CLINICAL STUDY PROTOCOL

A Placebo-controlled, Randomized, Multicenter, Double-blind, Parallel-Group Trial to Assess the Efficacy and Safety of ETC-1002 in Patients With Hypercholesterolemia

A Dose-finding Trial of ETC-1002 in Patients With Hypercholesterolemia

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

ETC-1002 (Nonproprietary name: Bempedoic acid)

CLINICAL PROTOCOL

Translation

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CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ACL	Adenosine triphosphate citrate lyase
ALT	Alanine aminotransferase
apo B	Apolipoprotein B
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
CCDS	Company Core Data Sheet
CK	Creatine kinase
C_{max}	Maximum (peak) plasma concentration of the drug
CRO	Contract research organization
CSR	Clinical study report
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FBR	Future biospecimen research
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HEENT	Head, eyes, ears, nose, throat
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HoFH	Homozygous familial hypercholesterolemia
hsCRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational medicinal product
IRB	Institutional review board
IRE	Immediately reportable event
IWRS	Interactive web response system
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
non-HDL-C	Non-high-density lipoprotein cholesterol
OAT	Organic anion transporter

Abbreviation	Definition
PCSK9	Proprotein convertase subtilisin/kexin type 9
PPAR	Peroxisome proliferator-activated receptor
PQC	Product quality complaint
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
t_{max}	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

1 Protocol Summary

1.1 Synopsis

Name of Sponsor:

Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product:

ETC-1002 (Nonproprietary name: Bempedoic acid)

Protocol No.:

346-102-00001

Protocol Title:

A placebo-controlled, randomized, multicenter, double-blind, parallel-group trial to assess the efficacy and safety of ETC-1002 in patients with hypercholesterolemia

Protocol Lay Person Short Title:

A dose-finding trial of ETC-1002 in patients with hypercholesterolemia

Clinical Phase/Trial Type:

Phase 2 trial/Dose-finding trial

Treatment/Indication:

Patients with hypercholesterolemia

Objectives and Endpoