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram [ECG] readings, and weight.

New Text:

Safety Assessments:

Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, coagulation, glycosylated hemoglobin type A_{1c} [HbA_{1c}], ~~fasting~~ glucose, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram [ECG] readings, and weight.

CHANGE 11 UPDATE CLINICAL LABORATORY PARAMETERS

Location:

Synopsis; Criteria for evaluation

Original Text:

Clinical Laboratory Assessments:

- Coagulation: Prothrombin time (PT), activated partial thromboplastin time (PTT)

New Text:

Clinical Laboratory Assessments:

- Coagulation: Prothrombin time (PT), ~~activated partial thromboplastin time (PTT)~~

CHANGE 12 UPDATE CLINICAL LABORATORY PARAMETERS

Location:

Synopsis; Criteria for evaluation

Original Text:

Clinical Laboratory Assessments:

- Insulin

New Text:

Clinical Laboratory Assessments:

- ~~Insulin~~

CHANGE 13 UPDATE CLINICAL LABORATORY PARAMETERS

Location:

Synopsis; Criteria for evaluation

Original Text:

Other Screening Laboratories:

- Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), serum pregnancy test (only for females who are of childbearing potential), thyroid-stimulating hormone (TSH)

New Text:

Other Screening Laboratories:

- Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), serum pregnancy test (only for females who are of childbearing potential), *FSH (only for females who are <55 years old and >1 year without menses)*, ~~thyroid-stimulating hormone (TSH)~~

CHANGE 14 REVISE SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

Synopsis; Safety and Monitoring:

Original Text:

Monitoring and Management Plans for Lipid Elevations:

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is $\geq 25\%$ from the patient's baseline value at Week 0 (Visit T1)

New Text:

Monitoring and Management Plans for Lipid Elevations:

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is $>170 \text{ mg/dL}$ (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0 (Visit T1)

CHANGE 15 REVISE SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

Synopsis; Safety and Monitoring:

Original Text:

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. Potential cases of reversible hypoglycemia and metabolic acidosis will be identified by routine safety monitoring of AEs and clinical safety laboratories.

New Text:

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. *Patients will be educated on the signs and symptoms of hypoglycemia and provided with a wallet card that gives instructions for treatment and for reporting the experienced signs and symptoms to the investigator. Investigator confirmed occurrences of hypoglycemia will be reported as AEs.* Potential cases of reversible hypoglycemia and metabolic acidosis will be identified by routine safety monitoring of AEs and clinical safety laboratories.

CHANGE 16 REVISE SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

Synopsis; Safety and Monitoring:

Original Text:

Diabetes and Glycemia:

Cases of new onset of diabetes will be recorded as AEs. Clinical laboratories, including HbA_{1c}, glucose, and insulin will also be evaluated across treatment groups during this study and all ongoing studies to identify potential cases of new onset of diabetes.

New Text:

Diabetes and ~~Glycemia~~Hyperglycemia:

Cases of new onset of diabetes will be recorded as AEs. Clinical laboratories, including HbA_{1c}, *and* glucose, ~~and insulin~~ will also be evaluated across treatment groups during this study and all ongoing studies to identify potential cases of new onset of diabetes.

CHANGE 17 REVISE SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

Synopsis; Safety and Monitoring:

Original Text:

Cardiovascular Events (MACE):

MACE will be monitored and adjudicated by an independent expert CEC for this study and other ongoing studies in the ETC-1002 program.

New Text:

~~Cardiovascular Events (MACE)~~ *Clinical Endpoints:*

~~MACE~~ *Clinical endpoints* will be monitored and adjudicated by an independent expert CEC for this study and other ongoing studies in the ETC-1002 program.

CHANGE 18 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

Sample Size

The sample size of 600 patients randomized to ETC-1002 and 300 patients randomized to placebo will provide 900 total patients. This sample size was selected to provide a robust long-term safety profile in patients considered to have an unmet need for additional lipid lowering in a chronic setting.

New Text:

Sample Size

A total of 900 patients will be enrolled in this study with 600 patients randomized to ETC-1002 and 300 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥6 Months</i>	<i>Patients ≥12 Months</i>
<i>ETC-1002</i>	<i>555</i>	<i>540</i>
<i>Placebo</i>	<i>278</i>	<i>270</i>

Absolute risk will be addressed by 600 patients randomized to ETC-1002 and will provide at least 95% power to detect Adverse Events (AEs) that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events [2]. In this study adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of 600 patients randomized to ETC-1002 and 300 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits):

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
0.5%	0.5%	1.0	(0.1, 7.0)
0.5%	1.0%	2.0	(0.3, 11.9)
13.6%	13.6%	1.0	(0.7, 1.4)
13.6%	27.2%	2.0	(0.5, 2.3)

~~The sample size of 600 patients randomized to ETC-1002 and 300 patients randomized to placebo will provide 900 total patients. This sample size was selected to provide a robust long term safety profile in patients considered to have an unmet need for additional lipid lowering in a chronic setting.~~

CHANGE 19 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

Analysis Populations

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

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

New Text:

Analysis Populations

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

The Full Analysis Set (FAS), used for *the LDL-C analyses and the all of the* lipid and cardiometabolic summaries, is defined as all randomized patients and is also known as the intention-to-treat (ITT) set of patients.

CHANGE 20 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

Primary Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

No statistical analyses will be performed on any of the safety data in this study. The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. AE

summaries will be provided overall and for subgroups such as gender, age, and HeFH status. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

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

New Text:

Primary Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

No statistical analyses will be performed on any of the safety data in this study. The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. AE summaries *will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. These AE summaries* will be provided overall and for subgroups such as gender, age, and HeFH status. *If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates.* Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

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

CHANGE 21 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

Diabetes and Glycemia

Cases of new onset of diabetes will be recorded as AEs. Clinical laboratories, including HbA_{1c}, glucose, and insulin will also be evaluated across treatment groups during this study and all ongoing studies to identify potential cases of new onset of diabetes.

New Text

Diabetes and Glycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group. ~~insulin~~, Glucose and HbA_{1C} will be monitored at baseline and at Weeks 12, 24, and 52, and be summarized.

CHANGE 22 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

Renal Safety

Baseline estimated glomerular filtration rate (eGFR) will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. If needed, post-baseline eGFR categories will be modified to include the possibility of patients with eGFR values <45 mL/min/1.73 m². Shift tables of urine protein (negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

New Text:

Renal Safety

Baseline estimated glomerular filtration rate (eGFR) will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. ~~If needed, post-baseline eGFR categories will be modified to include the possibility of patients with eGFR values <45 mL/min/1.73 m².~~ Shift tables of urine protein (negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

CHANGE 23 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

Cardiovascular Events (MACE)

MACE will be monitored and adjudicated by an independent blinded expert CEC for ongoing studies the ETC-1002 program. Adjudicated MACE will be summarized by event type and treatment group. Additional details regarding MACE and MACE definitions will be included in CEC charter.

New Text:

~~Cardiovascular Events (MACE)~~Clinical Endpoints

~~MACE~~-Clinical endpoints will be monitored and adjudicated by an independent blinded expert CEC for ongoing studies the ETC-1002 program. Adjudicated ~~MACE~~-clinical endpoints will be summarized by event type and treatment group. Additional details regarding ~~MACE~~-clinical endpoints and ~~MACE~~ clinical endpoint definitions will be included in CEC charter.

CHANGE 24 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

Lipids

LDL-C, HDL-C, TG, TC, non-HDL-C, and apoB values at Weeks 12, 24, and 52 will be summarized. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. Missing values for any of the lipid parameters will not be imputed; that is, only observed case data will be used.

New Text:

Secondary Endpoint Lipids

Percent change from baseline to Week 12 in LDL-C will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors and baseline LDL-C as a covariate. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). For each ANCOVA (observed case; imputation via PMM), output will include the least squares mean (LSM) and standard error (SE) for each treatment group, along with the placebo-correct LSM and its 95% confidence interval (CI) and p-value.

Tertiary Endpoint Lipids

LDL-C, HDL-C, TG, TC, non-HDL-C, and apoB values at Weeks 12, 24, and 52 will be summarized. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. In addition, a summary using the FAS, excluding patients who received additional lipid-lowering therapy by that timepoint (by Week 24 for the Week 24 timepoint; by Week 52 for the Week 52 timepoint), will be provided. For both summaries, only observed case data will be used (no imputation for missing data).

Percent change from baseline to Week 24 and to Week 52 on LDL-C will be analyzed similarly, with patients in the FAS who did not receive additional lipid-lowering therapy by that timepoint (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI and p-value.

~~LDL-C, HDL-C, TG, TC, non-HDL-C, and apoB values at Weeks 12, 24, and 52 will be summarized. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. Missing values for any of the lipid parameters will not be imputed; that is, only observed case data will be used.~~

CHANGE 25 REVISED STATISTICS

Location:

Synopsis; Statistical Methods:

Original Text:

PK and Other biomarkers

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. Missing values for hs-CRP will not be imputed; only observed case data will be used.

In addition, trough plasma concentrations will be collected at Weeks 12, 24, and 52 for use in further developing the population pharmacokinetic (PK) model.

New Text:

PK and Other biomarkers

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. *The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).* ~~Missing values for hs-CRP will not be imputed; only observed case data will be used.~~

In addition, trough plasma concentrations will be collected at Weeks 12, 24, and 52 for use in further developing the population pharmacokinetic (PK) model.

CHANGE 26 TYPOGRAPHICAL AND FORMATTING

Location:

Table 1: Abbreviations and Specialist Terms

Original Text:

Abbreviation or Specialist Term	Explanation
ACL	Adenosine triphosphate-citrate lyase
ACS	Acyl-CoA synthetase
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
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

Abbreviation or Specialist Term	Explanation
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CABG	Coronary artery bypass graft
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CK	Creatine kinase
Cl	Chloride
C _{max}	Time to peak maximum concentrations
CMV	Cytomegalovirus
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO ₂	Carbon dioxide
CrCL	Creatinine clearance
CT	Computed tomography
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
eGFR	Estimated glomerular filtration rate
EU	European Union
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA _{1c}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit

Abbreviation or Specialist Term	Explanation
HCV	Hepatitis C virus
HCV-AB	Hepatitis C antibodies
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
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
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 cardiovascular events and mortality
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MED ID	Medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging

Abbreviation or Specialist Term	Explanation
Na	Sodium
NIMP	Non-investigational medicinal product(s)
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
PT	Prothrombin time
PTT	Partial thromboplastin time
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
SOP	Standard operating procedures
SP	Safety population
t _½	Terminal elimination half-live
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
TQT	Thorough QT/QTc
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

New Text:

Abbreviation or Specialist Term	Explanation
ACL	Adenosine triphosphate-citrate lyase
ACS	Acyl-CoA synthetase
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
<i>ANCOVA</i>	<i>Analysis of covariance</i>
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
CABG	Coronary artery bypass graft
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Coronary heart disease
<i>CI</i>	<i>Confidence interval</i>
CK	Creatine kinase
Cl	Chloride
C _{max}	Time to peak maximum concentrations
CMV	Cytomegalovirus
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO ₂	Carbon dioxide
CrCL	Creatinine clearance
CT	Computed tomography
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
EMA	European Medicines Agency
eGFR	Estimated glomerular filtration rate
<i>EOS</i>	<i>End of Study</i>
EU	European Union
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA _{1c}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-AB	Hepatitis C antibodies
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
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
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat

Abbreviation or Specialist Term	Explanation
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
<i>LSM</i>	<i>Least square mean</i>
MACE	Major adverse cardiovascular cardiac event and mortality
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MED ID	Medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
NIMP	Non-investigational medicinal product(s)
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
<i>PMM</i>	<i>Pattern mixed model</i>
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation or Specialist Term	Explanation
SBP	Systolic blood pressure
<i>SE</i>	<i>Standard error</i>
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SOP	Standard operating procedures
SP	Safety population
<i>SUSARS</i>	<i>Suspected and unexpected serious adverse reactions</i>
$t_{1/2}$	Terminal elimination half-life
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
TQT	Thorough QT/QTc
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

CHANGE 27 TYPOGRAPHICAL AND FORMATTING

Location:

4.1 Lipid-Regulating Drugs and Cardiovascular Disease

7.2 Subject Exclusion Criteria

11.4 Adverse Events of Special Interest

Note:

References were updated to include an additional reference in the amendment and renumbered accordingly. The new reference numbers within the text are not highlighted as edited text.

CHANGE 28 TYPOGRAPHICAL AND FORMATTING

Location:

4.1 Lipid-Regulating Drugs and Cardiovascular Disease

Original Text:

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 [12]. The National Lipid Association (NLA) adult recommendations achievement of $\geq 50\%$ reduction in LDL-C using statins.

New Text:

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 [12]. The National Lipid Association (NLA) ~~adult recommendations~~ *recommends* achievement of $\geq 50\%$ reduction in LDL-C *in adult patients* using statins.

CHANGE 29 ADDITION OF SECONDARY AND TERTIARY STUDY OBJECTIVES

Location:

5 TRIAL OBJECTIVES AND PURPOSE

Original Text:

5. TRIAL OBJECTIVES AND PURPOSE

5.1 Primary Objective

The primary objective is to evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

5.2 Secondary Objectives

- To assess lipid values LDL-C, high-density lipoprotein cholesterol [HDL-C], non-HDL-C, total cholesterol [TC], and TG) at 12, 24, and 52 weeks
- To assess apoB and high-sensitivity C-reactive protein (hs-CRP) at 12, 24, and 52 weeks

New Text:

5. TRIAL OBJECTIVES AND PURPOSE

5.1 Primary Objective

The primary objective is to evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

5.2 Secondary Objectives

- *To assess percent change from baseline to Week 12 in LDL-C*
- ~~To assess lipid values LDL-C, high-density lipoprotein cholesterol [HDL-C], non-HDL-C, total cholesterol [TC], and TG) at 12, 24, and 52 weeks~~
- ~~To assess apoB and high-sensitivity C-reactive protein (hs-CRP) at 12, 24, and 52 weeks~~

5.3 *Tertiary Objectives*

- *To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy*
- *To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and TG at Weeks 12, 24, and 52*
- *To assess apoB and high-sensitivity C-reactive protein (hs-CRP) at Weeks 12, 24, and 52*

CHANGE 30 ADDITION OF PROTOCOL REQUIREMENTS TO ADDRESS THE AVAILABILITY OF PCSK9 INHIBITORS

Location:

6.1 Overall Study Design

Original Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil], evolocumab, and alirocumab). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day will be excluded from this study.

New Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil], ~~evolocumab, and alirocumab~~). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 80 mg per day, *or who are currently taking a PCSK9 inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1)* will be excluded from enrolling in this study. *PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.*

CHANGE 31 TYPOGRAPHICAL AND FORMATTING

Location:

6.1 Overall Study Design

Table 2, footnotes

Original Text:

-
- ^a Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)
- ^b Atorvastatin 80 mg is not allowed in this study
- ^c Rosuvastatin 40 mg is not allowed in this study
- ^d Simvastatin 40 mg is not allowed in this study

New Text:

Note: The highest dose statins are allowed if given on less than a daily basis.

- ^a Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)
- ^b Atorvastatin 80 mg *daily* is not allowed in this study.
- ^c Rosuvastatin 40 mg *daily* is not allowed in this study
- ^d Simvastatin 40-80 mg *daily* is not allowed in this study

CHANGE 32 TYPOGRAPHICAL AND FORMATTING

Location:

6.1 Overall Study Design

Table 3, footnotes

Original Text:

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

^a Atorvastatin 80 mg, rosuvastatin 40 mg, and simvastatin 40 mg are not allowed in this study.

New Text:

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

^a Atorvastatin 80 mg, rosuvastatin 40 mg, and simvastatin 40-80 mg *daily* are not allowed in this study.

CHANGE 33 DEFINITION OF CLINICAL ENDPOINTS

Location:

6.1 Overall Study Design

Original Text:

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety data from this and other ongoing studies of ETC-1002. All CV events, including death, will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions. Until the CEC has been established, CV events will be reported as both SAE and major adverse cardiovascular events and mortality (MACE).

New Text:

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety *and efficacy* data from this and other ongoing studies of ETC-1002. All ~~CV events~~ *clinical endpoints, including all major 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), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions. Until the CEC has been established, CV* Any clinical endpoints that meet SAE criteria will be reported as both SAEs and major adverse cardiovascular events and mortality (MACE).

CHANGE 34 TYPOGRAPHICAL AND FORMATTING

Location:

6.2 Study Hypothesis

Original Text:

The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = 900) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option.

New Text:

The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin *alone or in combination with other lipid-lowering therapies*, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = 900) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option.

CHANGE 35 CLARIFICATION OF DURATION OF TREATMENT AND END OF STUDY

Location:

6.3 End of Study

Original Text:

The study will end when the last randomized patient completes 52 weeks of treatment (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 22 months.

New Text:

The study will end when the last randomized patient completes ~~52 weeks of their last study visit treatment~~ (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 22 months.

CHANGE 36 REVISED INCLUSION/EXCLUSION CRITERIA

Location:

7.1 Subject Inclusion Criteria

Original Text:

5. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin, at a stable dose for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed). Regimens other than daily dosing, including those at very low doses, are acceptable.

A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

New Text:

5. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin *either alone or in combination with other lipid-lowering therapies*, at a stable doses for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed). Regimens other than daily dosing, including those at very low doses, are acceptable.

A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

CHANGE 37 REVISED INCLUSION/EXCLUSION CRITERIA

Location:

7.2 Subject Exclusion Criteria

Original Text:

4. Concomitant use of high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg
5. Recent (within 3 months prior to the screening visit [Week -2 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was

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

6. Current clinically significant cardiovascular disease, including but not limited to:
 - New York Heart Association (NYHA) Functional Classification Class III or IV heart failure
 - Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥ 160 mmHg and diastolic blood pressure (DBP) ≥ 100 mmHg after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the Investigator, the screening period may be extended up to 2 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria, or
7. Hemoglobin A_{1C} (HbA_{1C}) $\geq 10\%$ at Week -2 (Visit S1)
8. History of chronic, unstable musculoskeletal symptoms that may require changes in background medications or, in the opinion of the Investigator, may confound an evaluation of AEs associated with muscle symptoms. Patients with stable musculoskeletal diseases on stable therapy may enroll at the discretion of the Investigator.
9. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $> 1.5 \times$ the upper limit of normal (ULN) at Week -2 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.
10. Liver disease or dysfunction, including:
 - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or
 - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 1.5 \times$ ULN, and/or total bilirubin (TB) $\geq 1.2 \times$ ULN at Week -2 (Visit S1).

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.
11. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band[®] or gastric bypass) that may affect drug absorption

12. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <12.0 g/dL (120 g/L) at Week -2 (Visit S1)
13. History of Acquired Immunodeficiency Syndrome or a positive test for human immunodeficiency virus (HIV)
14. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed)
15. Unexplained creatine kinase (CK) $>3 \times$ ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK $\leq 3 \times$ ULN prior to randomization.
16. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
17. Blood donation, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization
18. Blood transfusion for any reason within 90 days prior to randomization
19. Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer
20. Prior participation in a previous ETC-1002 clinical study. Prior participation in a clinical study with ETC-1002 is defined as having been enrolled in an ETC-1002 study.
21. Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study;
 - New or planned dose changes of systemic corticosteroids
 - Requirement for mipomersen or lomitapide or apheresis therapy
22. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
 - Hormone replacement (6 weeks prior to randomization)
 - Thyroid replacement (6 weeks prior to randomization)
 - Diabetes medications (4 weeks prior to randomization)
 - Obesity medication (6 months prior to randomization)
23. Any current condition, laboratory finding, family history, or electrocardiogram (ECG) finding that in either the Investigator's, Sponsor's, or authorized Medical Monitor's opinion may compromise patient safety or ability to complete the study or interfere with study data interpretation
24. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

New Text:

4. Concomitant use of high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg *daily*
5. *Concomitant use of a PCSK9 inhibitor (Praluent[®] [alirocumab] or Repatha[®] [evolocumab]) at Week -2 (Visit S1) or prior use of a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.*

Note: Patients are allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.

56. Recent (within 3 months prior to the screening visit [Week -2 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.
 - ~~Current clinically significant cardiovascular disease, including but not limited to: New York Heart Association (NYHA) Functional Classification Class III or IV heart failure~~
- 7. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥ 160 mmHg and diastolic blood pressure (DBP) ≥ 100 mmHg after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the Investigator, the screening period may be extended up to 2 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria; ~~or~~
8. Hemoglobin A_{1C} (HbA_{1C}) $\geq 10\%$ at Week -2 (Visit S1)
9. ~~History of chronic, unstable musculoskeletal symptoms that may require changes in background medications or, in the opinion of the Investigator, may confound an evaluation of AEs associated with muscle symptoms. Patients with stable musculoskeletal diseases on stable therapy may enroll at the discretion of the Investigator.~~
9. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $> 1.5 \times$ the upper limit of normal (ULN) at Week -2 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.

10. Liver disease or dysfunction, including:

- Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 1.5 \times$ ULN, and/or total bilirubin (TB) $\geq 1.2 \times$ ULN at Week -2 (Visit S1).

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.

11. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band[®] or gastric bypass) that may affect drug absorption
12. Hematologic or coagulation disorders or a hemoglobin (Hgb) level $< 12/10.0$ g/dL (~~120/100~~ g/L) at Week -2 (Visit S1)
- ~~13. History of Acquired Immunodeficiency Syndrome or a positive test for human immunodeficiency virus (HIV)~~
13. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed)
14. Unexplained creatine kinase (CK) $> 3 \times$ ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK $\leq 3 \times$ ULN prior to randomization.
15. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
16. Blood donation, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization
17. Blood transfusion for any reason within 90 days prior to randomization
18. Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer
19. Prior participation in a previous ETC-1002 clinical study. Prior participation in a clinical study with ETC-1002 is defined as having been enrolled in an ETC-1002 study.
20. Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study;
- New or planned dose changes of systemic corticosteroids
 - Requirement for mipomersen or lomitapide or apheresis therapy
21. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
- Hormone replacement (6 weeks prior to randomization)

- Thyroid replacement (6 weeks prior to randomization)
- Diabetes medications (4 weeks prior to randomization)
- Obesity medication (6 months prior to randomization)

~~22. Any current condition, laboratory finding, family history, or electrocardiogram (ECG) finding that in either the Investigator's, Sponsor's, or authorized Medical Monitor's opinion may compromise patient safety or ability to complete the study or interfere with study data interpretation~~

22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.



CHANGE 38 CLARIFICATION OF IMP

Location:



8.1 Description of IMP

Table 4

Original Text:

	Investigational Medicinal Product	
Product Name:	ETC-1002	Placebo
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure	35 and/or 100 count bottle (depending upon visit) with screw on, non-child proof cap	35 and/or 100 count bottle (depending upon visit) with screw on, non-child proof cap
Route of Administration:	Oral, daily in the morning, with or without food	Oral, daily in the morning, with or without food
Physical Description:	Oval, white to off-white film-coated tablet debossed with "ABC" on one face and debossed with "000" on the opposite face	Oval, white to off-white film-coated tablet debossed with "ABC" on one face and debossed with "000" on the opposite face
Manufacturer (Fill/Finish):		

New Text:

	Investigational Medicinal Product	
Product Name:	ETC-1002	Placebo
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure^a	35- and/or 100-count bottle (depending upon visit) with screw on, non-child proof cap	35- and/or 100-count bottle (depending upon visit) with screw on, non-child proof cap
Route of Administration:	Oral, daily in the morning, with or without food	Oral, daily in the morning, with or without food
Physical Description:	Oval, white to off-white film-coated tablet debossed with “ABC” on one face and debossed with “000” on the opposite face	Oval, white to off-white film-coated tablet debossed with “ABC” on one face and debossed with “000” on the opposite face
Manufacturer (Fill/Finish):		

^a A 100-day supply of IMP will be included in the 100-count bottle and a 35-day supply of IMP will be included in the 35-count bottle.

CHANGE 39 ADDITION OF PROTOCOL REQUIREMENTS TO ADDRESS THE AVAILABILITY OF PCSK9 INHIBITORS

Location:

8.2.1 Lipid-Regulating Medications and Supplements

Original Text:

Patients will be required to be on stable lipid-modifying therapy(s), including a maximally tolerated statin for at least 4 weeks prior to screening. Use of fibrates must be stable at least 6 weeks prior to screening. Gemfibrozil, a fibrate, is prohibited. Stable lipid-modifying therapy(s) includes, but is not limited to, monotherapies or combination therapies containing the compounds below:

Statins

- Atorvastatin (Lipitor[®], Sortis[®]), with doses <80 mg
- Fluvastatin (Lescol[®])
- Lovastatin (Mevacor[®], Altoprev[™])
- Pravastatin (Pravachol[®])
- Pitavastatin (Livalo[®], Lipostat[®])
- Rosuvastatin (Crestor[®]), with doses <40 mg
- Simvastatin (Zocor[®]), with doses <40 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestyramine (Questran[®], Questran Light[®], Prevalite[®], Locholest[®], Locholest[®] Light)
- Colestipol (Colestid[®])
- Colesevelam hydrochloride (Welchol[®], Cholestagel[®])
- Ezetimibe (Zetia[®], Ezetrol[®])

Fibrates

- Fenofibrate (Antara[®], Lofibra[®], Tricor[®], Triglide[™], Lipantil[®], Supralip[®])
- Bezafibrate (Bezalip[®])
- Ciprofibrate (Modalim[®])

Other

- Simvastatin/ezetimibe (Vytorin[®], Inegy[®]) with dose of simvastatin <40 mg
- Lovastatin/niacin (Advicor[®])
- Simvastatin/niacin (Simcor[®]) with dose of simvastatin <40 mg
- Atorvastatin/ezetimibe (Liptruset[®], Atozet[®]) with dose of atorvastatin <80 mg

New Text:

Patients will be required to be on stable lipid-modifying therapy(s), including a maximally tolerated statin for at least 4 weeks prior to screening. Use of fibrates must be stable at least 6 weeks prior to screening. Gemfibrozil, a fibrate, is prohibited. *Patients may not currently be taking or have taken a PCSK9 inhibitor within 4 weeks prior to Screening (Week -2, Visit S1); however, they may be allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.* Stable lipid-modifying therapy(s) includes, but is not limited to, monotherapies or combination therapies containing the compounds below:

Statins

- Atorvastatin (Lipitor[®], Sortis[®]), with doses <80 mg
- Fluvastatin (Lescol[®])
- Lovastatin (Mevacor[®], Altoprev[™])
- Pravastatin (Pravachol[®])
- Pitavastatin (Livalo[®], Lipostat[®])
- Rosuvastatin (Crestor[®]), with doses <40 mg
- Simvastatin (Zocor[®]), with doses <40 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestyramine (Questran[®], Questran Light[®], Prevalite[®], Locholest[®], Locholest[®] Light)
- Colestipol (Colestid[®])
- Colesevelam hydrochloride (Welchol[®], Cholestagel[®])
- Ezetimibe (Zetia[®], Ezetrol[®])

Fibrates

- Fenofibrate (Antara[®], Lofibra[®], Tricor[®], Triglide[™], Lipantil[®], Supralip[®])
- Bezafibrate (Bezalip[®])
- Ciprofibrate (Modalim[®])

PCSK9 inhibitors (allowed as adjunctive therapy beginning at Week 24 [Visit T5]; see Section 11.1.6.3.5)

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

Other

- Simvastatin/ezetimibe (Vytorin[®], Inegy[®]) with dose of simvastatin <40 mg
- Lovastatin/niacin (Advicor[®])
- Simvastatin/niacin (Simcor[®]) with dose of simvastatin <40 mg
- Atorvastatin/ezetimibe (Liptruset[®], Atozet[®]) with dose of atorvastatin <80 mg

**CHANGE 40 ADDITION OF PROTOCOL REQUIREMENTS TO ADDRESS THE
AVAILABILITY OF PCSK9 INHIBITORS**

Location:

8.2.2 Prohibited Medications

Original Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥ 4 weeks). Short-term intermittent use (< 14 days) of pulse steroids are allowed.
- Gemfibrozil (Lopid[®])
- Cholestin (red yeast rice, also known as monascus purpureus extract)
- Atorvastatin (Lipitor[®], Sortis[®]) 80 mg, Simvastatin (Zocor[®]) 40-80 mg, and Rosuvastatin (Crestor[®]) 40 mg alone or in fixed-dose combinations (eg, Liptruzet[®], Vytorin[®]/Inegy[®], Simcor[®])

New Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥ 4 weeks). Short-term intermittent use (< 14 days) of pulse steroids are allowed.
- Gemfibrozil (Lopid[®])
- Cholestin (red yeast rice, also known as monascus purpureus extract)
- Atorvastatin (Lipitor[®], Sortis[®]) 80 mg, Simvastatin (Zocor[®]) 40-80 mg, and Rosuvastatin (Crestor[®]) 40 mg alone or in fixed-dose combinations (eg, Liptruzet[®], Vytorin[®]/Inegy[®], Simcor[®])

Patients will not have used the medications listed below within 4 weeks prior to screening:

- Alirocumab (Praluent[®])
- Evolocumab (Repatha[®])
- *Note: Patients may be allowed to initiate a PCSK9 inhibitor as adjunctive therapy at Week 24 if the LDL-C threshold has been met as described in Section 11.1.6.3.5.*

**CHANGE 41 ADDITION OF PROTOCOL REQUIREMENTS TO ADDRESS THE
AVAILABILITY OF PCSK9 INHIBITORS**

Location:

8.2.3 Allowable Medications

Original Text:

Other concomitant medication must be stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety.

The following must be stable for a minimum of 6 weeks prior to randomization:

- Postmenopausal hormone therapy
- Thyroid hormone supplements
- Fibrates (excluding gemfibrozil)

The following must be stable for: a minimum of 4 weeks prior to screening:

- Hypertriglyceridemia therapy
- Lipid-lowering therapy, including dietary supplements and herbal remedies used for the purposes of lipid lowering
- Diabetes medications

The following must be stable for a minimum of 6 months prior to screening and, if possible not be adjusted during the study except for reasons of safety:

- Antiobesity medications

New Text:

Other concomitant medication must be stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety.

The following must be stable for a minimum of 6 weeks prior to randomization:

- Postmenopausal hormone therapy
- Thyroid hormone supplements
- Fibrates (excluding gemfibrozil)

The following must be stable for: a minimum of 4 weeks prior to screening:

- Hypertriglyceridemia therapy
- Lipid-lowering therapy, including dietary supplements and herbal remedies used for the purposes of lipid lowering
- Diabetes medications

The following must be stable for a minimum of 6 months prior to screening and, if possible not be adjusted during the study except for reasons of safety:

- Antiobesity medications

The following may not be taken within 4 weeks of Screening (Week -2, Visit S1), but may be initiated beginning at Week 24 if LDL-C threshold criteria have been met and it is needed as adjunctive LDL-C-lowering therapy.

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

CHANGE 42 UPDATE CLINICAL LABORATORY PARAMETERS

Location:

8.4 Blinding

Original Text:

Postrandomization values for individual laboratory measures for LDL-C, TG, apoB, and hs-CRP, including any plasma concentration of ETC-1002 and its metabolite, that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, [REDACTED]

New Text:

Postrandomization values for individual laboratory measures for LDL-C, TG, TC, HDL-C, non-HDL, apoB, and hs-CRP, including any plasma concentration of ETC-1002 and its metabolite, that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, and [REDACTED]

CHANGE 43 DEFINITION OF CLINICAL ENDPOINTS

Location:

8.4 Blinding

Original Text:

An independent blinded expert CEC will adjudicate all CV events, including death, using standardized definitions. Until the CEC has been established, CV events will be reported as both SAE and MACE. Additional details and definitions will be provided in a CEC Charter.

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

New Text:

An independent blinded expert CEC will adjudicate all ~~CV events~~ clinical endpoints, including death, using standardized definitions. *Clinical endpoints will also be reported as SAEs.* ~~Until the~~

~~CEC has been established, CV events will be reported as both SAE and MACE.~~ Additional details and definitions will be provided in a CEC Charter.

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

CHANGE 44 CLARIFICATION OF IMP

Location:

8.4 Blinding

Original Text:

Double-blind IMP will be dispensed in 90 day supply increments (one 90-day supply bottle) to patients by appropriate clinical site personnel at Week 0 (Visit T1), Week 12 (Visit T4), and Week 24 (Visit T5). Double-blind IMP will be dispensed in 125-day supply increments (2 bottles; one 90-day supply bottle and one 35-day supply bottle) to patients at Week 36 (Visit T6).

New Text:

Double-blind IMP will be dispensed in ~~90~~100 day supply increments (one ~~90~~100-day supply bottle) to patients by appropriate clinical site personnel at Week 0 (Visit T1), Week 12 (Visit T4), and Week 24 (Visit T5). Double-blind IMP will be dispensed in ~~125~~35-day supply increments (2 bottles; one ~~90~~100-day supply bottle and one 35-day supply bottle) to patients at Week 36 (Visit T6).

CHANGE 45 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

10.2.1 Screening Week -2 (Visit S1; Days -16 to -4)

Original Text:

The screening period will begin with a screening visit that will occur 2 weeks prior to randomization. Visit S1 will allow the Investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Demographics
- Clinically relevant medical history, including assessment of HeFH status and ASCVD
- Concomitant and prohibited medication review
- Height (cm), weight (kg), waist circumference (cm), BMI
- Vital signs

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - HbA_{1C}
 - TSH
 - Serum pregnancy test (on appropriate female patients)
- Serology (including HBsAg, HCV)
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Conduct diet and exercise counseling
- Contact IWRS to register the patient

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their therapy(s) for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. Patients who fail to meet any entry criterion that can be assessed at Visit S1 are considered to be screen failures and are not required to return for additional visits (although a patient can be seen at any time for safety reasons).

Note:

- An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, they have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) no longer meet exclusionary values.
- An optional visit between Visits S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- Patients who are considered to be screen failures due to not meeting stability requirements for a condition or concurrent medication may be considered for rescreening after consultation with the Sponsor (or designee). These patients must be re-consented, re-registered in the IWRS, and will have a new patient ID number assigned.

New Text:

The screening period will begin with a screening visit that will occur 2 weeks prior to randomization. Visit S1 will allow the Investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Demographics
- Clinically relevant medical history, including assessment of HeFH status and ASCVD
- Concomitant and prohibited medication review
- Height (cm), weight (kg), ~~waist circumference (cm)~~, BMI
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - HbA_{1C}
 - TSH
 - *FSH (in appropriate female patients)*
 - Serum pregnancy test (on appropriate female patients)
- Serology (including HBsAg, HCV)
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Conduct diet and exercise counseling
- Contact IWRS to register the patient

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their therapy(s) for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. Patients who fail to meet any entry criterion that can be assessed at Visit S1 are considered to be screen failures and are not required to return for additional visits (although a patient can be seen at any time for safety reasons).

Note:

- An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- *An optional visit between Visits S1 and T1 may be scheduled to collect screening fasting labs in the event that the patient arrives at Visit S1 in a nonfasted state.*
- An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, they have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) no longer meet exclusionary values.
- An optional visit between Visits S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

- Patients who are considered to be screen failures due to not meeting stability requirements for a condition or concurrent medication may be considered for rescreening after consultation with the Sponsor (or designee). These patients must be re-consented, re-registered in the IWRS, and will have a new patient ID number assigned.

CHANGE 46 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

10.2.2 Treatment Week 0 (Visit T1; Days 1)

Original Text:

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing the informed consent document)
- Physical examination (PE)
- Weight
- 12-Lead ECG
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - Insulin
 - hs-CRP
 - Reserve sample
- Review inclusion/exclusion criteria to establish patient eligibility
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions
- Schedule next visit

New Text:

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical examination (PE)
- Weight
- 12-Lead ECG
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - ~~Insulin~~
 - hs-CRP
 - Reserve sample
- Review inclusion/exclusion criteria to establish patient eligibility
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions
- Schedule next visit

CHANGE 47 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

10.2.3 Treatment Week 4 (Visit T2; ± 3 days)

Original Text:

Patients will undergo the following assessments and procedures at Week 4 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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)
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- Return IMP container from Visit T1 to patient for continued dosing and provide dosing instruction
- Schedule next visit

New Text:

Patients will undergo the following assessments and procedures at Week 4 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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)
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- Return IMP container from Visit T1 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.*

CHANGE 48 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

10.2.4 Treatment Week 8 (Visit T3; \pm 3 days)

Original Text:

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments 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 and current health status.

New Text:

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 medications*, and current health status.

CHANGE 49 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

10.2.5 Treatment Week 12 (Visit T4; \pm 3 days)

Original Text:

Patients will undergo the following assessments and procedures at Week 12 (Visit T4):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- Weight
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - Insulin

- hs-CRP
- PK sample
- Reserve sample
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP
- Schedule next visit

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments after withdrawing from IMP treatment, all assessments except for those procedures pertaining to apoB, hs-CRP, PK samples, reserve samples, and 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 and current health status.

New Text:

Patients will undergo the following assessments and procedures at Week 12 (Visit T4):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- Weight
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - ~~Insulin~~
 - hs-CRP
 - PK sample
 - Reserve sample
- Conduct diet and exercise counseling

- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP
- 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 apoB, hs-CRP, PK samples, reserve samples, and 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 medications*, and current health status.

CHANGE 50 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

10.2.6 Treatment Week 24 (Visit T5; \pm 3 days)

Original Text:

Patients will undergo the following assessments and procedures at Week 24 (Visit T5):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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
 - Insulin
 - hs-CRP
 - PK sample
 - Reserve sample
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP

- Dispense IMP
- Schedule next visit

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments after withdrawing from IMP treatment, all assessments except for those procedures pertaining to apoB, hs-CRP, PK samples, reserve samples, and IMP (IMP dispensing, IMP compliance, IMP accountability) management 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 and current health status.

New Text:

Patients will undergo the following assessments and procedures at Week 24 (Visit T5):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- 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
 - ~~Insulin~~
 - hs-CRP
 - PK sample
 - Reserve sample
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP
- 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 apoB, hs-CRP,

PK samples, reserve samples, and IMP (IMP dispensing, IMP compliance, IMP accountability) management 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 medications*, and current health status.

CHANGE 51 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

10.2.7 Treatment Week 36 (Visit T6; \pm 3 days)

Original Text:

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments 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 and current health status.

New Text:

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 medications*, and current health status.

CHANGE 52 UPDATED STUDY PROCEDURES

Location:

10.2.8 Treatment Week 52 (Visit T7; \pm 7 days)

Original Text:

Patients will undergo the following assessments and procedures at Week 52 (Visit T7):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- PE
- Weight

- 12-Lead ECG
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - Insulin
 - hs-CRP
 - PK sample
 - Reserve sample
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study)

Note: For patients who withdraw from IMP treatment:

- Determine whether the patient will or will not consent for follow-up visits through study completion
- If the patient provides consent to continue to be followed for safety assessments per the protocol visit schedule, schedule follow-up visits as they would have occurred if the patient were continuing in the study and complete the visit required procedures listed in the appropriate visit specific section within Section 10 and Appendix 1. No further IMP will be dispensed for patients who withdraw from IMP treatment.
- If the patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), this visit (Visit T7) will be considered the EOS/Early Withdrawal from study visit and no further visits will be scheduled.

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments after withdrawing from IMP treatment, all assessments except for those procedures pertaining to apoB, hs-CRP, PK samples, reserve samples, and IMP (IMP dispensing, IMP compliance, IMP accountability) management 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 and current health status.

New Text:

Patients will undergo the following assessments and procedures at Week 52 (Visit T7):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- PE
- Weight
- 12-Lead ECG
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - ~~Insulin~~
 - hs-CRP
 - PK sample
 - Reserve sample
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study)

Note: For patients who withdraw from IMP treatment:

- *Capture the reason for withdrawing from IMP treatment and record on the eCRF*
- Determine whether the patient will or will not consent for follow-up visits through study completion
- If the patient provides consent to continue to be followed for safety assessments per the protocol visit schedule, schedule follow-up visits as they would have occurred if the patient were continuing in the study and complete the visit required procedures listed in the appropriate visit specific section within Section 10 and Appendix 1. No further IMP will be dispensed for patients who withdraw from IMP treatment.
- If the patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), this visit (Visit T7) will be considered the EOS/Early Withdrawal from study visit and no further visits will be scheduled.

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 apoB, hs-CRP, PK samples, reserve samples, and IMP (IMP dispensing, IMP compliance, IMP accountability) management 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 medications*, and current health status.

CHANGE 53 ADDED INSTRUCTIONS FOR SUBJECT WITHDRAWAL AND RESTARTING IMP

Location:

10.3.1 Early Withdrawal from the Study

Original Text:

Patients must remain in the study until the last scheduled visit at Week 52 (Visit T7) to be considered as having completed participation in the study.

Patients who withdraw from IMP prior to Week 52 (Visit T7) for any reason will be asked to continue to be followed for safety assessments 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 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 52 weeks, to collect information on AEs 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.

New Text:

Patients who withdraw from IMP prior to Week 52 (Visit T7) 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 Week 52 (Visit T7) for any reason may restart IMP providing that 1) the patient and the investigator are in agreement regarding this course of action, 2) the patient has been off of IMP for 4 weeks or less; and 3) IMP can be started as soon as possible. For cases where the patient has been off of IMP for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting IMP.

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 52 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.

CHANGE 54 ADDED INSTRUCTION FOR SUBJECT WITHDRAWAL AND RESTARTING IMP

Location:

10.3.2 Procedures for Early Withdrawal

Original Text:

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 through Week 52 (Visit T7).

New Text:

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 Week 52 (Visit T7).

CHANGE 55 UPDATED STUDY PROCEDURES AND SCHEDULE OF EVENTS

Location:

11.1.3 Weight, Height, and Body Mass Index

Original Text:

11.1.3 Weight, Height, Waist Circumference, and Body Mass Index

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

Waist circumference will be measured around the bare abdomen just above the hipbone. Tape should be snug (but not compress skin) and parallel to the floor. The patient should be asked to relax and exhale prior to measurement.

New Text:

11.1.3 Weight, Height, ~~Waist Circumference~~, and Body Mass Index

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

~~Waist circumference will be measured around the bare abdomen just above the hipbone. Tape should be snug (but not compress skin) and parallel to the floor. The patient should be asked to relax and exhale prior to measurement.~~

CHANGE 56 UPDATE CLINICAL LABORATORY PARAMETERS

Location:

11.1.6.1 Laboratory Parameters (Safety)

Table 5

Original Text:

Clinical Laboratory Test	Clinical Laboratory Test
<ul style="list-style-type: none"> Hematology Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood (RBC) cell count White blood (WBC) cell count with differential (absolute values only) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> Albumin (Alb) Alkaline phosphatase (Alk-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO₂) Chloride (Cl) Creatinine Creatine kinase (CK) Glucose Insulin Lactate dehydrogenase (LDH) Phosphorus Potassium (K) Sodium (Na) Total and direct bilirubin (TB) Total protein Uric acid
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> Clarity Bilirubin Color Glucose Ketones Leukocyte esterase Nitrate Occult blood pH Protein Specific gravity Urobilinogen 	

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> Bacteria Casts Crystals Epithelial cells Red blood cell (RBC) WBC 	<u>Coagulation</u> <ul style="list-style-type: none"> Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International normalized ration (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), Serum pregnancy test (only for females of childbearing potential) Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> Hemoglobin A_{1C} (HbA_{1C}) Reserve blood samples for potential future measurement of ETC-1002 safety or pharmacodynamic biomarkers PK sample Reserve genetic blood sample (optional)

New Text:

Clinical Laboratory Test	Clinical Laboratory Test
<ul style="list-style-type: none"> Hematology Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood (RBC) cell count White blood (WBC) cell count with differential (absolute values only and %) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> Albumin (Alb) Alkaline phosphatase (Alk-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO₂) Chloride (Cl) Creatinine

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult blood • pH • Protein • Specific gravity • Urobilinogen 	

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC 	<u>Coagulation</u> <ul style="list-style-type: none"> • Prothrombin time (PT) • Activated partial thromboplastin time (aPTT) • International normalized ration (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) • Serum pregnancy test (only for females of childbearing potential) • <i>Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses)</i> • Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> • Hemoglobin A_{1C} (HbA_{1C}) • Reserve blood samples for potential future measurement of ETC-1002 safety or pharmacodynamic biomarkers • PK sample • Reserve genetic blood sample (optional)

CHANGE 57 REVISED SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

11.1.6.3 General Monitoring and Management of Abnormal Clinical Labs

Original Text:

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

New Text:

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.

CHANGE 58 REVISED SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

11.1.6.3.2 Monitoring and Management of Elevated Serum Creatinine

Original Text:

If at any time after randomization a patient experiences a marked creatinine elevation >1.0 mg/dL ($44 \mu\text{mol/L}$) above ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

If repeat creatinine assessment confirms serum creatinine >1.0 mg/dL ($44 \mu\text{mol/L}$) above ULN or MDRD creatinine clearance (CrCL) <30 mL/min, 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)

New Text:

~~If at any time after randomization a patient experiences a marked creatinine elevation >1.0 mg/dL ($44 \mu\text{mol/L}$) above ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.~~

~~If at any time after randomization, a patient experiences a decrease in repeat creatinine assessment confirms serum creatinine >1.0 mg/dL ($44 \mu\text{mol/L}$) above ULN or MDRD creatinine clearance (CrCL) <30 mL/min, 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)~~

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)

CHANGE 59 REVISED SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

11.1.6.3.3 Monitoring and Management of Hemoglobin Change

Original Text:

If at any time after randomization a patient experiences Hgb <10 g/dL (100 g/L) and/or a decrease >2.0 g/dL (20 g/L) from baseline (Week 0 [Visit T1]), the patient will undergo repeat confirmatory hematology testing as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat hematology assessment will include: 1) measurement of Hgb, hematocrit (Hct), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, reticulocyte count (percent and absolute), red blood cell count (RBC), and white blood cell count (WBC) with differential (absolute values only); 2) history of concomitant medication use; and 3) query for related symptoms. Additionally, further testing may be warranted to rule out additional pathology depending on clinical presentation, and should be discussed with Esperion Therapeutics personnel or the authorized [REDACTED] Medical Monitor.

- If repeat Hgb assessment confirms Hgb <10 g/dL (100 g/L) and/or a decrease >2.0 g/dL (20 g/L) from baseline, the patient should be monitored carefully during the study and return at 2 week intervals after study completion for additional Hgb measurement until the level returns to baseline or reaches a stable level.

New Text:

If at any time after randomization a patient experiences ~~Hgb <10 g/dL (100 g/L) and/or a~~ decrease >2.0 g/dL (20 g/L) from baseline (Week 0 [Visit T1]), the patient will undergo repeat confirmatory hematology testing as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat hematology assessment will include: 1) measurement of Hgb, hematocrit (Hct), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, reticulocyte count (percent and absolute), red blood cell count (RBC), and white blood cell count (WBC) with differential (absolute values only); 2) history of concomitant medication use; and 3) query for related symptoms. Additionally, further testing may be warranted to rule out additional pathology depending on clinical presentation, and should be discussed with Esperion Therapeutics personnel or the authorized [REDACTED] Medical Monitor.

- If repeat Hgb assessment confirms ~~Hgb <10 g/dL (100 g/L) and/or a~~ decrease >2.0 g/dL (20 g/L) from baseline, the patient should be monitored carefully during the study and return at 2 week intervals after study completion for additional Hgb measurement until the level returns to baseline or reaches a stable level.

CHANGE 60 REVISED SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

11.1.6.3.4 Monitoring and Management of Elevated Creatine Kinase

Original Text:

If at any time after randomization a patient experiences a marked CK elevation $>5 \times \text{ULN}$, 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 $>5 \times \text{ULN}$, if asymptomatic the investigator with input from the Sponsor may consider continuing study medication with continued CK assessments every 1-2 weeks. If symptomatic, 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:
 - $>5 \times \text{ULN}$ that is associated with symptoms of muscle pain, muscle weakness, or dark urine; or
 - $>10 \times \text{ULN}$, even in the absence of symptoms.
- 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).

New Text:

If at any time after randomization a patient experiences a marked CK elevation $>5 \times \text{ULN}$, 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 $>5 \times \text{ULN}$, if asymptomatic the investigator with input from the Sponsor may consider continuing study medication with continued CK assessments every 1-2 weeks.
- 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:
 - ~~— $>5 \times \text{ULN}$ that is associated with symptoms of muscle pain, muscle weakness, or dark urine; or~~
 - $>10 \times \text{ULN}$, 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)

CHANGE 61 REVISED SAFETY MONITORING AND MANAGEMENT INSTRUCTIONS

Location:

11.1.6.3.5 Monitoring and Management of Elevated LDL-C

Original Text:

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is $\geq 25\%$ from the patient's baseline value at Week 0, (Visit T1)

New Text:

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value *is* $>170 \text{ mg/dL}$ (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0, (Visit T1)

Location:

11.1.6.4 Monitoring and Management of Potential Hypoglycemia and Metabolic Acidosis

■■■■■■■■■■

[REDACTED]

11/1/2013

CHANGE 63 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.2.4 Severity

Original Text:

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.

New Text:

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, *life-threatening*, or *fatal* 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
- *Life-threatening: Events that are life-threatening with urgent intervention indicated*
- *Fatal: Death related to AE*

CHANGE 64 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.2.6 Monitoring and Follow-up of Adverse Events

Original Text:

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 study drug that are ongoing at study completion or study withdrawal must be followed until resolution or for 30 days after the last dose of study drug, whichever comes first, with the exception of patients reporting SAEs (see [Section 11.3](#)).

New Text:

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), *or until the patient is lost to follow-up or dies*.

Patients with AEs ~~related to study drug~~ that are ongoing at study completion or study withdrawal must be followed until resolution or for 30 days after the last ~~dose of study drug~~ *visit*, whichever comes first, ~~with the exception of patients reporting SAEs~~ (see [Section 11.3](#)).

CHANGE 65 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.2.7.1 Definition of Serious Adverse Event

Original Text:

Until the CEC has been established, MACE events that also meet the definition of an SAE will be reported as both MACE and SAEs. The CEC will adjudicate MACE in a blinded fashion, but the DMC will review MACE and SAEs in an unblinded fashion.

New Text:

~~Until the CEC has been established, MACE events that also meet the definition of an SAE will be reported as both MACE and SAEs. The CEC will adjudicate MACE clinical endpoints in a blinded fashion, but the DMC will review MACE clinical endpoints and SAEs in an unblinded fashion.~~
Any clinical endpoints that meet SAE criteria

CHANGE 66 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.3 Reporting Serious Adverse Events

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CHANGE 67 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.3.1 Reporting of Serious Adverse Events to Regulatory Authorities

Original Text:

The Sponsor (and/or designee) is responsible for submitting expedited reports of suspected serious and unexpected adverse reactions to the appropriate regulatory authorities. All Investigators responsible for ongoing clinical studies with the study drug will be notified by the Sponsor (or designee) of all SAEs that require prompt submission to their IRB/IEC. Reports of all SAEs must be communicated as soon as possible to the appropriate IRB/IEC 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.

New Text:

The Sponsor (and/or designee) is responsible for submitting expedited reports of suspected ~~serious~~ and unexpected *serious* adverse reactions (*SUSARS*) to the appropriate regulatory authorities. All Investigators ~~responsible for participating in~~ ongoing clinical studies with the study drug will be notified by the Sponsor (or designee) of ~~all SAEs that require prompt submission to their IRB/IEC~~ *SUSARS*. ~~Reports of all SAEs~~ *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 11.3](#). 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*

CHANGE 68 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.3.2 Reporting of Patient Death

Original Text:

The death of any patient during the study or within 30 days after study completion (regardless of the cause, must be reported to [REDACTED] Medical and Safety Services as detailed in [Section 11.3](#).

New Text:

The death of any patient during the study, or within ~~the 30-day~~ *day follow-up period* after they have completed the study ~~study completion~~ (regardless of the cause), must be reported to [REDACTED] Medical and Safety Services as detailed in [Section 11.3](#).

CHANGE 69 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.4 Adverse Events of Special Interest

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CHANGE 70 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.4 Adverse Events of Special Interest

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CHANGE 71 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.5 Data Monitoring Committee

Original Text:

An independent DMC will monitor unblinded accumulating patient safety data until the last patient has completed study treatment. In addition, data on SAEs and deaths, including MACE, will be monitored by the DMC during this period. At each DMC review, relevant unblinded safety information from ongoing studies of ETC-1002 will be provided to the DMC by an independent unblinded [REDACTED] statistician and programmer. Additional details will be provided in a DMC Charter.

New Text:

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 ~~MACE~~*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 ETC-1002 will be provided to the DMC by an independent unblinded [REDACTED] statistician and programmer. Additional details will be provided in a DMC Charter.

CHANGE 72 CLARIFIED REPORTING REQUIREMENTS FOR AES, SAES, AND PREGNANCIES

Location:

11.6 Clinical Event Committee (CEC)

Original Text:

A blinded independent expert CEC will adjudicate MACE. Additional details regarding MACE and MACE 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. MACE from this study and other studies within the ETC-1002 Phase 3 development program will be aggregated to allow for a safety assessment across the entire development program.

New Text:

A blinded independent expert CEC will adjudicate ~~MACE~~*clinical endpoints*. Additional details regarding ~~MACE~~*clinical endpoints* and ~~MACE~~*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. ~~MACE~~*Clinical endpoints* from this study and other studies within the ETC-1002 Phase 3 development program will be aggregated to allow for a safety assessment across the entire development program.

CHANGE 73 UPDATED THE LIPID ENDPOINT ASSESSMENTS

Location:

11.7.1 Lipid Parameters

Original Text:

After randomization, patients will return to clinic every 4 weeks for the first 12 weeks, then approximately every 12-16 weeks through Week 52 (Visit T7). 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 will be collected at baseline and all clinic visits and analyzed at Weeks 12, 24, and 52.

New Text:

After randomization, patients will return to clinic every 4 weeks for the first 12 weeks, then approximately every 12-16 weeks through Week 52 (Visit T7). 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 ~~will be collected~~ at baseline and all clinic

visits ~~and analyzed at~~ *for evaluation of ETC-1002 effects on lipids and cardiometabolic parameters* ~~Weeks 12, 24, and 52.~~

CHANGE 74 UPDATE CLINICAL LABORATORY PARAMETERS

Location:

11.7.2 Clinical Laboratory Tests (Lipids)

Original Text:

Clinical laboratory samples will be collected at all clinic visits and analyzed at Weeks 12, 24, and 52.

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

New Text:

Clinical laboratory samples will be collected at all clinic visits ~~and analyzed at Weeks 12, 24, and 52.~~

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

CHANGE 75 TYPOGRAPHICAL AND FORMATTING

Location:

11.7.2 Clinical Laboratory Tests (Lipids)

Original Text:

Table 6: Clinical Laboratory Parameters (Lipids)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Basic Lipid Parameters</u>	<u>Other Parameters</u>
<ul style="list-style-type: none">• Total cholesterol (TC)	<ul style="list-style-type: none">• High-sensitivity C-reactive protein (hs-CRP)
<ul style="list-style-type: none">• Calculated low-density lipoprotein cholesterol (LDL-C) and non-HDL-C• High-density lipoprotein cholesterol (HDL-C)• Triglycerides (TG)	<ul style="list-style-type: none">• apoB

New Text:

Table 6: Clinical Laboratory Parameters (Lipids) and Cardiometabolic Biomarkers

Clinical Laboratory Test	Clinical Laboratory Test
<u>Basic Lipid Parameters</u>	<u>Other Parameters</u>
<ul style="list-style-type: none"> Total cholesterol (TC) Calculated low-density lipoprotein cholesterol (LDL-C) and non-HDL-C High-density lipoprotein cholesterol (HDL-C) Triglycerides (TG) 	<ul style="list-style-type: none"> High-sensitivity C-reactive protein (hs-CRP) apoB

CHANGE 76 REVISED STATISTICS

Location:

12.2 Determination of Sample Size

Original Text:

The sample size of 600 patients randomized to ETC-1002 and 300 patients randomized to placebo will provide 900 total patients. This sample size was selected to provide a robust long-term safety profile in patients considered to have an unmet need for additional lipid lowering in a chronic setting.

New Text:

A total of 900 patients will be enrolled in this study with 600 patients randomized to ETC-1002 and 300 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥6 Months</i>	<i>Patients ≥12 Months</i>
<i>ETC-1002</i>	<i>555</i>	<i>540</i>
<i>Placebo</i>	<i>278</i>	<i>270</i>

Absolute risk will be addressed by 600 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events [2]. In this study adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of 600 patients randomized to ETC-1002 and 300 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits):

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
0.5%	0.5%	1.0	(0.1, 7.0)
0.5%	1.0%	2.0	(0.3, 11.9)
13.6%	13.6%	1.0	(0.7, 1.4)
13.6%	27.2%	2.0	(0.5, 2.3)

CHANGE 77 REVISED STATISTICS

Location:

12.3 Analysis Population

Original Text:

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

New Text:

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

CHANGE 78 REVISED STATISTICS

Location:

12.5 Primary Endpoint

Original Text:

No statistical analyses will be performed on any of the safety data in this study. The summarization of AEs will include only TEAEs, defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. AE summaries will be provided overall and for subgroups such as gender, age, and HeFH status. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

New Text:

No statistical analyses will be performed on any of the safety data in this study. The summarization of AEs will include only TEAEs, defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. AE summaries *will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. These AE summaries* will be provided overall and for subgroups such as gender, age, and HeFH status. *If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates.* Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will

each be summarized by treatment group. ~~Cumulative incidence (percent of patients experiencing the AE) and patient year adjusted incidence rates will be presented. If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates.~~

CHANGE 79 REVISED STATISTICS

Location:

12.5 Primary Endpoint

Original Text:

Diabetes and Glycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity, and relationship to study drug for each treatment group. Fasting insulin, glucose, and HbA_{1C} will be monitored at baseline and at Weeks 12, 24, and 52, and be summarized.

New Text:

Diabetes and ~~Glycemia~~Hyperglycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity, and relationship to study drug for each treatment group. ~~Fasting insulin, g~~Glucose, and HbA_{1C} will be monitored at baseline and at Weeks 12, 24, and 52, and be summarized.

CHANGE 80 REVISED STATISTICS

Location:

12.5 Primary Endpoint

Original Text:

Renal Safety

Baseline eGFR will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. If needed, postbaseline eGFR categories will be modified to include the possibility of patients with eGFR values <45 mL/min/1.73 m². Shift tables of urine protein (negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

New Text:

Renal Safety

Baseline eGFR will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. ~~If needed, postbaseline eGFR categories will be modified to include the possibility of patients with eGFR values <45 mL/min/1.73 m².~~ Shift tables of urine protein

(negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

CHANGE 81 REVISED STATISTICS

Location:

12.5 Primary Endpoint

Original Text:

Cardiovascular Events (MACE)

MACE will be monitored and adjudicated by an independent blinded expert CEC for this study and other ongoing studies the ETC-1002 program. Adjudicated MACE will be summarized by event type and treatment group. Additional details regarding MACE and MACE definitions will be included in CEC charter.

New Text:

Cardiovascular Events (MACE Clinical Cardiovascular Endpoints)

Clinical cardiovascular endpoints will be monitored and adjudicated by an independent blinded expert CEC for this study and other ongoing studies the ETC-1002 program. Adjudicated ~~MACE~~*clinical endpoints* will be summarized by event type and treatment group. Additional details regarding ~~MACE~~*clinical endpoints* and ~~MACE~~*clinical endpoint* definitions will be included in CEC charter.

CHANGE 82 REVISED STATISTICS

Location:

12.6 Secondary and Tertiary Lipids

Original Text:

12.6 Lipids

LDL-C, HDL-C, TG, TC, non-HDL-C, and apoB values at Weeks 12, 24, and 52 will be summarized. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. Missing values for any of the lipid parameters will not be imputed; that is, only observed case data will be used.

New Text:

12.6 Secondary and Tertiary Lipids

12.6.1 Secondary Lipids

Percent change from baseline to Week 12 in LDL-C will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors and baseline LDL-C as a covariate. Baseline LDL-C is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. Two methods for data handling will be

used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). For each ANCOVA (observed case; imputation via PMM), output will include the least squares mean (LSM) and standard error (SE) for each treatment group, along with the placebo-correct LSM and its 95% confidence interval (CI) and p-value. Specific details on how the PMM will be implemented will be included in the SAP.

12.6.2 Tertiary Lipids

LDL-C, HDL-C, TG, TC, non-HDL-C, and apoB values at Weeks 12, 24, and 52 will be summarized. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. Baseline for each lipid is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. In addition, a summary using the FAS, excluding patients who received additional lipid-lowering therapy by that timepoint (by Week 24 for the Week 24 timepoint; by Week 52 for the Week 52 timepoint), will be provided. For both summaries, only observed case data will be used (no imputation for missing data).

Percent change from baseline to Week 24 and to Week 52 LDL-C will be analyzed similarly, with patients in the FAS who did not receive additional lipid-lowering therapy by that timepoint (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each timepoint will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI and p-value.

CHANGE 83 REVISED STATISTICS

Location:

12.7 PK and Other Biomarkers

Original Text:

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. Missing values for hs-CRP will not be imputed; only observed case data will be used

New Text:

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. Baseline for hs-CRP is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data). ~~Missing values for hs-CRP will not be imputed; only observed case data will be used.~~

CHANGE 84 REVISED STATISTICS

Location:

12.7 PK and Other Biomarkers

Original Text:

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. Missing values for hs-CRP will not be imputed; only observed case data will be used

New Text:

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. *Baseline for hs-CRP is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).* ~~Missing values for hs-CRP will not be imputed; only observed case data will be used.~~

CHANGE 85 UPDATED STUDY PROCEDURES

Location:

Appendix 1

Visit	Screen	Treatment						
	S1 ^{1,2}	T1	T2	T3	T4	T5	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 169±7	Day 253±7	Day 365±7
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
HeFH Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight ⁴	X	X	X	X	X	X	X	X
Height/BMI	X							
Waist Circumference	X							
12-Lead ECG ⁵		X						X
Vital Signs ⁶	X	X	X	X	X	X	X	X
Serology ⁷	X							
Serum Pregnancy ⁸	X							
TSH	X							

Clinical Safety Labs ⁹	X	X	X	X	X	X	X	X
Basic Fasting Lipids ¹⁰	X	X	X	X	X	X	X	X
HbA _{1C}	X	X			X			X
Insulin		X			X	X		X
10 mL reserve sample		X			X	X		X
apoB		X			X	X		X
hs-CRP		X			X	X		X
Diet and exercise counseling ¹¹	X	X	X	X	X	X	X	
Plasma PK					X	X		X
Establish Patient Eligibility		X						
Randomization		X						
IWRS Contact	X	X			X	X	X	X ¹²
Double-blind Drug Dispensing ¹³		X			X	X	X	
Drug Return/Compliance			X	X	X	X	X	X

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.

² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.

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

⁵ Single 12-lead ECG will be collected prior to any blood sample collection.

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

⁷ Serology for HBsAg, HCV-AB

⁸ Pregnancy test completed in premenopausal women only

⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1), Baseline (Visit T1), Week 12 (Visit T4), and at EOS (Visit T7). Please refer to [REDACTED] laboratory manual for detailed schedule of tests.

¹⁰ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.

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

¹² IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

¹³ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.

New Text:

Visit	Screen	Treatment						
	S1 ^{1,2}	T1	T2	T3	T4	T5	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 169±7	Day 253±7	Day 365±7
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
HeFH Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight ⁴	X	X	X	X	X	X	X	X
Height/BMI	X							
Waist Circumference								
12-Lead ECG ⁵		X						X
Vital Signs ⁶	X	X	X	X	X	X	X	X
Serology ⁷	X							
Serum Pregnancy <i>and/or</i> FSH ⁸	X							
TSH	X							
Clinical Safety Labs ⁹	X	X	X	X	X	X	X	X
Basic Fasting Lipids ¹⁰	X	X	X	X	X	X	X	X
HbA _{1c}	X	X			X			X
Insulin		X			X	X		X
10 mL reserve sample		X			X	X		X
apoB		X			X	X		X
hs-CRP		X			X	X		X
Diet and exercise counseling ¹¹	X	X	X	X	X	X	X	
Plasma PK					X	X		X
Establish Patient Eligibility		X						
Randomization		X						
IWRS Contact	X	X			X	X	X	X ¹²
Double-blind Drug Dispensing ¹³		X			X	X	X	
Drug Return/Compliance			X	X	X	X	X	X
<i>Schedule next visit</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i> ¹⁴

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCVAB
- ⁸ Pregnancy test completed in premenopausal women only. *FSH test is completed in women < 55 years old and > 1 year without menses*
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1), Baseline (Visit T1), Week 12 (Visit T4), and at EOS (Visit T7). Please refer to [REDACTED] laboratory manual for detailed schedule of tests.
- ¹⁰ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.
- ¹¹ Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.
- ¹² IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.
- ¹³ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.
- ¹⁴ *If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events*

APPENDIX 7. SUMMARY OF CHANGES IN AMENDMENT 2

SUMMARY OF CHANGES CLINICAL STUDY PROTOCOL

Study Number: 1002-040

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Protocol Version Incorporating Current Summary of Changes: Amendment 2: Amended Protocol 23 February 2016

Preceding Protocol Version: Amendment 1: Amended Protocol 28 January 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:

- For program consistency, revision of severity categories for adverse events to the 3 categories of severity.
- Typographical errors and formatting were corrected or revised to improve clarity and consistency
- This amendment represents cumulative changes to the original protocol.

CHANGE 1 REVISION OF ADVERSE EVENT SEVERITY

Location:

Section 11.2.4, Severity

Original Text:

The severity of the AE will be characterized as mild, moderate, ~~or~~ severe, *life-threatening*, or *fatal* 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
- *Life-threatening: Events that are life-threatening with urgent intervention indicated*
- *Fatal: Death related to AE*

New Text:

The severity of the AE will be characterized as mild, moderate, ~~or~~ or severe, ~~life-threatening~~, or ~~fatal~~ 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
- ~~*Life-threatening: Events that are life threatening with urgent intervention indicated*~~
- ~~*Fatal: Death related to AE*~~

APPENDIX 8. SUMMARY OF CHANGES IN AMENDMENT 3

SUMMARY OF CHANGES CLINICAL STUDY PROTOCOL

Study Number: 1002-040

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Protocol Version Incorporating Current Summary of Changes: Amendment 3: Amended Protocol 28 July 2016

Preceding Protocol Version: Amendment 2: Amended Protocol 23 February 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:

- Increased sample size from 900 randomized patients to 1950 randomized patients to support the assessment of safety for the bempedoic acid (ETC-1002) program.
- Applicable statistical sections were updated to align with other revisions in this amendment.
- Revised the high-dose statin exclusion to allow patients on high-dose statins with the exception of patients on simvastatin taking average daily doses that are greater than 40 mg. [REDACTED]
- Increased overall study duration to account for additional recruitment time required to randomize additional patients
- Revised inclusion criteria to be consistent with current safety data and to comply with Health Canada requests
 - Revised to include tubal ligation in the study definition for ‘surgically sterile’
 - Revised to include the birth control requirement as requested by Health Canada. This revision only applies to Canadian sites.
- Revised exclusion criteria to be consistent with current safety data. This includes:
 - Increasing the total fasting triglyceride level from >400 mg/dL (4.5 mmol/L) to >500 mg/dL (5.6 mmol/L)
 - Decreasing the eGFR level from <45 mL/min/1.73 m² to <30 mL/min/1.73 m²
 - Allowing patients with positive HCV-AB results to have a reflex HCV RNA performed so that those patients without active disease may be considered for enrollment
 - Allowing patients whose total bilirubin levels exceeding $\geq 1.2 \times \text{ULN}$ to have a reflex indirect (unconjugated) bilirubin test so that those patients with results that are consistent with Gilbert’s disease may be considered for enrollment
 - Shorten the duration from when a patient may have had, for any reason, a blood transfusion from 90 days to 30 days
 - Decrease the amount of time patients should be stable on obesity medications from 6 months to 3 month.
- Revised references to clinical safety laboratories, other screening laboratories, and lipid assessments (Study Procedures, Assessment of Safety, Schedule of Study Events) for consistency with new or revised assessments and procedures

- Revised to include a section in the protocol to address overdose
- Revised administration instructions for IMP for consistency across the development program
- Revised testing requirement for coagulation for consistency across the development program
- Revised the Monitoring and Management of Elevated Liver Function Tests to include additional clarity and testing for patients with Gilbert's disease
- Revised the Monitoring and Management of Elevated LDL-C to allow for the use of high-dose statins, excluding average daily doses of simvastatin that are greater than 40 mg. Additionally, 4 weeks after patients have their lipid-lowering medications modified should return to the clinic for a safety laboratory assessment.
- Revised the Monitoring and Management of Elevated Triglycerides for consistency across the development program
- 
- Removed the collection of blood samples for pharmacokinetic assessment for those patients who randomize into the study after the implementation of Protocol Amendment 3
- For consistency across the development program, revised the adverse event relationship to study drug scale to include 'Unlikely'
- Typographical errors and formatting were corrected or revised to improve clarity and consistency. Only substantive changes are included in the Summary of Changes document.
- This amendment represents cumulative changes to the original protocol.

CHANGE 1 INCREASE IN SAMPLE SIZE

Location:

Synopsis, Study Hypothesis

Original Text:

The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = 900) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option.

New Text:

The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = ~~900~~1950) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option.

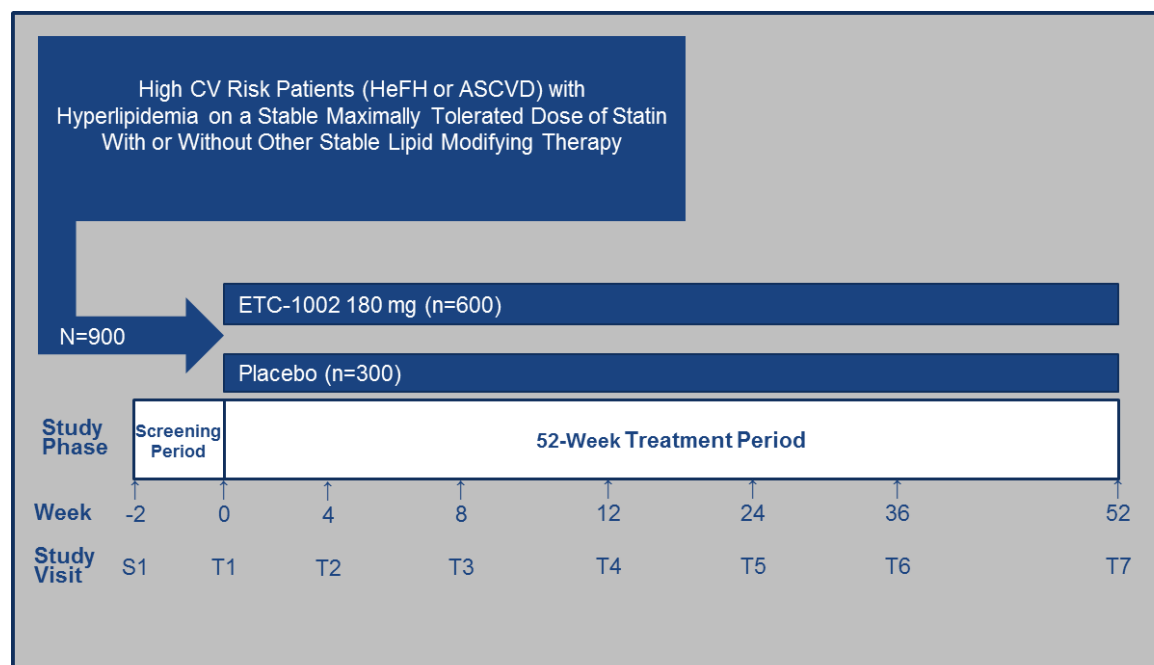
CHANGE 2 INCREASED SAMPLE SIZE

Location:

Synopsis, Methodology

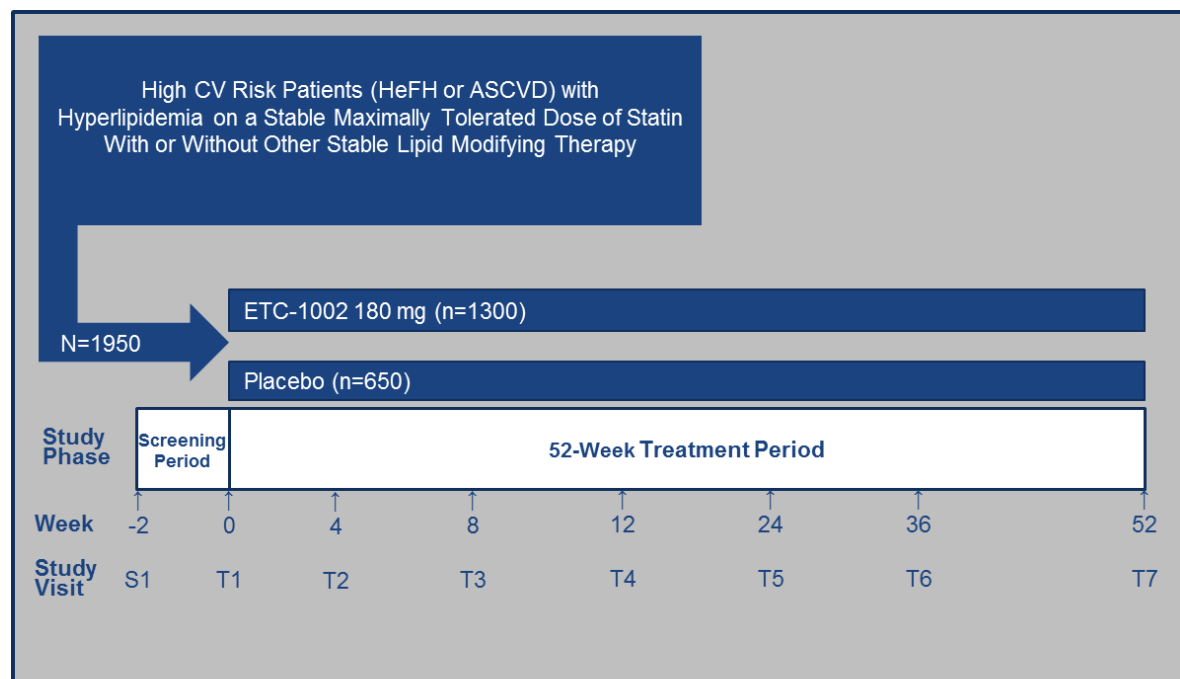
Section 6.1., Overall Study Design, Figure 1

Original Text:



ASCVD=atherosclerotic cardiovascular disease; HeFH=Heterozygous Familial Hypercholesterolemia

New Text:



ASCVD=atherosclerotic cardiovascular disease; HeFH=Heterozygous Familial Hypercholesterolemia

CHANGE 3 REVISED HIGH-DOSE STATIN EXCLUSION

Location:

Synopsis, Study Design

Original Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil]). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day, or who are currently taking a PCSK9 inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from enrolling in this study. PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.

New Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia

(patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil]). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, ~~patients who are currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin at average daily doses that are greater than 40 or 80 mg per day or who are currently taking a PCSK9 inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from enrolling in this study. PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.~~

CHANGE 4 INCREASED SAMPLE SIZE

Location:

Synopsis, Study Design

Original Text:

Screening (Visit S1) will occur approximately 2 weeks prior to Day 1 (Visit T1). Patients on maximally tolerated lipid-lowering therapy, as determined by the investigator, will be stratified based on the patient's CV risk and baseline statin dose. There will be no cap placed on randomization into any particular stratum. Approximately 1950 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either ETC-1002 180 mg (n = 1300), or placebo (n = 650) once daily for 52 weeks. Randomized patients will continue in the study until they have completed Week 52 (Visit T7). Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), Week 12 (Visit T4), Week 24 (Visit T5), Week 36 (Visit T6), and Week 52 (Visit T7). 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 *and procedures*. For details of study assessments, see the Schedule of Events in Appendix 1.

New Text:

Screening (Visit S1) will occur approximately 2 weeks prior to Day 1 (Visit T1). Patients on maximally tolerated lipid-lowering therapy, as determined by the investigator, will be stratified based on the patient's CV risk and baseline statin dose. There will be no cap placed on randomization into any particular stratum. Approximately ~~900~~1950 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either ETC-1002 180 mg (n = ~~600~~1300), or placebo (n = ~~300~~650) once daily for 52 weeks. Randomized patients will continue in the study until they have completed Week 52 (Visit T7). Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), Week 12 (Visit T4), Week 24 (Visit T5), Week 36 (Visit T6), and Week 52 (Visit T7). 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 *and procedures*. For details of study assessments, see the Schedule of Events in Appendix 1.

CHANGE 5 INCREASED SAMPLE SIZE

Location:

Synopsis, Number of patients planned

Original Text:

Approximately 900 adult male and female patients

New Text:

Approximately ~~900~~1950 adult male and female patients

CHANGE 6 INCREASED STUDY DURATION

Location:

Synopsis, End of Study

Original Text:

The study will end when the last randomized patient completes *their last study visit*. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 22 months

New Text:

The study will end when the last randomized patient completes *their last study visit*. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately ~~22~~28 months

CHANGE 7 REVISED INCLUSION CRITERIA

Location:

Synopsis, Diagnosis and criteria for patient eligibility, Inclusion Criteria

Original Text:

- Men and nonpregnant, nonlactating women. *Women must be either:*
 - *Naturally postmenopausal (as reported by the patient, 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, but not tubal ligation alone) or;*
 - *Women of childbearing potential must be willing to use 1 acceptable method of birth control. 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:

- Men and nonpregnant, nonlactating women. *Women must be either:*
 - *Naturally postmenopausal (as reported by the patient, 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, ~~but not~~ tubal ligation~~alone~~) or;*
 - *Women of childbearing potential must be willing to use 1 acceptable method of birth control. The minimal requirement for adequate contraception is that it should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include: 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).*

Original Text:

- Be on maximally tolerated lipid-modifying therapy, including a *maximally tolerated statin either alone or in combination with other lipid-lowering therapies*, at stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; *however, gemfibrozil is not allowed*). Regimens other than daily dosing, including those at very low doses, are acceptable.

A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

Patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day will be excluded from this study.

Patients who are currently taking a PCSK9 inhibitor (Praluent[®] [alirocumab] or Repatha[®] [evolocumab]) or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.

New Text:

- Be on maximally tolerated lipid-modifying therapy, including a *maximally tolerated statin either alone or in combination with other lipid-lowering therapies*, at stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; *however, gemfibrozil is not allowed*). Regimens other than daily dosing, including those at very low doses, are acceptable.
- A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

Patients currently taking ~~an average daily dose of high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg~~ that is greater than 40 mg per day will be excluded from this study.

Patients who are currently taking a PCSK9 inhibitor (Praluent[®] [alirocumab] or Repatha[®] [evolocumab]) or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from this study.

CHANGE 8 REVISED EXCLUSION CRITERIA

Location:

Synopsis, Diagnosis and criteria for patient eligibility, Exclusion Criteria

Original Text:

- Total fasting triglyceride >400 mg/dL (4.5 mmol/L) at Week -2 (Visit S1)
Note: TG may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG, the mean of the first value and the repeat value will be used to determine eligibility.
- Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <45 mL/min/1.73 m² at Week -2 (Visit S1) [1].

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

New Text:

- Total fasting triglyceride >400/500 mg/dL (4.5/5.6 mmol/L) at Week -2 (Visit S1)
Note: TG may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG, the mean of the first value and the repeat value will be used to determine eligibility.
- Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <45/30 mL/min/1.73 m² at Week -2 (Visit S1) [1].

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

Original Text:

- Concomitant use of high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg daily.

New Text:

- Concomitant use of ~~high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin at 40 or 80 mg~~ average daily doses greater than 40 mg.

Original Text:

- *Liver disease or dysfunction, including:*
 - *Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or*
 - *Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 1.5 \times \text{ULN}$, and/or total bilirubin (TB) $\geq 1.2 \times \text{ULN}$ at Week -2 (Visit S1).*
- Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.*

New Text:

- *Liver disease or dysfunction, including:*
 - *Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or*
 - *Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 1.52 \times \text{ULN}$, and/or total bilirubin (TB) $\geq 1.2 \times \text{ULN}$ at Week -2 (Visit S1).*
- Note: If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease. Patients without active disease may be enrolled in the study.*
- Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.*
- If TB $\geq 1.2 \times \text{ULN}$, a reflex indirect (unconjugated) bilirubin will be obtained and if the results are consistent with Gilbert's disease, the patient may be enrolled in the study.*

Original Text:

- *Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed).*

New Text:

- *Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Patients with a history of nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed).*

Original Text:

- *Blood donation, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization*
- *Blood transfusion for any reason within 90 days prior to randomization*

New Text:

- *Blood donation, blood transfusion for any reason, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization*
- ~~*Blood transfusion for any reason within 90 days prior to randomization*~~

Original Text:

- *Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:*
 - *Hormone replacement (6 weeks prior to randomization)*
 - *Thyroid replacement (6 weeks prior to randomization)*
 - *Diabetes medications (4 weeks prior to randomization)*
 - *Obesity medication (6 months prior to randomization)*

New Text:

- *Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:*
 - *Hormone replacement (6 weeks prior to randomization)*
 - *Thyroid replacement (6 weeks prior to randomization)*
 - *Diabetes medications (4 weeks prior to randomization)*
 - *Obesity medication (~~6~~3 months prior to randomization)*

CHANGE 9 REVISED ADMINISTRATION INSTRUCTIONS FOR IMP

Location:

Synopsis, IMP, dosage and mode of administration

Original Text:

- All IMP will be ingested once daily in the morning with or without food.

New Text:

- All IMP will be ingested once daily ~~in the morning~~ (once every 24 hours, at approximately the same time each day) with or without food.

**CHANGE 10 REVISED REFERENCES TO CLINICAL SAFETY LABORATORIES,
OTHER SCREENING LABORATORIES, AND LIPID ASSESSMENTS**

Location:

Synopsis, Criteria for evaluation

Original Text:

Other Screening Laboratories:

- Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), serum pregnancy test (only for females who are of childbearing potential), *FSH (only for females who are <55 years old and >1 year without menses)*, TSH

New Text:

Other Screening Laboratories:

- Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) (*if HCV is positive, a reflex HCV RNA will be performed to rule out active disease*), serum pregnancy test (only for females who are of childbearing potential), FSH (*only for females who are <55 years old and >1 year without menses*), urine pregnancy test Day 1 prior to randomization (*only in Canada, for females who are of childbearing potential*), TSH

CHANGE 11 REVISED THE MONITORING AND MANAGEMENT OF ELEVATED LDL-C

Location:

Synopsis, Safety and Monitoring

Original Text:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is $>170 \text{ mg/dL}$ (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of using high doses of statins excluded from the study (rosuvastatin 40 mg, atorvastatin 80 mg, and simvastatin 40 or 80 mg) and the fibrate gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).
 - The initiation and or dose change of these medications will be documented on the electronic case report form (eCRF) as a concomitant medication with the associated start date
 - Adjunctive therapy medications will not be provided by the sponsor
 - Patients continuing to exceed the LDL-C threshold after maximizing the standard-of-care LDL-C-lowering therapy and, in the opinion of the investigator, require therapies that are prohibited by the protocol will be discontinued from IMP

treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

New Text:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of ~~using high doses of statins excluded from the study (rosuvastatin 40 mg, atorvastatin 80 mg, and simvastatin at average daily doses greater than 40 mg40 or 80 mg)~~ and the fibrate gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).
 - The initiation of any new ~~and/or~~ dose changes of ~~these medications~~any lipid-lowering treatment will be documented on the electronic case report form (eCRF) as a concomitant medication with the associated start date
 - *Patients who have their lipid-lowering treatments modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine safety laboratory assessment. Additional safety laboratory assessments may be conducted at the investigator's discretion.*
 - Adjunctive therapy medications will not be provided by the sponsor
 - Patients continuing to exceed the LDL-C threshold after maximizing the standard-of-care LDL-C-lowering therapy and, in the opinion of the investigator, require therapies that are prohibited by the protocol will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

CHANGE 12 REVISED THE MONITORING AND MANAGEMENT OF ELEVATED TRIGLYCERIDES

Location:

Synopsis, Safety and Monitoring

Original Text:

Elevated Triglycerides:

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds 500 mg/dL (5.6 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >500 mg/dL (5.6 mmol/L), will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value meets the threshold criteria
- Any patient with a confirmed TG >500 mg/dL (5.6 mmol/L) may initiate standard-of-care therapy (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.
- Patients continuing to exceed the TG threshold after maximizing the standard-of-care triglyceride-lowering therapy will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

New Text:

Elevated Triglycerides:

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds ~~500~~1000 mg/dL (~~5.6~~11.3 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >~~500~~1000 mg/dL (~~11.35~~6 mmol/L), will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value meets the threshold criteria
- Any patient with a confirmed TG >~~500~~1000 mg/dL (~~5.6~~11.3 mmol/L) may initiate standard-of-care therapy (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the

case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.

- Patients continuing to exceed the TG threshold after maximizing the standard-of-care triglyceride-lowering therapy will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CHANGE 14 INCREASED SAMPLE SIZE AND APPLICABLE STATISTICAL SECTIONS WERE UPDATED TO ALIGN WITH OTHER REVISIONS IN THIS AMENDMENT

Location:

Synopsis, Statistical methods

Original Text:

Sample Size

A total of 900 patients will be enrolled in this study with 600 patients randomized to ETC-1002 and 300 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥6 Months</i>	<i>Patients ≥12 Months</i>
<i>ETC-1002</i>	555	540
<i>Placebo</i>	278	270

Absolute risk will be addressed by 600 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events [2]. In this study, adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of 600 patients randomized to ETC-1002 and 300 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits:

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
0.5%	0.5%	1.0	(0.1, 7.0)
0.5%	1.0%	2.0	(0.3, 11.9)
13.6%	13.6%	1.0	(0.7, 1.4)
13.6%	27.2%	2.0	(0.5, 2.3)

New Text:

Sample Size

A total of ~~900~~1950 patients will be enrolled in this study with ~~600~~1300 patients randomized to ETC-1002 and ~~300~~650 patients randomized to placebo. Using an anticipated overall dropout

rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥6 Months</i>	<i>Patients ≥12 Months</i>
<i>ETC-1002</i>	555 1,202	540 1,170
<i>Placebo</i>	278 601	270 585

Absolute risk will be addressed by ~~600~~1300 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled *Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events* [2]. In this study, adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of ~~600~~1300 patients randomized to ETC-1002 and ~~300~~650 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits:

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
0.5%	0.5%	1.0	(0.1, 7.0) (0.3, 3.8)
0.5%	1.0%	2.0	(0.3, 11.9) (0.6, 6.7)
13.6%	13.6%	1.0	(0.7, 1.4) (0.8, 1.3)
13.6%	27.2%	2.0	(0.5, 2.3) (1.6, 2.5)

CHANGE 15 APPLICABLE STATISTICAL SECTIONS WERE UPDATED TO ALIGN WITH OTHER REVISIONS IN THIS AMENDMENT

Location:

Synopsis, Statistical methods

Original Text:

Hepatic Safety

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

New Text:

Hepatic Safety

Liver-associated enzymes and TB will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST, and TB. Hy's law criteria ($\geq 3 \times \text{ULN}$ for either ALT or AST, with accompanying TB $> 2 \times \text{ULN}$) 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 $2 \times \text{ULN}$ will be based upon direct (conjugated) bilirubin.*

**CHANGE 16 REMOVED THE COLLECTION OF BLOOD SAMPLES FOR
PHARMACOKINETIC ASSESSMENT**

Location:

Synopsis, Statistical methods

Original Text:

PK and Other biomarkers

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. *The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).*

In addition, trough plasma concentrations will be collected at Weeks 12, 24, and 52 for use in further developing the population pharmacokinetic (PK) model.

New Text:

PK and Other biomarkers

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. *The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).*

In addition, trough plasma concentrations will be collected at Weeks 12, 24, and 52 *from patients randomized into the study prior to the implementation of Protocol Amendment 3* for use in further developing the population pharmacokinetic (PK) model. *Trough plasma concentrations will not be collected from patients randomized into the study after the implementation of Protocol Amendment 3.*

CHANGE 17 TYPOGRAPHICAL ERRORS AND FORMATTING

Location:

Section 4.2.3., Previous Human Experience

Original Text:

In clinical drug-drug interaction studies, ETC-1002 240 mg showed less than a 2-fold transient increase in the exposure of atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg, and rosuvastatin 10 mg in 2 statin drug-drug interaction studies (Studies 1002-007 and 1002-012).

New Text:

~~In~~Two clinical (*Studies 1002-007 and 1002-012*) ~~drug-drug interaction~~ studies that evaluated drug-drug interactions of ETC-1002 240 mg with statins showed less than a 2-fold transient increase in the exposure of atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg, and rosuvastatin 10 mg ~~in 2 statin drug-drug interaction studies (Studies 1002-007 and 1002-012)~~. Likewise, when ETC-1002 180 mg was dosed in combination with high-dose statins (atorvastatin 80 mg, pravastatin 80 mg, rosuvastatin 40 mg, and simvastatin 40 mg) exposure of these statins increased between approximately 1.4- and 2-fold (*Study 1002-035*).

CHANGE 18 REVISED HIGH-DOSE STATIN EXCLUSION

Location:

Section 6.1., Overall Study Design

Original Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil]). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, patients currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day, *or who are currently taking a PCSK9 inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1)* will be excluded from enrolling in this study. *PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.*

New Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC-1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies

(eg, ezetimibe, fibrates [except gemfibrozil]). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy. However, ~~patients who are currently taking high-dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin at average daily doses that are greater than 40 or 80 mg per day or who are currently taking a PCSK9 inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from enrolling in this study. PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL-C threshold criteria have been met as described in Section 11.1.6.3.5.~~

Original Text:

Statin dose categories and randomization strata are defined in the Table 2 and Table 3 below, respectively:

Table 2: Baseline Statin Dose Categories

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins ^a
Atorvastatin 40-80 ^b mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 ^c mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 ^d mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

Note: The highest dose statins are allowed if given on less than a daily basis.

^a Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)

^b Atorvastatin 80 mg *daily* is not allowed in this study.

^c Rosuvastatin 40 mg *daily* is not allowed in this study

^d Simvastatin 40-80 mg *daily* is not allowed in this study

New Text:

Statin dose categories, *based on average daily dose*, and randomization strata are defined in the Table 2 and Table 3 below, respectively:

Table 2: Baseline Statin Dose Categories

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins ^a
Atorvastatin 40-80 ^b mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 ^e mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 ^{db} mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

Note: The highest dose statins are allowed if given on less than a daily basis.

^a Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)

^b ~~Atorvastatin 80 mg daily is not allowed in this study.~~

^e ~~Rosuvastatin 40 mg daily is not allowed in this study~~

^{db} ~~Simvastatin average daily doses greater than 40-80 mg daily is are not allowed in this study~~

Original Text:

Table 3: Randomization Strata

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH+ Low Intensity Statins	ASCVD + Low Intensity Statins
HeFH+ Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH+ High Intensity Statins ^a	ASCVD + High Intensity Statins ^a

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

^a Atorvastatin 80 mg, rosuvastatin 40 mg, and simvastatin 40-80 mg daily are not allowed in this study.

New Text:

Table 3: Randomization Strata

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH+ Low Intensity Statins	ASCVD + Low Intensity Statins
HeFH+ Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH+ High Intensity Statins ^a	ASCVD + High Intensity Statins ^a

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

^a ~~Atorvastatin 80 mg, rosuvastatin 40 mg, and s~~Simvastatin average daily doses greater than 40-80 mg daily are not allowed in this study

CHANGE 19 INCREASED SAMPLE SIZE

Location:

Section 6.2., Study Hypothesis

Original Text:

The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin *alone or in combination with other lipid-lowering therapies*, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = 900) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option

New Text:

The study will characterize the long-term safety and tolerability of ETC-1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin *alone or in combination with other lipid-lowering therapies*, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = ~~900~~1950) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC-1002 once daily, orally bioavailable option

CHANGE 20 INCREASED STUDY DURATION

Location:

Section 6.4., End of Study

Original Text:

The study will end when the last randomized patient completes *their last study visit* (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 22 months.

New Text:

The study will end when the last randomized patient completes *their last study visit* (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately ~~22~~28 months.

CHANGE 21 INCREASED SAMPLE SIZE

Location:

Section 6.5., Number of Patients

Original Text:

The study will enroll approximately 900 adult male and female HeFH and/or ASCVD patients with hyperlipidemia from approximately 125 clinical sites.

New Text:

- The study will enroll approximately ~~900~~/950 adult male and female HeFH and/or ASCVD patients with hyperlipidemia from approximately 125 clinical sites.

CHANGE 22 REVISED INCLUSION CRITERIA

Location:

Section 7.1., Subject Inclusion Criteria

Original Text:

2. Men and nonpregnant, nonlactating women. Women must be either:
 - Naturally postmenopausal (as reported by the patient, 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, but not tubal ligation alone) or;
 - Women of childbearing potential must be willing to use 1 acceptable method of birth control. 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:

2. Men and nonpregnant, nonlactating women. Women must be either:
 - Naturally postmenopausal (as reported by the patient, 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, ~~but not~~ tubal ligation~~alone~~) or;
 - Women of childbearing potential must be willing to use 1 acceptable method of birth control. *The minimal requirement for adequate contraception is that it should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug.* Acceptable methods of birth control include: 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).

CHANGE 23 REVISED INCLUSION CRITERIA

Location:

Section 7.2., Subject Exclusion Criteria

Original Text:

1. Total fasting triglyceride >400 mg/dL (4.5 mmol/L) at Week -2 (Visit S1)

Note: TG may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG, the mean of the first value and the repeat value will be used to determine eligibility.

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <45 mL/min/1.73m² at Week -2 (Visit S1) [1].

New Text:

1. Total fasting triglyceride >~~400~~500 mg/dL (~~4.5~~5.6 mmol/L) at Week -2 (Visit S1)

Note: TG may be repeated 1 time with the screening period extended up to 2 weeks. For those patients who have a repeat TG, the mean of the first value and the repeat value will be used to determine eligibility.

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <~~45~~30 mL/min/1.73 m² at Week -2 (Visit S1) [1].

Original Text:

4. Concomitant use of high dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg *daily*.

New Text:

4. Concomitant use of high dose statins, defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg *at average daily doses greater than 40 mg*.

Original Text:

10. Liver disease or dysfunction, including:

- Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 1.5 \times \text{ULN}$, and/or total bilirubin (TB) $\geq 1.2 \times \text{ULN}$ at Week -2 (Visit S1).

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.

New Text:

10. Liver disease or dysfunction, including:

- Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -2 (Visit S1); or
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 1.5 \times \text{ULN}$, and/or total bilirubin (TB) $\geq 1.2 \times \text{ULN}$ at Week -2 (Visit S1).

Note: If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease. Patients without active disease may be enrolled in the study.

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat of ALT, AST, and/or TB. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility.

If TB $\geq 1.2 \times \text{ULN}$, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease, the patient may be enrolled in the study.

Original Text:

16. Blood donation, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization
17. Blood transfusion for any reason within 90 days prior to randomization

New Text:

16. Blood donation, *blood transfusion for any reason*, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization
17. Blood transfusion for any reason within 90 days prior to randomization

Original Text:

21. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
- Hormone replacement (6 weeks prior to randomization)
 - Thyroid replacement (6 weeks prior to randomization)
 - Diabetes medications (4 weeks prior to randomization)
 - Obesity medication (6 months prior to randomization)

New Text:

20. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:

- Hormone replacement (6 weeks prior to randomization)
- Thyroid replacement (6 weeks prior to randomization)
- Diabetes medications (4 weeks prior to randomization)
- Obesity medication (63 months prior to randomization)

CHANGE 24 REVISED ADMINISTRATION INSTRUCTIONS FOR IMP

Location:

Section 7.3., Patient Lifestyle and Dietary Guidelines

Original Text:

Each dose of study drug is comprised of 1 tablet from 1 bottle that will be dispensed at each scheduled clinic visit. Study drug should be taken each morning and may be taken with or without food.

New Text:

Each dose of study drug is comprised of 1 tablet from 1 bottle that will be dispensed at each scheduled clinic visit. Study drug should be taken ~~each morning~~ *once a day (once every 24 hours)* at approximately the same time every day and may be taken with or without food.

CHANGE 25 REVISED HIGH-DOSE STATIN EXCLUSION

Location:

Section 8.2.1., Lipid-Regulating Medications and Supplements

Original Text:

Statins

- Atorvastatin (Lipitor[®], Sortis[®]), with doses <80 mg
- Fluvastatin (Lescol[®])
- Lovastatin (Mevacor[®], Altoprev[™])
- Pravastatin (Pravachol[®])
- Pitavastatin (Livalo[®], Lipostat[®])
- Rosuvastatin (Crestor[®]), with doses <40 mg
- Simvastatin (Zocor[®]), with doses <40 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestyramine (Questran[®], Questran Light[®], Prevalite[®], Locholest[®], Locholest[®] Light)
- Colestipol (Colestid[®])
- Colesevelam hydrochloride (Welchol[®], Cholestagel[®])
- Ezetimibe (Zetia[®], Ezetrol[®])

Fibrates

- Fenofibrate (Antara[®], Lofibra[®], Tricor[®], Triglide[™], Lipantil[®], Supralip[®])
- Bezafibrate (Bezalip[®])
- Ciprofibrate (Modalim[®])

PCSK9 inhibitors (allowed as adjunctive therapy beginning at Week 24 [Visit T5]; see Section 11.1.6.3.5)

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

Other

- Simvastatin/ezetimibe (Vytorin[®], Inegy[®]) with dose of simvastatin <40 mg
- Lovastatin/niacin (Advicor[®])
- Simvastatin/niacin (Simcor[®]) with dose of simvastatin <40 mg
- Atorvastatin/ezetimibe (Liptruset[®], Atozet[®]) with dose of atorvastatin <80 mg

New Text:

Statins

- Atorvastatin (Lipitor[®], Sortis[®]), ~~with doses <80 mg~~
- Fluvastatin (Lescol[®])
- Lovastatin (Mevacor[®], Altoprev[™])
- Pravastatin (Pravachol[®])
- Pitavastatin (Livalo[®], Lipostat[®])
- Rosuvastatin (Crestor[®]), ~~with doses <40 mg~~
- Simvastatin (Zocor[®]), with *daily* doses <40 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestyramine (Questran[®], Questran Light[®], Prevalite[®], Locholest[®], Locholest[®] Light)
- Colestipol (Colestid[®])
- Colesevelam hydrochloride (Welchol[®], Cholestagel[®])
- Ezetimibe (Zetia[®], Ezetrol[®])

Fibrates

- Fenofibrate (Antara[®], Lofibra[®], Tricor[®], Triglide[™], Lipantil[®], Supralip[®])
- Bezafibrate (Bezalip[®])

- Ciprofibrate (Modalim[®])

PCSK9 inhibitors (allowed as adjunctive therapy beginning at Week 24 [Visit T5]; see Section 11.1.6.3.5)

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

Other

- Simvastatin/ezetimibe (Vytorin[®], Inegy[®]) with the average daily dose of simvastatin ≤ 40 mg
- ~~Lovastatin/niacin (Advicor[®])~~
- ~~Simvastatin/niacin (Simcor[®]) with dose of simvastatin < 40 mg~~
- Atorvastatin/ezetimibe (Liptruset[®], Atozet[®]) with dose of atorvastatin < 80 mg

CHANGE 26 REVISED HIGH-DOSE STATIN EXCLUSION

Location:

Section 8.2.2., Prohibited Medications

Original Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥ 4 weeks). Short-term intermittent use (< 14 days) of pulse steroids are allowed.
- Gemfibrozil (Lopid[®])
- Cholestin (red yeast rice, also known as monascus purpureus extract)
- Atorvastatin (Lipitor[®], Sortis[®]) 80 mg, Simvastatin (Zocor[®]) 40-80 mg, and Rosuvastatin (Crestor[®]) 40 mg alone or in fixed-dose combinations (eg, Liptruzet[®], Vytorin[®]/Inegy[®], Simcor[®])

New Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥ 4 weeks). Short-term intermittent use (< 14 days) of pulse steroids are allowed.
- Gemfibrozil (Lopid[®])
- Cholestin (red yeast rice, also known as monascus purpureus extract)

- ~~Atorvastatin (Lipitor[®], Sortis[®]) 80 mg, Simvastatin (Zocor[®]), average daily doses greater than 40-80 mg, and Rosuvastatin (Crestor[®]) 40 mg alone or in fixed-dose combinations (eg, Liptruzet[®], Vytorin[®], Inegy[®], Simecor[®], with average daily doses greater than 40 mg/10 mg)~~

CHANGE 27 DECREASE THE AMOUNT OF TIME PATIENTS SHOULD BE STABLE ON OBESITY MEDICATIONS

Location:

Section 8.2.3., Allowable Medications

Original Text:

The following must be stable for a minimum of 6 months prior to screening and, if possible not be adjusted during the study except for reasons of safety:

- Antiobesity medications

New Text:

The following must be stable for a minimum of 63 months prior to screening and, if possible not be adjusted during the study except for reasons of safety:

- Antiobesity medications

CHANGE 28 INCLUDE A SECTION IN THE PROTOCOL TO ADDRESS OVERDOSE

Location:

Section 8.5

Original Text:

Note: No original text as it was not included in the previous versions of the protocol

New Text:

8.5. Overdose

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

CHANGE 29 REVISED ADMINISTRATION INSTRUCTIONS FOR IMP

Location:

Section 9.2., Administration of Investigational Medicinal Product

Original Text:

Patients will be instructed to ingest IMP orally once daily in the morning with up to 16 ounces of water with or without food.

New Text:

Patients will be instructed to ingest IMP orally once daily (*once every 24 hours in the morning at approximately the same time each day* with up to 16 ounces of water. IMP may be taken with or without food.

**CHANGE 30 REVISED REFERENCES TO CLINICAL SAFETY LABORATORIES,
OTHER SCREENING LABORATORIES, AND LIPID ASSESSMENTS**

Location:

Section 10.2.2., Treatment Week 0 (Visit T1; Day1)

Original Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - Reserve sample
- Review inclusion/exclusion criteria to establish patient eligibility

New Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, ~~coagulation~~, and urinalysis
Note: Urine pregnancy test (only in Canada for appropriate female patients)
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - Reserve sample
 - *Genetic sample (if the patient has consented to provide a genetic sample)*
- Review inclusion/exclusion criteria to establish patient eligibility

**CHANGE 31 REVISED REFERENCES TO CLINICAL SAFETY LABORATORIES,
OTHER SCREENING LABORATORIES, AND LIPID ASSESSMENTS**

Location:

10.2.5., Treatment Week 12 (Visit T4; \pm 3 days)

Original Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - PK sample
 - Reserve sample
- Conduct diet and exercise counseling

New Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, ~~coagulation~~, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - PK sample (*for patients who were randomized into the study prior to the implementation of Protocol Amendment 3*)
 - Reserve sample
- Conduct diet and exercise counseling

**CHANGE 32 REVISED REFERENCES TO CLINICAL SAFETY LABORATORIES,
OTHER SCREENING LABORATORIES, AND LIPID ASSESSMENTS**

Location:

10.2.6., Treatment Week 24 (Visit T5; \pm 7 days)

Original Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - hs-CRP
 - PK sample
 - Reserve sample
- Conduct diet and exercise counseling

New Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - hs-CRP
 - PK sample (*for patients who were randomized into the study prior to the implementation of Protocol Amendment 3*)
 - Reserve sample
- Conduct diet and exercise counseling

**CHANGE 33 REVISED REFERENCES TO CLINICAL SAFETY LABORATORIES,
OTHER SCREENING LABORATORIES, AND LIPID ASSESSMENTS**

Location:

Section 10.2.8., Treatment Week 52 (Visit T7; \pm 7 days)

Original Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB

- HbA_{1C}
- hs-CRP
- PK sample
- Reserve sample

New Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, ~~coagulation~~, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - PK sample (*for patients who were randomized into the study prior to the implementation of Protocol Amendment 3*)
 - Reserve sample

**CHANGE 34 REVISED REFERENCES TO CLINICAL SAFETY LABORATORIES,
OTHER SCREENING LABORATORIES, AND LIPID ASSESSMENTS**

Location:

Section 11.1.6.1., Laboratory Parameters, Table 5

Original Text:

Table 5: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
<ul style="list-style-type: none"> 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 <i>and</i> %) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> Albumin (Alb) Alkaline phosphatase (Alk-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO₂) Chloride (Cl) Creatinine Creatine kinase (CK) Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium (K) Sodium (Na) Total and direct bilirubin (TB) Total protein Uric acid
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> Clarity Bilirubin Color Glucose Ketones Leukocyte esterase Nitrate Occult blood pH Protein Specific gravity Urobilinogen 	

Table 5: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC 	<u>Coagulation</u> <ul style="list-style-type: none"> • Prothrombin time (PT) • International normalized ration (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) • Serum pregnancy test (only for females of childbearing potential) • <i>Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses)</i> • Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> • Hemoglobin A_{1C} (HbA_{1C}) • Reserve blood samples for potential future measurement of ETC-1002 safety or pharmacodynamic biomarkers • PK sample • Reserve genetic blood sample (optional)

New Text:

Table 5: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
<ul style="list-style-type: none"> 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 <i>and</i> %) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> Albumin (Alb) Alkaline phosphatase (Alk-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO₂) Chloride (Cl) Creatinine Creatine kinase (CK) Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium (K) Sodium (Na) Total and direct bilirubin (TB)^a Total protein Uric acid
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> Clarity Bilirubin Color Glucose Ketones Leukocyte esterase Nitrate Occult blood pH Protein Specific gravity Urobilinogen 	

Table 5: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> Bacteria Casts Crystals Epithelial cells Red blood cell (RBC) WBC 	<u>Coagulation—In all patients at screening, then only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Visit T1 and 3 to 5 days post Visit T1</u> <ul style="list-style-type: none"> Prothrombin time (PT) International normalized ration (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV)^b Serum pregnancy test (only for females of childbearing potential) Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) Urine pregnancy test prior to randomization (only in Canada for appropriate female patients) Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> Hemoglobin A_{1C} (HbA_{1C}) Reserve blood samples for potential future measurement of ETC-1002 safety or pharmacodynamic biomarkers PK sample (for patients who were randomized into the study prior to the implementation of Protocol Amendment 3) Reserve genetic blood sample (optional)

^a If TB $\geq 1.2 \times$ ULN, a reflex indirect (unconjugated) bilirubin will be obtained.

^b If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease.

CHANGE 35 REVISED THE MONITORING AND MANAGEMENT OF ELEVATED LIVER FUNCTION TESTS

Location:

11.1.6.3.1., Monitoring and Management of Elevated Liver Function Tests

Original Text:

- If repeat LFT assessment confirms ALT and/or AST $>3 \times$ 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 $>2 \times$ ULN
 - INR $>1.5 \times$ 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

New Text:

- If repeat LFT assessment confirms ALT and/or AST $>3 \times$ 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 $>2 \times$ ULN
 - *Note: In the case of patients with Gilbert's disease, TB will be fractionated and the determination of $2 \times$ ULN will be based upon direct (conjugated) bilirubin.*
 - INR $>1.5 \times$ 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

CHANGE 36 REVISED THE MONITORING AND MANAGEMENT OF ELEVATED LDL-C

Location:

Section 11.1.6.3.5., Monitoring and Management of Elevated LDL-C

Original Text:

- Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
- After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of using high doses of statins excluded from the study (rosuvastatin 40 mg, atorvastatin 80 mg, and simvastatin 40 or 80 mg *daily*) and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).
- The initiation and or dose change of these medications will be documented on the eCRF as a concomitant medication with the associated start date
- Adjunctive therapy medications will not be provided by the sponsor

New Text:

- Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
- After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of ~~using high doses of~~

~~statins excluded from the study (rosuvastatin 40 mg, atorvastatin 80 mg, and simvastatin at average daily doses greater than 40 mg 40 or 80 mg daily)~~ and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).

- ~~– The initiation of any new and or dose changes of any existing lipid-lowering treatment of these medications~~ will be documented on the eCRF as a concomitant medication with the associated start date
- Patients who have their lipid-lowering medications modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine safety laboratory assessment that will include hematology, blood chemistry, and urinalysis. Additional safety laboratory assessments may be conducted at the investigator's discretion.*
- Adjunctive therapy medications will not be provided by the sponsor

CHANGE 37 REVISED THE MONITORING AND MANAGEMENT OF ELEVATED TRIGLYCERIDES

Location:

Section 11.1.6.3.6., Monitoring and Management of Elevated Triglycerides

Original Text:

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds 500 mg/dL (5.6 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >500 mg/dL (5.6 mmol/L), will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value meets the threshold criteria
- Any patient with a confirmed TG >500 mg/dL (5.6 mmol/L) may initiate standard-of-care therapy (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.

New Text:

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an

opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds ~~1000~~500 mg/dL (~~5.6~~11.3 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >~~500~~1000 mg/dL (~~5.6~~11.3 mmol/L), will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value meets the threshold criteria
- Any patient with a confirmed TG >1000 mg/dL (~~5.6~~11.3 mmol/L) may initiate standard-of-care therapy (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



**CHANGE 39 REMOVED THE COLLECTION OF BLOOD SAMPLES FOR
PHARMACOKINETIC ASSESSMENT**

Location:

Section 11.1.6.5., Pharmacokinetic Assessments

Original Text:

Pharmacokinetic assessments to measure plasma concentrations of ETC-1002 and its metabolite ESP15228 will be conducted from 6 mL whole blood samples collected. At the time of sample collection, the date and time of blood draw and the last 2 doses of study medication will be collected. Pharmacokinetic sample analyses for ETC-1002 and ESP15228 will be conducted by the Bioanalytical Laboratory.

New Text:

~~Pharmacokinetic assessments~~ Plasma to measure plasma concentrations of ETC-1002 and its metabolite ESP15228 will be ~~conducted~~ determined from 6 mL whole blood samples collected from patients at Weeks 12, 24, and 52. At the time of sample collection, the date and time of blood draw and the last 2 doses of study medication will be collected. ~~Pharmacokinetic sample analyses for ETC-1002 and ESP15228 will be conducted by the Bioanalytical Laboratory.~~

**CHANGE 40 REMOVED THE COLLECTION OF BLOOD SAMPLES FOR
PHARMACOKINETIC ASSESSMENT**

Location:

Section 11.1.6.6., Collection and Assessment of Pharmacokinetic Samples

Original Text:

Plasma concentrations of ETC-1002 and its metabolite (ESP15228) will be determined using validated methods. Plasma PK samples will be labeled with preprinted information, including study number, patient identification number, study day, nominal time of sample collection, matrix, and a text identification (ie, "Plasma PK"). See the study laboratory manual for further instructions

New Text:

Pharmacokinetic samples will be collected from patients who were randomized into the study prior to the implementation of Protocol Amendment 3.

Pharmacokinetic samples will not be collected for patients randomized into the study after initiation of Protocol Amendment 3.

- Plasma concentrations of ETC-1002 and its metabolite (ESP15228) will be determined using validated methods. Plasma PK samples will be labeled with preprinted information, including study number, patient identification number, study day, nominal time of sample collection, matrix, and a text identification (ie, “Plasma PK”). See the study laboratory manual for further instructions

CHANGE 41 REVISED THE ADVERSE EVENT RELATIONSHIP TO STUDY DRUG SCALE

Location:

Section 11.2.5., Relationship

Original Text:

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

- Not Related: No temporal association and other etiologies are likely the cause
- Possible: Temporal association, but other etiologies are likely the cause. However, involvement of the study drug cannot be excluded.
- Probable: Temporal association, other etiologies are possible but unlikely. The event may respond if the study drug is discontinued.
- Definite: Established temporal association with administration of the study drug with no other more probable cause. Typically, the event should resolve when the study drug is discontinued and recur on re-challenge.

New Text:

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

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

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CHANGE 43 INCREASED SAMPLE SIZE AND APPLICABLE STATISTICAL SECTIONS WERE UPDATED TO ALIGN WITH OTHER REVISIONS IN THIS AMENDMENT

Location:

Section 12.2., Determination of Sample Size

Original Text:

A total of 900 patients will be enrolled in this study with 600 patients randomized to ETC-1002 and 300 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥ 6 Months</i>	<i>Patients ≥ 12 Months</i>
<i>ETC-1002</i>	<i>555</i>	<i>540</i>
<i>Placebo</i>	<i>278</i>	<i>270</i>

Absolute risk will be addressed by 600 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events[2]. In this study adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of 600 patients randomized to ETC-1002 and 300 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits:

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
<i>0.5%</i>	<i>0.5%</i>	<i>1.0</i>	<i>(0.1, 7.0)</i>
<i>0.5%</i>	<i>1.0%</i>	<i>2.0</i>	<i>(0.3, 11.9)</i>
<i>13.6%</i>	<i>13.6%</i>	<i>1.0</i>	<i>(0.7, 1.4)</i>
<i>13.6%</i>	<i>27.2%</i>	<i>2.0</i>	<i>(0.5, 2.3)</i>

New Text:

A total of ~~900~~1950 patients will be enrolled in this study with ~~600~~1300 patients randomized to ETC-1002 and ~~300~~650 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months and 10.0% at 12 months in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	<i>Patients ≥6 Months</i>	<i>Patients ≥12 Months</i>
ETC-1002	555 1,202	540 ,170
Placebo	278 601	270 585

Absolute risk will be addressed by ~~600~~1300 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events[2]. In this study adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of ~~600~~1300 patients randomized to ETC-1002 and ~~300~~650 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002:placebo) with the following approximate 95% confidence limits:

<i>% Placebo Patients Experiencing AE</i>	<i>% ETC-1002 Patients Experiencing AE</i>	<i>Relative Risk</i>	<i>Approximate 95% Confidence Interval</i>
0.5%	0.5%	1.0	(0.1, 7.0) (0.3, 3.8)
0.5%	1.0%	2.0	(0.3, 11.9) (0.6, 6.7)
13.6%	13.6%	1.0	(0.7, 1.4) (0.8, 1.3)
13.6%	27.2%	2.0	(0.5, 2.3) (1.6, 2.5)

CHANGE 44 STATISTICAL SECTIONS WERE UPDATED TO ALIGN WITH OTHER REVISIONS IN THIS AMENDMENT

Location:

Section 12.5., Primary Endpoint

Original Text:

Hepatic Safety

Liver-associated enzymes and TB will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST and TB. Hy's law criteria ($\geq 3 \times \text{ULN}$ for either ALT or AST, with

accompanying TB $>2 \times$ ULN) will also be applied to the data; any potential Hy's law cases will be listed separately.

New Text:

Hepatic Safety

- Liver-associated enzymes and TB will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST and TB. Hy's law criteria ($\geq 3 \times$ ULN for either ALT or AST, with accompanying TB $>2 \times$ ULN) will also be applied to the data; any potential Hy's law cases will be listed separately. *Note: In the case of patients with Gilbert's disease, TB will be fractionated and the determination of $2 \times$ ULN will be based upon direct (conjugated) bilirubin.*

CHANGE 45 STATISTICAL SECTIONS WERE UPDATED TO ALIGN WITH OTHER REVISIONS IN THIS AMENDMENT

Location:

Section 12.7., PK and Other Biomarkers

Original Text:

In addition, trough plasma concentrations of ETC-1002 and ESP15228 will be collected at Weeks 12, 24, and 52 for use in further developing the population PK model.

New Text:

In addition, trough plasma concentrations of ETC-1002 and ESP15228 will be collected *from patients randomized before the implementation of Protocol Amendment 3* at Weeks 12, 24, and 52 for use in further developing the population PK model. *Trough plasma concentrations will not be collected from patients randomized after the implementation of Protocol Amendment 3.*

CHANGE 46 REVISED REFERENCES TO CLINICAL SAFETY LABORATORIES, OTHER SCREENING LABORATORIES, AND LIPID ASSESSMENTS (STUDY PROCEDURES, ASSESSMENT OF SAFETY, SCHEDULE OF STUDY EVENTS)

Location:

Appendix 1., Schedule of Events (Subject Visit Schedule)

Original Text:

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

Visit	Screen	Treatment						
	S1 ^{1,2}	T1	T2	T3	T4	T5	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 169±7	Day 253±7	Day 365±7
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
HeFH Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight ⁴	X	X	X	X	X	X	X	X
Height/BMI	X							
12-Lead ECG ⁵		X						X
Vital Signs ⁶	X	X	X	X	X	X	X	X
Serology ⁷	X							
Serum Pregnancy and/or FSH ⁸	X							
TSH	X							
Clinical Safety Labs ⁹	X	X	X	X	X	X	X	X
Basic Fasting Lipids ¹⁰	X	X	X	X	X	X	X	X
HbA _{1c}	X	X			X			X
10 mL reserve sample		X			X	X		X
apoB		X			X	X		X
hs-CRP		X			X	X		X
Diet and exercise counseling ¹¹	X	X	X	X	X	X	X	
Plasma PK					X	X		X
Establish Patient Eligibility		X						
Randomization		X						
IWRS Contact	X	X			X	X	X	X ¹²
Double-blind Drug Dispensing ¹³		X			X	X	X	
Drug Return/Compliance			X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X	X ¹⁴

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCV
- ⁸ Pregnancy test completed in premenopausal women only. *FSH test is completed in women <55 years old and >1 year without menses*
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1), Baseline (Visit T1), Week 12 (Visit T4), and at EOS (Visit T7). Please refer to [REDACTED] laboratory manual for detailed schedule of tests.
- ¹⁰ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.
- ¹¹ Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.
- ¹² IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.
- ¹³ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.
- ¹⁴ *If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events*

New Text:

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

Visit	Screen	Treatment						
	S1 ^{1,2}	T1	T2	T3	T4	T5	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 169±7	Day 253±7	Day 365±7
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
HeFH Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight ⁴	X	X	X	X	X	X	X	X
Height/BMI	X							
12-Lead ECG ⁵		X						X
Vital Signs ⁶	X	X	X	X	X	X	X	X
Serology ⁷	X							
Serum Pregnancy and/or FSH ⁸	X							
Urine Pregnancy Test ⁸		X						
TSH	X							
Clinical Safety Labs ⁹	X	X	X	X	X	X	X	X
Basic Fasting Lipids ¹⁰	X	X	X	X	X	X	X	X
HbA _{1c}	X	X			X			X
10 mL reserve sample		X			X	X		X
Genetic sample		X						
apoB		X			X	X		X
hs-CRP		X			X	X		X
Diet and exercise counseling ¹¹	X	X	X	X	X	X	X	
Plasma PK ¹²					X	X		X
Establish Patient Eligibility		X						
Randomization		X						
IWRS Contact	X	X			X	X	X	X ^{13a}
Double-blind Drug Dispensing ^{14b}		X			X	X	X	
Drug Return/Compliance			X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X	X ^{14c} X ¹⁵

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCV
- ⁸ *Serum pregnancy test completed in premenopausal women only. Urine pregnancy test is completed in premenopausal women who are able to become pregnant in Canada only. FSH test is completed in women <55 years old and >1 year without menses*
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. *These will also be conducted 4 weeks after any changes in the patient's lipid-modifying treatment. Coagulation is included at Screening (Visit S1) for all patients, and then only in patients receiving anticoagulant therapy that in the investigator's judgement requires monitoring at Baseline (Visit T1) and 3 to 5 days post Visit T1. Please refer to [REDACTED] laboratory manual for detailed schedule of tests.*
- ¹⁰ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.
- ¹¹ Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.
- ^{12/12} *PK samples will be collected from patients who were randomized prior to the implementation of Protocol Amendment 3.*
- ¹³ IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.
- ¹⁴ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.
- ¹⁵ *If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events*

APPENDIX 9. SUMMARY OF CHANGES IN AMENDMENT 4

SUMMARY OF CHANGES CLINICAL STUDY PROTOCOL

Study Number: 1002-040

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Protocol Version Incorporating Current Summary of Changes: Amendment 4: Amended Protocol 14 October 2016

Preceding Protocol Version: Amendment 3: Amended Protocol 28 July 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:

- Revised exclusion criteria to be consistent with current safety data and comply with US Food and Drug Administration request. Excluded are renally impaired patients receiving an average daily dose of simvastatin 40 mg with eGFR below $<45 \text{ mL/min/1.73 m}^2 \text{ g}$.
- To comply with US Food and Drug Administration request, additional visits (2 in the clinic and 2 by telephone) were added for clinical safety laboratory evaluations and adverse event monitoring for patients receiving an average daily dose of simvastatin 40 mg.
- Specify urine pregnancy test (for females of childbearing potential) for all countries.

- Typographical errors and formatting were corrected or revised to improve clarity and consistency. Only substantive changes are included in the Summary of Changes document.

CHANGE 1 EXCLUSION CRITERIA MODIFICATION

Location:

Synopsis Exclusion Criteria; Section 7.2

Original Text:

- *Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) $<30 \text{ mL/min/1.73 m}^2$ at Week -2 (Visit S1) [1].*

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

New Text:

- *Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) $<30 \text{ mL/min/1.73 m}^2$ at Week -2 (Visit S1) [1].*

Note: At the discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

Note: Also excluded are renally impaired patients receiving an average daily dose of simvastatin 40 mg with eGFR below $<45 \text{ mL/min/1.73 m}^2$.

CHANGE 2 URINE PREGNANCY TEST REQUIREMENT

Location:

Synopsis

Original Text:

Other Screening Laboratories:

- *Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) (if HCV is positive, a reflex HCV RNA will be performed to rule out active disease), serum pregnancy test (only for females who are of childbearing potential), FSH (only for females who are <55 years old and >1 year without menses), urine pregnancy test Day 1 prior to randomization (only in Canada for females who are of childbearing potential), TSH*

New Text:

Other Screening Laboratories:

- *Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) (if HCV is positive, a reflex HCV RNA will be performed to rule out active disease), serum pregnancy test (only for females who are of childbearing potential), FSH (only for females who are <55 years old and >1 year without menses), urine pregnancy test Day 1 prior to randomization (only ~~in Canada~~ for females who are of childbearing potential), TSH*

CHANGE 3 ADDITIONAL SAFETY VISITS FOR PATIENTS WITH LIPID- LOWERING TREATMENT MODIFICATIONS

Location:

Synopsis; Section 11.1.6.3.5

Original Text:

Patients who have their lipid-lowering treatments modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine safety laboratory assessment. Additional safety laboratory assessments may be conducted at the investigator's discretion.

New Text:

Patients who have their lipid-lowering treatments modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine safety laboratory assessment. Additional safety laboratory assessments may be conducted at the investigator's discretion. Patients receiving an average daily dose of simvastatin 40 mg based on lipid-lowering treatment modification, should adhere to the additional safety visits as described in Sections 10.2.5 and 10.2.6.

CHANGE 4 CORRECTION OF SYMBOL

Location:

Section 8.2.1

Original Text:

Simvastatin (Zocor[®]), with daily doses <40 mg

New Text:

Simvastatin (Zocor[®]), with daily doses ≤40 mg

CHANGE 5 URINE PREGNANCY TEST REQUIREMENT

Location:

Section 10.2.2; Table 5

Original Text:

- Hematology, blood chemistry, and urinalysis

Note: Urine pregnancy test (only in Canada for appropriate female patients)

- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)

New Text

- Hematology, blood chemistry, and urinalysis

Note: Urine pregnancy test (~~only in Canada for appropriate female patients for females of childbearing potential~~)

- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)

CHANGE 6 EXCLUSION OF PATIENTS FROM PK SAMPLING

Location:

Sections 10.2.5; 10.2.6; 10.2.8; Table 5

Original Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - PK sample (*for patients who were randomized into the study prior to the implementation of Protocol Amendment 3*)

New Text:

- Clinical laboratory evaluations:
 - Hematology, blood chemistry, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - PK sample (~~for patients who were~~ *randomized into the study prior to the implementation of after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling*)

**CHANGE 7 ADDITIONAL SAFETY VISITS FOR PATIENTS RECEIVING AN
AVERAGE DAILY DOSE OF SIMVASTATIN 40 MG AFTER VISITS T4
AND T5 (identical except for visit numbers)**

Location:

Sections 10.2.5.1, 10.2.5.2, 10.2.6.1, 10.2.6.2; Appendix 1, Schedule of Events

New Text:

10.2.5.1 Treatment Week 16 (Visit T4.1; ± 3 days)

Patients on an average daily dose of simvastatin 40 mg will be scheduled for the additional Visit T4.1 for clinical safety laboratory evaluations specifically to monitor changes in creatine phosphokinase (CPK) and liver function tests (LFTs). Should changes be noted, the procedures described in Section 11.1.6.3.1 will apply.

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Clinical laboratory evaluations:*
 - *Hematology, blood chemistry, and urinalysis*
- *Conduct diet and exercise counseling*

10.2.5.2 Treatment Week 20 (Visit T4.2; ± 3 days)

Patients on an average daily dose of simvastatin 40 mg will be contacted by telephone for the additional Visit T4.2 to

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Remind subjects to take IMP as scheduled*

New Text:

10.2.6.1 Treatment Week 28 (Visit T5.1; ± 7 days)

Patients on an average daily dose of simvastatin 40 mg will be scheduled for the additional Visit T5.1 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs. Should changes be noted, the procedures described in Section 11.1.6.3.1 will apply.

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Clinical laboratory evaluations:*
 - *Hematology, blood chemistry, and urinalysis*
- *Conduct diet and exercise counseling*

10.2.6.2 Treatment Week 32 (Visit T5.2; ± 7 days)

Patients on an average daily dose of simvastatin 40 mg will be contacted by telephone for the additional Visit T5.2 to

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- Remind subjects to take IMP as scheduled

Original Text:

Visit	Screen	Treatment						
	S1 ^{1,2}	T1	T2	T3	T4	T5	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29 \pm 3	Day 57 \pm 3	Day 85 \pm 3	Day 169 \pm 7	Day 253 \pm 7	Day 365 \pm 7
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
HeFH Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight ⁴	X	X	X	X	X	X	X	X
Height/BMI	X							
12-Lead ECG ⁵		X						X
Vital Signs ⁶	X	X	X	X	X	X	X	X
Serology ⁷	X							
Serum Pregnancy and/or FSH ⁸	X							
Urine Pregnancy Test ⁸		X						
TSH	X							
Clinical Safety Labs ⁹	X	X	X	X	X	X	X	X
Basic Fasting Lipids ¹⁰	X	X	X	X	X	X	X	X
HbA _{1c}	X	X			X			X
10 mL reserve sample		X			X	X		X
Genetic sample		X						
apoB		X			X	X		X
hs-CRP		X			X	X		X
Diet and exercise counseling ¹¹	X	X	X	X	X	X	X	
Plasma PK ¹²					X	X		X
Establish Patient Eligibility		X						
Randomization		X						

IWRS Contact	X	X			X	X	X	X ¹³
Double-blind Drug Dispensing ¹⁴		X			X	X	X	
Drug Return/Compliance			X	X	X	X	X	X
<i>Schedule next visit</i>	X	X	X	X	X	X	X	X ¹⁵

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCV
- ⁸ *Serum pregnancy test completed in premenopausal women only. Urine pregnancy test is completed in premenopausal women who are able to become pregnant in Canada only. FSH test is completed in women <55 years old and >1 year without menses*
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. *These will also be conducted 4 weeks after any changes in the patient's lipid-modifying treatment. Coagulation is included at Screening (Visit S1) for all patients, and then only in patients receiving anticoagulant therapy that in the investigator's judgement requires monitoring at Baseline (Visit T1) and 3 to 5 days post Visit T1. Please refer to [REDACTED] laboratory manual for detailed schedule of tests.*
- ¹⁰ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.
- ¹¹ Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.
- ¹² *PK samples will be collected from patients who were randomized prior to the implementation of Protocol Amendment 3.*
- ¹³ IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.
- ¹⁴ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.
- ¹⁵ *If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events*

New Text:

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
Informed Consent	X											
Enrollment Criteria	X											
Demographics	X											
Medical History	X											
HeFH Status Determination	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X										X
Weight ⁴	X	X	X	X	X			X			X	X
Height/BMI	X											
12-Lead ECG ⁵		X										X
Vital Signs ⁶	X	X	X	X	X			X			X	X
Serology ⁷	X											
Serum Pregnancy and/or FSH ⁸	X											
Urine Pregnancy Test ⁸		X										
TSH	X											
Clinical Safety Labs ⁹	X	X	X	X	X			X			X	X
Additional Clinical Safety Labs ¹⁰						X			X			
Basic Fasting Lipids ¹¹	X	X	X	X	X			X			X	X
HbA _{1c}	X	X			X							X
10 mL reserve sample		X			X			X				X
Genetic sample		X										
apoB		X			X			X				X
hs-CRP		X			X			X				X
Diet and exercise counseling ¹²	X	X	X	X	X	X		X	X		X	
Plasma PK ¹³					X			X				X
Establish Patient Eligibility		X										
Randomization		X										
IWRS Contact	X	X			X			X			X	X ¹⁴

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
Double-blind Drug Dispensing ¹⁵		X			X			X			X	
Drug Return/Compliance			X	X	X			X			X	X
Schedule next visit	X	X	X	X	X			X			X	X ¹⁶

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.

² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.

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

⁵ Single 12-lead ECG will be collected prior to any blood sample collection.

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

⁷ Serology for HBsAg, HCV

⁸ Serum pregnancy test completed in premenopausal women only. Urine pregnancy test is completed in premenopausal women who are able to become pregnant. FSH test is completed in women <55 years old and >1 year without menses

⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. These will also be conducted 4 weeks after any changes in the patient's lipid-modifying treatment. Coagulation is included at Screening (Visit S1) for all patients, and then only in patients receiving anticoagulant therapy that in the investigator's judgement requires monitoring at Baseline (Visit T1) and 3 to 5 days post Visit T1. Please refer to [REDACTED] laboratory manual for detailed schedule of tests.

¹⁰ Patients on an average daily dose of simvastatin 40 mg will be scheduled for additional Visits T4.1 and T5.1 to monitor clinical laboratory assessments and AE and SAE occurrence. These patients will also be contacted by telephone at Visits T4.2 and T5.2 to monitor AE and SAE occurrence.

¹¹ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.

¹² Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

¹³ Patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling.

¹⁴ IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

¹⁵ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.

¹⁶ If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

APPENDIX 10. SUMMARY OF CHANGES IN AMENDMENT 5

SUMMARY OF CHANGES CLINICAL STUDY PROTOCOL

Study Number: 1002-040

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Protocol Version Incorporating Current Summary of Changes: Amendment 5: Amended Protocol 10 May 2017

Preceding Protocol Version: Amendment 4: Amended Protocol 14 October 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:

- 
- Revised the collection of reserve samples to allow Sponsor to discontinue collection after it has been determined that a sufficient number of samples have been collected
- Revised procedures for Visits T4.1, T4.2, T5.1, and T5.2 to indicate that patients who were on 40 mg or greater simvastatin that were discontinued from IMP and who have provided consent to be followed in the safety follow-up should be scheduled for these visits
- Added a procedure to Visit T7 for patients who are completing the study while taking IMP to collect information regarding whether: 1) the patient was offered the open-

label extension study (Study 1002-050) and 2) if not, the reason that the open-label extension study was not offered to the patient

- To further ensure patient safety, the monitoring and management of Creatine Kinase (CK) has been revised to include additional instructions for the investigator in cases where the repeat CK is confirmed to be greater than 5 x ULN and the patient is asymptomatic
- The study objectives and statistical section has been revised to be consistent with the revised version of the Statistical Analysis Plan (SAP)
- Appendix 1; Schedule of Events (Subject Visit Schedule) revised to reflect all necessary changes in the amendment
- Administrative Change:
 - 
 - Revised header format to align with new Esperion Therapeutics, INC. protocol template

Note: These changes will not be reflected in italics in the final amended protocol

- Typographical errors and formatting were corrected or revised to improve clarity and consistency.
- Only substantive changes are included in the Summary of Changes document

**CHANGE 1 REVISION OF STUDY OBJECTIVES AND STATISTICAL SECTION TO
ALIGN WITH REVISED SAP**

Location:

Synopsis; Objectives

Original Text:

Primary:

- To evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular diseases [ASCVD]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy

Secondary:

- *To assess percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL-C)*

Tertiary:

- *To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy*
- *To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and triglycerides (TG) values at Week 12, 24, and 52*
- *To assess apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hs-CRP) values at Week 12, 24, and 52*

New Text:

Primary Safety:

- To evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular diseases [ASCVD]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy

Secondary Efficacy:

- *To assess percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL-C)*

Tertiary Efficacy:

- *To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy*
- *To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and triglycerides (TG) values at Week 12, 24, and 52*
- *To assess apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hs-CRP) values at Week 12, 24, and 52*

CHANGE 2 REMOVAL OF RESERVE SAMPLE COLLECTION

Location:

Synopsis; Other Biomarkers

Original Text:

Other Biomarkers:

- hs-CRP
- Reserve 10 mL blood samples for potential future measurement of ETC-1002 biomarkers

New Text:

Other Biomarkers:

- hs-CRP
- Reserve 10 mL blood samples for potential future measurement of ETC-1002 biomarkers. *Based upon Sponsor assessment and decision, reserve sample collection will be discontinued after a sufficient number of samples have been collected.*

CHANGE 3 ADDITION OF 40 MG SIMVASTATIN AS A PROHIBITED MEDICATION

Location:

Synopsis; Safety and Monitoring

Original Text:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin *at average daily doses greater than 40 mg* and the fibrate gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).

New Text:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is $>170 \text{ mg/dL}$ (4.4 mmol/L) and $\geq 25\%$ from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin *at average daily doses greater than $\geq 40 \text{ mg/day}$* and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).

CHANGE 4 REVISION OF STUDY OBJECTIVES AND STATISTICAL SECTION TO ALIGN WITH REVISED SAP

Location:

Synopsis; Statistical Methods

Original Text

Primary Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

No statistical analyses will be performed on any of the safety data in this study.

The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. AE summaries *will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. These AE summaries* will be provided overall and for subgroups such as gender, age, and HeFH status. *If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates.* Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

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

New Text

Primary Safety Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

~~No statistical analyses will be performed on any of the safety data in this study.~~ The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. ~~AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient year adjusted incidence rates. These AE summaries will be provided overall and for subgroups such as gender, age, and HeFH status. If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates.~~ Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

Original Text

Secondary Endpoint Lipids

Percent change from baseline to Week 12 in LDL-C will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors and baseline LDL-C as a covariate. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). For each ANCOVA (observed case; imputation via PMM), output will include the least squares mean (LSM) and standard error (SE) for each treatment group, along with the placebo-correct LSM and its 95% confidence interval (CI) and p-value.

Tertiary Endpoint Lipids

LDL-C, HDL-C, TG, TC, non-HDL-C, and apoB values at Weeks 12, 24, and 52 will be summarized. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. In addition, a summary using the FAS, excluding patients who received additional lipid-lowering therapy by that timepoint (by Week 24 for the Week 24 timepoint; by Week 52 for the Week 52 timepoint), will be provided. For both summaries, only observed case data will be used (no imputation for missing data).

Percent change from baseline to Week 24 and to Week 52 on LDL-C will be analyzed similarly, with patients in the FAS who did not receive additional lipid-lowering therapy by that timepoint (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each timepoint will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI and p-value.

Additional post-randomization adjunctive lipid-modifying therapy

The number and percent of patients in each treatment group requiring additional (post-randomization) adjunctive lipid-modifying therapy will be summarized. Medications and the reasons for their additional treatment (hyperlipidemia vs. hypertriglyceridemia) will be summarized separately.

PK and Other biomarkers

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. *The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).*

In addition, trough plasma concentrations will be collected at Weeks 12, 24, and 52 from patients randomized into the study prior to the implementation of Protocol Amendment 3 for use in further developing the population pharmacokinetic (PK) model. Trough plasma concentrations will not be collected from patients randomized into the study after the implementation of Protocol Amendment 3

New Text

Secondary Key Efficacy Endpoints-Lipids

~~Percent change from baseline to Week 12 or Week 24 in LDL-C, non-HDL-C, TC, apoB, and hs-CRP will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors and respective baseline value LDL-C as a covariate. The FAS will be used. Missing data for these endpoints will be imputed using multiple imputation taking account for treatment adherence. , with patients included in their randomized group, regardless of the treatment they actually received. Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). For each ANCOVA (observed case; imputation via PMM), output will include the least squares mean (LSM) and standard error (SE) for each treatment group, along with the placebo correct LSM and it's 95% confidence interval (CI) and p value.~~

Other Efficacy Tertiary Endpoints-Lipids

~~LDL-C, HDL-C, TG, TC, non-HDL-C, hs-CRP, and apoB values at other time points Weeks 12, 24, and 52 will be summarized and analyzed similarly to the key lipid endpoints. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. In addition, a summary using the FAS, excluding patients who received additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 time point; by Week 52 for the Week 52 time point), will be provided. For both summaries, only observed case data will be used (no imputation for missing data).~~

~~Percent change from baseline to Week 24 and to Week 52 on LDL C will be analyzed similarly, with patients in the FAS who did not receive additional lipid lowering therapy by that timepoint (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each timepoint will include the LSM and SE for each treatment group, as well as the placebo correct LSM, 95% CI and p value.~~

Additional post-randomization adjunctive lipid-modifying therapy

The number and percent of patients in each treatment group requiring additional (post-randomization) adjunctive lipid-modifying therapy will be summarized. Medications and the reasons for their additional treatment (hyperlipidemia vs. hypertriglyceridemia) will be summarized separately.

PK and Other biomarkers

~~hs CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).~~

~~In addition,~~ Trough plasma concentrations will be collected at Weeks 12, 24, and 52 from patients randomized into the study prior to the implementation of Protocol Amendment 3 for use in further developing the population pharmacokinetic (PK) model. Trough plasma concentrations will not be collected from patients randomized into the study after the implementation of Protocol Amendment 3.

**CHANGE 5 REVISION OF STUDY OBJECTIVES AND STATISTICAL SECTION TO
ALIGN WITH REVISED SAP**

Location:

Section 5 Trial Objectives and Purpose (including Sections 5.1; 5.2; 5.3)

Original Text:

5.1 Primary Objective

The primary objective is to evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

5.2 Secondary Objectives

- *To assess percent change from baseline to Week 12 in LDL-C*

5.3 Tertiary Objectives

- *To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy*
- *To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and TG at Weeks 12, 24, and 52*
- *To assess apoB and high-sensitivity C-reactive protein (hs-CRP) at Weeks 12, 24, and 52*

New Text:

5.1 Primary Safety Objective

The primary objective is to evaluate the long-term safety and tolerability of ETC-1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

5.2 Secondary Efficacy Objectives

- *To assess percent change from baseline to Week 12 in LDL-C*

5.3 Tertiary Efficacy Objectives

- *To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy*
- *To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and TG at Weeks 12, 24, and 52*
- *To assess apoB and high-sensitivity C-reactive protein (hs-CRP) at Weeks 12, 24, and 52*

CHANGE 6 ADDITION OF 40 MG SIMVASTATIN AS A PROHIBITED MEDICATION

Location:

Section 6.1; Tables 2 and 3

Original Text:

Table 2: Baseline Statin Dose Categories

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins ^a
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 ^b mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

^a Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)

^b Simvastatin *average daily doses greater than 40 mg* are not allowed in this study

New Text:

Table 2: Baseline Statin Dose Categories

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins ^a
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 ^b mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

^a Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)

^b Simvastatin ~~average with daily doses greater than or equal to~~ ≥ 40 mg/day are not allowed in this study.

Original Text:

Table 3: Randomization Strata

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH+ Low Intensity Statins	ASCVD + Low Intensity Statins
HeFH+ Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH+ High Intensity Statins ^a	ASCVD + High Intensity Statins ^a

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

^a Simvastatin *average daily doses greater than 40 mg* are not allowed in this study.

New Text:

Table 3: Randomization Strata

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH+ Low Intensity Statins	ASCVD + Low Intensity Statins
HeFH+ Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH+ High Intensity Statins ^a	ASCVD + High Intensity Statins ^a

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

^a Simvastatin ~~average with daily doses greater than or equal to~~ ≥ 40 mg/day are not allowed in this study.

CHANGE 7 ADDITION OF 40 MG SIMVASTATIN AS A PROHIBITED MEDICATION

Location:

Section 8.2.1 Lipid Regulating Medications and Supplements

Original Text:

Statins

- Atorvastatin (Lipitor[®], Sortis[®])
- Fluvastatin (Lescol[®])
- Lovastatin (Mevacor[®], Altoprev[™])
- Pravastatin (Pravachol[®])
- Pitavastatin (Livalo[®], Lipostat[®])
- Rosuvastatin (Crestor[®])
- Simvastatin (Zocor[®]), with *daily* doses ≤ 40 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestyramine (Questran[®], Questran Light[®], Prevalite[®], Locholest[®], Locholest[®] Light)

- Colestipol (Colestid[®])
- Colesevelam hydrochloride (Welchol[®], Cholestagel[®])
- Ezetimibe (Zetia[®], Ezetrol[®])

Fibrates

- Fenofibrate (Antara[®], Lofibra[®], Tricor[®], Triglide[™], Lipantil[®], Supralip[®])
- Bezafibrate (Bezalip[®])
- Ciprofibrate (Modalim[®])

PCSK9 inhibitors (allowed as adjunctive therapy beginning at Week 24 [Visit T5]; see Section 11.1.6.3.5)

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

Other

- Simvastatin/ezetimibe (Vytorin[®], Inegy[®]) with *the average daily* dose of simvastatin ≤40 mg
- Atorvastatin/ezetimibe (Atozet[®])

New Text:

Statins

- Atorvastatin (Lipitor[®], Sortis[®])
- Fluvastatin (Lescol[®])
- Lovastatin (Mevacor[®], Altoprev[™])
- Pravastatin (Pravachol[®])
- Pitavastatin (Livalo[®], Lipostat[®])
- Rosuvastatin (Crestor[®])
- Simvastatin (Zocor[®]), with *daily* doses *less than* 40 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/*Colestyramine* (Questran[®], Questran Light[®], Prevalite[®], Locholest[®], Locholest[®] Light)
- Colestipol (Colestid[®])
- Colesevelam hydrochloride (Welchol[®], Cholestagel[®])
- Ezetimibe (Zetia[®], Ezetrol[®])

Fibrates

- Fenofibrate (Antara[®], Lofibra[®], Tricor[®], Triglide[™], Lipantil[®], Supralip[®])
- Bezafibrate (Bezalip[®])
- Ciprofibrate (Modalim[®])

PCSK9 inhibitors (allowed as adjunctive therapy beginning at Week 24 [Visit T5]; see Section 11.1.6.3.5)

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

Other

- Ezetimibe/simvastatin/~~ezetimibe~~ (Vytorin[®], Inegy[®]) ~~with the average daily dose of~~ where simvastatin is less than 40 mg/day (Vytorin[®] 10 mg/10 mg and 10 mg/20 mg, Inegy[®] 10 mg/20 mg are allowed)
- Atorvastatin/ezetimibe (Atozet[®])

CHANGE 8 ADDITION OF 40 MG SIMVASTATIN AS A PROHIBITED MEDICATION

Location:

Section 8.2.2 Prohibited Medications

Original Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥ 4 weeks). Short-term intermittent use (< 14 days) of pulse steroids are allowed.
- Gemfibrozil (Lopid[®])
- Cholestin (red yeast rice, also known as monascus purpureus extract)
- Simvastatin (Zocor[®]), *average daily doses greater than 40 mg alone or in fixed-dose combination (eg, Vytorin[®], with average daily doses greater than 40 mg/10 mg)*

New Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥ 4 weeks). Short-term intermittent use (< 14 days) of pulse steroids are allowed.
- Gemfibrozil (Lopid[®])

- Cholestin (red yeast rice, also known as monascus purpureus extract)
- Simvastatin (Zocor[®]), ~~average daily doses greater than or equal to 40 mg/day alone or in fixed dose combination (eg, Vytorin[®], with average daily doses greater than 40 mg/10 mg)~~
- Ezetimibe/simvastatin where simvastatin doses are greater than or equal to 40 mg/day (Vytorin[®] 10 mg/40 mg and 10 mg/80 mg and Inegy[®] 10 mg/40 mg and 10 mg/80 mg per day are prohibited)

CHANGE 9 REVISED STUDY PROCEDURES

Locations:

Section 10.2.5.1 Treatment Week 16 (Visit T4.1; ± 3 days) and Section 10.2.5.2 Treatment Week 20 (Visit T4.2; ± 3 days)

Original Text:

Section 10.2.5.1 Treatment Week 16 (Visit T4.1; ± 3 days)

Patients on an average daily dose of simvastatin 40 mg will be scheduled for the additional Visit T4.1 for clinical safety laboratory evaluations specifically to monitor changes in creatine phosphokinase (CPK) and liver function tests (LFTs). Should changes be noted, the procedures described in Section 11.1.6.3.1 will apply.

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Clinical laboratory evaluations:*
 - *Hematology, blood chemistry, and urinalysis*
- *Conduct diet and exercise counseling*

Section 10.2.5.2 Treatment Week 20 (Visit T4.2; ± 3 days)

Patients on an average daily dose of simvastatin 40 mg will be contacted by telephone for the additional Visit T4.2 to

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Remind subjects to take IMP as scheduled*

New Text:

Section 10.2.5.1 Treatment Week 16 (Visit T4.1; ± 3 days)

Patients on ~~an average daily dose of~~ simvastatin 40 mg/day will be scheduled for the additional Visit T4.1 for clinical safety laboratory evaluations specifically to monitor changes in creatine phosphokinase (CPK) and liver function tests (LFTs). Should changes be noted, the procedures described in Section 11.1.6.3.1 will apply.

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, and urinalysis
- Conduct diet and exercise counseling

Section 10.2.5.2 Treatment Week 20 (Visit T4.2; ± 3 days)

Patients on ~~an average daily dose of~~ simvastatin 40 mg/day will be contacted by telephone for the additional Visit T4.2 ~~to~~

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- ~~Remind subjects to take IMP as scheduled~~

CHANGE 10 REVISED STUDY PROCEDURES

Locations:

Section 10.2.6.1 Treatment Week 28 (Visit T5.1; ± 7 days) and Section 10.2.6.2 Treatment Week 32 (Visit T5.2; ± 7 days)

Original Text:

Section 10.2.6.1 Treatment Week 28 (Visit T5.1; ± 7 days)

Patients on an average daily dose of simvastatin 40 mg will be scheduled for the additional Visit T5.1 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs. Should changes be noted, the procedures described in Section 11.1.6.3.1 will apply.

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, including muscle-related AEs (ongoing)
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, and urinalysis
- Conduct diet and exercise counseling

Section 10.2.6.2 Treatment Week 32 (Visit T5.2; ± 7 days)

Patients on an average daily dose of simvastatin 40 mg will be contacted by telephone for the additional Visit T5.2 to

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Remind subjects to take IMP as scheduled*

New Text:

Section 10.2.6.1 Treatment Week 28 (Visit T5.1; ± 7 days)

Patients on ~~an average daily dose of~~ simvastatin 40 mg/day will be scheduled for the additional Visit T5.1 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs. Should changes be noted, the procedures described in Section 11.1.6.3.1 will apply.

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- *Clinical laboratory evaluations:*
 - *Hematology, blood chemistry, and urinalysis*
- *Conduct diet and exercise counseling*

Section 10.2.6.2 Treatment Week 32 (Visit T5.2; ± 7 days)

Patients on ~~an average daily dose of~~ simvastatin 40 mg/day will be contacted by telephone for the additional Visit T5.2 ~~to~~

- *Concomitant and prohibited medication review (ongoing)*
- *Assess AEs, including muscle-related AEs (ongoing)*
- ~~*Remind subjects to take IMP as scheduled*~~

CHANGE 11 REVISED STUDY PROCEDURES

Location:

Section 10.2.8 Treatment Week 52 (Visit T7; ± 7 days)

Original Text:

- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study)

Note: For patients who withdraw from IMP treatment:

New Text:

- Return of IMP; assessment and recording of IMP compliance

- Complete study status in IWRS (ie, early withdrawal or completed study)
- *Review and offer the open-label extension study (Study 1002-050) to the patient*

Note: For patients who withdraw from IMP treatment:

CHANGE 12 REVISED MONITORING AND MANAGEMENT OF ELEVATED CK

Location:

Section 11.1.6.3.4 Monitoring and Management of Elevated Creatine Kinase

Original Text:

If at any time after randomization a patient experiences a marked CK elevation $>5 \times \text{ULN}$, 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 $>5 \times \text{ULN}$, if asymptomatic the investigator with input from the Sponsor may consider continuing study medication with continued CK assessments every 1-2 weeks.

New Text:

If at any time after randomization a patient experiences a marked CK elevation $>5 \times \text{ULN}$, 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 $>5 \times \text{ULN}$, 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 13 ADDITION OF 40 MG SIMVASTATIN AS A PROHIBITED MEDICATION

Location:

Section 11.1.6.3.5 Monitoring and Management of Elevated LDL-C

Original Text:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to

investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is *>170 mg/dL (4.4 mmol/L) and $\geq 25\%$* from the patient's baseline value at Week 0, (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin *at average daily doses greater than 40 mg* and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).

New Text:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is *>170 mg/dL (4.4 mmol/L) and $\geq 25\%$* from the patient's baseline value at Week 0, (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
 - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
 - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin *at average daily doses ~~greater than~~ ≥ 40 mg/day* and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).

CHANGE 14 REMOVAL OF RESERVE SAMPLE COLLECTION

Location:

Section 11.1.6.7 Exploratory Biomarker Measurement

Original Text:

Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from reserve sample.

New Text:

Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from reserve samples. *Based upon Sponsor assessment and decision, reserve sample collection will be discontinued after a sufficient number of samples have been collected. Study centers will be notified in writing informing them that sufficient samples have been collected and that further collection may be discontinued.*

CHANGE 15 REVISION OF STUDY OBJECTIVES AND STATISTICAL SECTION TO ALIGN WITH REVISED SAP

Location:

Section 12.5 Primary Safety Endpoint

Original Text:

12.5 Primary Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

No statistical analyses will be performed on any of the safety data in this study. The summarization of AEs will include only TEAEs, defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. These AE summaries will be provided overall and for subgroups such as gender, age, and HeFH status.

New Text:

12.5 Primary Safety Endpoint

The primary endpoint for this study is general safety, which includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs.

~~No statistical analyses will be performed on any of the safety data in this study. The summarization of AEs will include only TEAEs, defined as AEs that begin or worsen after randomization and ingestion of the first dose of study drug. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. AE summaries will include cumulative incidence (percent of patients experiencing the AE) and~~

~~patient-year adjusted incidence rates.~~ These AE summaries will be provided overall and for subgroups such as gender, age, and HeFH status.

CHANGE 16 REVISION OF STUDY OBJECTIVES AND STATISTICAL SECTION TO ALIGN WITH REVISED SAP

Location:

Section 12.6 *Efficacy Endpoints*

Original Text:

12.6 Secondary and Tertiary Lipids

12.6.1 Secondary Lipids

Percent change from baseline to Week 12 in LDL-C will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors and baseline LDL-C as a covariate. Baseline LDL-C is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). For each ANCOVA (observed case; imputation via PMM), output will include the least squares mean (LSM) and standard error (SE) for each treatment group, along with the placebo-correct LSM and its 95% confidence interval (CI) and p-value. Specific details on how the PMM will be implemented will be included in the SAP.

New Text:

12.6 ~~Secondary and Tertiary Lipids~~ Efficacy Endpoints

12.6.1 ~~Secondary~~ Key Lipids-Efficacy Endpoints

Selected efficacy endpoints will be included in a step-down testing procedure to control overall type I error. Below endpoints will be tested sequentially at alpha level of 0.05. Each endpoint will be tested only if the previous endpoint achieved statistical significance.

- 1. percent change from baseline to Week 12 in LDL-C*
- 2. percent change from baseline to Week 24 in LDL-C*
- 3. percent change from baseline to Week 12 in non-HDL-C*
- 4. percent change from baseline to Week 12 in TC*
- 5. percent change from baseline to Week 12 in apoB*
- 6. percent change from baseline to Week 12 in hs-CRP*

Percent change ~~from baseline to Week 12 in LDL-C~~ will in lipid parameters will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors and respective baseline ~~LDL-C~~ value as a covariate. Baseline ~~LDL-C~~ value is defined as the average of the last screening and the predose

Day 1/Week 0 value. When only one assessment or value is available, that single assessment/value will be used as baseline.

The FAS will be used for efficacy endpoints, with patients included in their randomized group, regardless of the treatment they actually received. ~~Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using~~ Missing data for key lipid endpoints will be imputed using a multiple imputation method that accounts for treatment adherence. ~~A pattern mixture model (PMM) will be used to specify different imputation strategies depending on whether the patient is still on study treatment. For each~~ The ANCOVA (~~observed case; imputation via PMM~~), output will include the least squares mean (LSM) and standard error (SE) for each treatment group, along with the placebo-correct LSM and its 95% confidence interval (CI) and p-value. Specific details on how the PMM will be implemented will be included in the SAP.

Additional sensitivity analyses based on subsets of the FAS or alternative missing data handling will be performed and the details will be provided in the SAP.

Original Text:

12.6.2 Tertiary Lipids

LDL-C, HDL-C, TG, TC, non-HDL-C, and apoB values at Weeks 12, 24, and 52 will be summarized. For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. Baseline for each lipid is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. In addition, a summary using the FAS, excluding patients who received additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 time point; by Week 52 for the Week 52 time point), will be provided. For both summaries, only observed case data will be used (no imputation for missing data).

Percent change from baseline to Week 24 and to Week 52 LDL-C will be analyzed similarly, with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI and p-value.

New Text:

12.6.2 Tertiary Other Lipids Efficacy Endpoints

Percent change or change in LDL-C, HDL-C, TG, TC, non-HDL-C, hs-CRP, and apoB values at ~~Weeks 12, 24, and 52 will be summarized~~ other protocol-scheduled time points will be analyzed similarly using the ANCOVA model. The FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received. No imputation for missing data will be performed.

For each parameter at each time point, the value of the parameter and the percent change from baseline in the parameter will be summarized by treatment group. ~~Baseline for each lipid is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their~~

~~randomized group, regardless of the treatment they actually received. In addition, a summary using the FAS, excluding patients who received additional lipid lowering therapy by that timepoint (by Week 24 for the Week 24 timepoint; by Week 52 for the Week 52 timepoint), will be provided. For both summaries, only observed case data will be used (no imputation for missing data).~~

In addition, Percent change from baseline to Week 24 and to Week 52 LDL-C will be analyzed similarly, with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI and p-value.

CHANGE 18 REVISION OF STUDY OBJECTIVES AND STATISTICAL SECTION TO ALIGN WITH REVISED SAP

Location:

Section 12.7 PK and Other Biomarkers

Original Text:

hs-CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. *Baseline for hs-CRP is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).*

In addition, trough plasma concentrations of ETC-1002 and ESP15228 will be collected from patients randomized before the implementation of Protocol Amendment 3 at Weeks 12, 24, and 52 for use in further developing the population PK model. Trough plasma concentrations will not be collected from patients randomized after the implementation of Protocol Amendment 3.

New Text:

~~hs CRP values and percent change from baseline in values will be summarized by treatment group at Weeks 12, 24, and 52. Baseline for hs CRP is defined as the predose Day 1/Week 0 value. The FAS will be used, with patients included in their randomized treatment group, regardless of the treatment they actually received. Only observed case data will be used (no imputation for missing data).~~

~~In addition, †Trough plasma concentrations of ETC-1002 and ESP15228 will be collected from patients randomized before the implementation of Protocol Amendment 3 at Weeks 12, 24, and 52 for use in further developing the population PK model. Trough plasma concentrations will not be collected from patients randomized after the implementation of Protocol Amendment 3.~~

CHANGE 19 REVISIONS TO SCHEDULE OF EVENTS

Location:

Appendix 1; Schedule of Events (Subject Visit Schedule)

Original Text:

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
Informed Consent	X											
Enrollment Criteria	X											
Demographics	X											
Medical History	X											
HeFH Status Determination	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X										X
Weight ⁴	X	X	X	X	X			X			X	X
Height/BMI	X											
12-Lead ECG ⁵		X										X
Vital Signs ⁶	X	X	X	X	X			X			X	X
Serology ⁷	X											
Serum Pregnancy and/or FSH ⁸	X											
Urine Pregnancy Test ⁸		X										
TSH	X											
Clinical Safety Labs ⁹	X	X	X	X	X			X			X	X
Additional Clinical Safety Labs ¹⁰						X			X			
Basic Fasting Lipids ¹¹	X	X	X	X	X			X			X	X
HbA _{1c}	X	X			X							X
10 mL reserve sample		X			X			X				X
Genetic sample		X										
apoB		X			X			X				X
hs-CRP		X			X			X				X
Diet and exercise counseling ¹²	X	X	X	X	X	X		X	X		X	
Plasma PK ¹³					X			X				X

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
Establish Patient Eligibility		X										
Randomization		X										
IWRS Contact	X	X			X			X			X	X ¹⁴
Double-blind Drug Dispensing ¹⁵		X			X			X			X	
Drug Return/Compliance			X	X	X			X			X	X
Schedule next visit	X	X	X	X	X			X			X	X ¹⁶

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.

² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.

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

⁵ Single 12-lead ECG will be collected prior to any blood sample collection.

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

⁷ Serology for HBsAg, HCV

⁸ Serum pregnancy test completed in premenopausal women only. Urine pregnancy test is completed in premenopausal women who are able to become pregnant. FSH test is completed in women <55 years old and >1 year without menses

⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. These will also be conducted 4 weeks after any changes in the patient's lipid-modifying treatment. Coagulation is included at Screening (Visit S1) for all patients, and then only in patients receiving anticoagulant therapy that in the investigator's judgement requires monitoring at Baseline (Visit T1) and 3 to 5 days post Visit T1. Please refer to [REDACTED] laboratory manual for detailed schedule of tests.

¹⁰ Patients on an average daily dose of simvastatin 40 mg will be scheduled for additional Visits T4.1 and T5.1 to monitor clinical laboratory assessments and AE and SAE occurrence. These patients will also be contacted by telephone at Visits T4.2 and T5.2 to monitor AE and SAE occurrence.

¹¹ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.

¹² Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

¹³ Patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling.

¹⁴ IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

¹⁵ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.

¹⁶ If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

New Text:

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
Informed Consent	X											
Enrollment Criteria	X											
Demographics	X											
Medical History	X											
HeFH Status Determination	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X										X
Weight ⁴	X	X	X	X	X			X			X	X
Height/BMI	X											
12-Lead ECG ⁵		X										X
Vital Signs ⁶	X	X	X	X	X			X			X	X
Serology ⁷	X											
Serum Pregnancy and/or FSH ⁸	X											
Urine Pregnancy Test ⁸		X										
TSH	X											
Clinical Safety Labs ⁹	X	X	X	X	X			X			X	X
Additional Clinical Safety Labs ¹⁰						X			X			
Basic Fasting Lipids ¹¹	X	X	X	X	X			X			X	X
HbA _{1c}	X	X			X							X
10 mL reserve sample ¹²		X			X			X				X
Genetic sample		X										
apoB		X			X			X				X
hs-CRP		X			X			X				X
Diet and exercise counseling ^{13a}	X	X	X	X	X	X		X	X		X	
Plasma PK ^{14a}					X			X				X

Visit	Screen	Treatment										
	S1 ^{1,2}	T1	T2	T3	T4	T4.1	T4.2 phone	T5	T5.1	T5.2 phone	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 112±3	Day 140±3	Day 169±7	Day 196±7	Day 224±7	Day 253±7	Day 365±7
Establish Patient Eligibility		X										
Randomization		X										
IWRS Contact	X	X			X			X			X	X ¹⁵⁴
Double-blind Drug Dispensing ¹⁶⁵		X			X			X			X	
Drug Return/Compliance			X	X	X			X			X	X
Offer Study 1002-050												X ¹⁷⁶
Schedule next visit	X	X	X	X	X			X			X	X ¹⁸⁷

NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCV
- ⁸ Serum pregnancy test completed in premenopausal women only. Urine pregnancy test is completed in premenopausal women who are able to become pregnant. FSH test is completed in women <55 years old and >1 year without menses
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. These will also be conducted 4 weeks after any changes in the patient's lipid-modifying treatment. Coagulation is included at Screening (Visit S1) for all patients, and then only in patients receiving anticoagulant therapy that in the investigator's judgement requires monitoring at Baseline (Visit T1) and 3 to 5 days post Visit T1. Please refer to [REDACTED] laboratory manual for detailed schedule of tests.
- ¹⁰ Patients on an average daily dose of simvastatin 40 mg/day will be scheduled for additional Visits T4.1 and T5.1 to monitor clinical laboratory assessments and AE and SAE occurrence. These patients will also be contacted by telephone at Visits T4.2 and T5.2 to monitor AE and SAE occurrence.
- ¹¹ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.
- ¹² Based upon Sponsor assessment and decision, reserve sample collection will be discontinued after a sufficient number of samples have been collected.

¹³² Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

¹⁴³ *Patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling.*

¹⁵⁴ IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

¹⁶⁵ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.

¹⁷⁶ *Review and offer the open-label extension study (Study 1002-050) to the patient. If the patient was not offered Study 1002-050, record the reason why in the eCRF*

¹⁸⁷ *If patient is discontinuing treatment ~~and completing the EOS visit~~, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events*

CHANGE18 ADMINISTRATIVE CHANGE

Location:

Appendix 2: Sponsor's Signature Page.

Original Text:

Study Title:	A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy
Study Number:	1002-040
Final Date:	14 October 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: _____

A large black rectangular redaction box covering the signature of the person.

Date: _____

New Text:

Study Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-040

Final Date: ~~14 October 2016~~ 10 May 2017

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

Signed: _____


Date: _____

CHANGE18 ADMINISTRATIVE CHANGE

Location:

Protocol Header: Synopsis, Protocol Body, Appendices

Original Format:

Synopsis, Protocol Body, Appendices 1 through 5
Esperion Therapeutics, Inc.
Final, DD Month YYYY

Summary of Changes for Amendments, Appendices 6 through 10:

Esperion Therapeutics, Inc.
Summary of Changes Amendment Number
Final, DD Month YYYY

New Format:

Synopsis, Protocol Body, Appendices 1 through 5:

Esperion Therapeutics, Inc.
Amendment 5, DD Month YYYY

Summary of Changes for Amendments, Appendices 6 through 10:

Esperion Therapeutics, Inc.

Summary of Changes Amendment Number (actual amendment number)

Amendment Number (current amendment number), DD Month YYYY

1002-040 Protocol Version: Amendment #2
Administrative Change Letter:
1002-040-Am2-CA-01-Admin
Canadian Sites Only



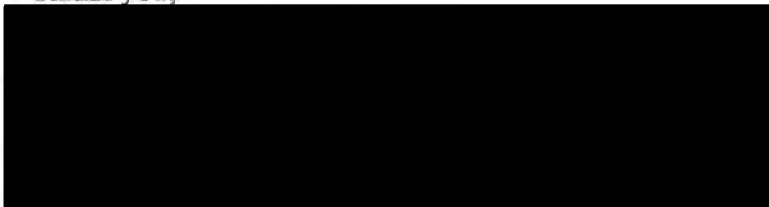
Date: 12 April 2016
To: 1002-040 Canadian Investigators and Study Staff
Re: 1002-040 Protocol Amendment #2,
Administrative Change Letter 1002-040-Am2-CA-01-Admin

Dear Investigators and Study Staff,

This letter serves to communicate administrative changes to the 1002-040 Protocol titled "*A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC-1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy*," (version: Protocol Amendment #2; dated 23 February 2016). These administrative changes were requested by Health Canada and are highlighted in the attached Summary of Change Document.

This Administrative Change Letter #1.CAN is important study documentation. Please retain this letter within your study file.

Thank you,



Esperion Therapeutics, Inc.

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SUMMARY OF CHANGE

The changes included in this Administrative Change Letter are:

- Clarification of adequate birth control requirements for women of childbearing potential
- The addition of a urine pregnancy test for women of childbearing potential prior to randomization
- The addition of instructions for management of a bempedoic acid overdose

The specific changes to protocol text with reference to location and rationale for change are provided below. Changes to text or added text are italicized. Deleted text will be indicated with strikethrough font.

1. SYNOPSIS

Previous Text [Diagnosis and criteria for patient eligibility]

1. Men and nonpregnant, nonlactating women. Women must be either:
 - Naturally postmenopausal (as reported by the patient, 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, but not tubal ligation alone) or;
 - Women of childbearing potential must be willing to use 1 acceptable method of birth control. 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).
 - There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.

New Text [Diagnosis and criteria for patient eligibility]

2. Men and nonpregnant, nonlactating women. Women must be either:
 - Naturally postmenopausal (as reported by the patient, 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, but not tubal ligation alone) or;

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- Women of childbearing potential must be willing to use 1 acceptable method of birth control. *The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug.* Acceptable methods of birth control include: 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).
- There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.

Rationale

Additional clarification to the start and duration of acceptable methods of birth control were required by Health Canada.

Previous Text [Criteria for evaluation)]

Other Screening Laboratories:

- Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), serum pregnancy test (only for females who are of childbearing potential), FSH (only for females who are <55 years old and >1 year without menses), TSH

New Text [Criteria for evaluation)]

Other Screening Laboratories:

- Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), serum pregnancy test (only for females who are of childbearing potential), FSH (only for females who are <55 years old and >1 year without menses), *urine pregnancy test Day 1 prior to randomization (only for females who are of childbearing potential)*, TSH

Rationale

Additional confirmation of pregnancy status of women of childbearing prior to randomization was required by Health Canada.

2. SECTION 7.1

Previous Text [Subject Inclusion Criteria]

2. Men and nonpregnant, nonlactating women. Women must be either:

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- a. Naturally postmenopausal (as reported by the patient, 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, but not tubal ligation alone) or;
- b. Women of childbearing potential must be willing to use 1 acceptable method of birth control. 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).
- c. There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.

New Text /Subject Inclusion Criteria/

- 2. Men and nonpregnant, nonlactating women. Women must be either:
 - a. Naturally postmenopausal (as reported by the patient, 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, but not tubal ligation alone) or;
 - b. Women of childbearing potential must be willing to use 1 acceptable method of birth control. *The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug.* Acceptable methods of birth control include: 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).
 - c. There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.

Rationale

Additional clarification to the start and duration of acceptable methods of birth control were required by Health Canada.

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3. SECTION 8.5

New Text-New Section [Overdose]

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

Rationale

Information regarding overdose of bempedoic acid was required by Health Canada.

4. SECTION 10.2.2

Previous Text [Treatment Week 0 (Visit T1; Day 1)]

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical examination (PE)
- Weight
- 12-Lead electrocardiogram (ECG)
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
- Reserve sample

New Text [Treatment Week 0 (Visit T1; Day 1)]

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

- Concomitant and prohibited medication review (ongoing)

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- Assess AEs (starting from signing *of* the informed consent document)
- Physical examination (PE)
- Weight
- 12-Lead electrocardiogram (ECG)
- Vital signs
- Clinical laboratory evaluations:
 - Hematology, blood chemistry, coagulation, and urinalysis
 - *Urine pregnancy test (only for females of childbearing potential)*
 - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
 - apoB
 - HbA_{1C}
 - hs-CRP
 - Reserve sample

Rationale

Additional confirmation of pregnancy status of women of childbearing prior to randomization was required by Health Canada.

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5. SECTION 11.1.6.1

Previous Text [Laboratory Parameters (Safety), Table 5]

Table 1: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
<ul style="list-style-type: none"> 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 <i>and</i> %) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> Albumin (Alb) Alkaline phosphatase (Alk-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO₂) Chloride (Cl) Creatinine Creatine kinase (CK) Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium (K) Sodium (Na) Total and direct bilirubin (TB) Total protein Uric acid
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> Clarity Bilirubin Color Glucose Ketones Leukocyte esterase Nitrate Occult blood pH Protein Specific gravity Urobilinogen 	

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Table 1: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> Bacteria Casts Crystals Epithelial cells Red blood cell (RBC) WBC 	<u>Coagulation</u> <ul style="list-style-type: none"> Prothrombin time (PT) International normalized ration (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) Serum pregnancy test (only for females of childbearing potential) <i>Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses)</i> Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> Hemoglobin A_{1C} (HbA_{1C}) Reserve blood samples for potential future measurement of ETC-1002 safety or pharmacodynamic biomarkers PK sample Reserve genetic blood sample (optional)

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New Text /Laboratory Parameters (Safety), Table 5/

Table 2: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
<ul style="list-style-type: none"> 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 <i>and</i> %) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> Albumin (Alb) Alkaline phosphatase (Alk-P) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO₂) Chloride (Cl) Creatinine Creatine kinase (CK) Glucose Lactate dehydrogenase (LDH) Phosphorus Potassium (K) Sodium (Na) Total and direct bilirubin (TB) Total protein Uric acid
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> Clarity Bilirubin Color Glucose Ketones Leukocyte esterase Nitrate Occult blood pH Protein Specific gravity Urobilinogen 	

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Table 2: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> Bacteria Casts Crystals Epithelial cells Red blood cell (RBC) WBC 	<u>Coagulation</u> <ul style="list-style-type: none"> Prothrombin time (PT) International normalized ration (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) Serum pregnancy test (only for females of childbearing potential) <i>Urine pregnancy test prior to randomization (only for females of childbearing potential)</i> Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> Hemoglobin A_{1C} (HbA_{1C}) Reserve blood samples for potential future measurement of ETC-1002 safety or pharmacodynamic biomarkers PK sample Reserve genetic blood sample (optional)

Rationale

Additional confirmation of pregnancy status of women of childbearing potential prior to randomization was required by Health Canada.

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6. APPENDIX 1

Previous Text [Schedule of Events (Subject Visit Schedule)]

Visit	Screen	Treatment						
	S1 ^{1,2}	T1	T2	T3	T4	T5	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 169±7	Day 253±7	Day 365±7
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
HeFH Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight ⁴	X	X	X	X	X	X	X	X
Height/BMI	X							
12-Lead ECG ⁵		X						X
Vital Signs ⁶	X	X	X	X	X	X	X	X
Serology ⁷	X							
Serum Pregnancy and/or FSH ⁸	X							
TSH	X							
Clinical Safety Labs ⁹	X	X	X	X	X	X	X	X
Basic Fasting Lipids ¹⁰	X	X	X	X	X	X	X	X
HbA _{1c}	X	X			X			X
10 mL reserve sample		X			X	X		X
apoB		X			X	X		X
hs-CRP		X			X	X		X
Diet and exercise counseling ¹¹	X	X	X	X	X	X	X	
Plasma PK					X	X		X
Establish Patient Eligibility		X						
Randomization		X						
IWRS Contact	X	X			X	X	X	X ¹²
Double-blind Drug Dispensing ¹³		X			X	X	X	
Drug Return/Compliance			X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X	X ¹⁴

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NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCV
- ⁸ Pregnancy test completed in premenopausal women only. FSH test is completed in women <55 years old and >1 year without menses
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1), Baseline (Visit T1), Week 12 (Visit T4), and at EOS (Visit T7). Please refer to [REDACTED] laboratory manual for detailed schedule of tests.
- ¹⁰ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.
- ¹¹ Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.
- ¹² IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.
- ¹³ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.
- ¹⁴ If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

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New Text /Schedule of Events (Subject Visit Schedule)/

Visit	Screen	Treatment						
	S1 ^{1,2}	T1	T2	T3	T4	T5	T6	T7 EOS ³
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	Day 169±7	Day 253±7	Day 365±7
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
HeFH Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight ⁴	X	X	X	X	X	X	X	X
Height/BMI	X							
12-Lead ECG ⁵		X						X
Vital Signs ⁶	X	X	X	X	X	X	X	X
Serology ⁷	X							
Serum Pregnancy and/or FSH ⁸	X							
Urine Pregnancy Test ⁸		X						
TSH	X							
Clinical Safety Labs ⁹	X	X	X	X	X	X	X	X
Basic Fasting Lipids ¹⁰	X	X	X	X	X	X	X	X
HbA _{1c}	X	X			X			X
10 mL reserve sample		X			X	X		X
apoB		X			X	X		X
hs-CRP		X			X	X		X
Diet and exercise counseling ¹¹	X	X	X	X	X	X	X	
Plasma PK					X	X		X
Establish Patient Eligibility		X						
Randomization		X						
IWRS Contact	X	X			X	X	X	X ¹²
Double-blind Drug Dispensing ¹³		X			X	X	X	
Drug Return/Compliance			X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X	X ¹⁴

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NOTE: For patients who withdraw from IMP 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 (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according to 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.
- ² An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.
- ³ All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.
- ⁴ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁵ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁶ Vital signs will include DBP, SBP, and HR and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
- ⁷ Serology for HBsAg, HCV
- ⁸ *Serum and urine pregnancy* tests completed in premenopausal women or women of childbearing potential only. FSH test is completed in women <55 years old and >1 year without menses
- ⁹ Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1), Baseline (Visit T1), Week 12 (Visit T4), and at EOS (Visit T7). Please refer to [REDACTED] laboratory manual for detailed schedule of tests.
- ¹⁰ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.
- ¹¹ Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.
- ¹² IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.
- ¹³ Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.
- ¹⁴ If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

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Rationale

Additional confirmation of pregnancy status of women of childbearing prior to randomization was required by Health Canada.

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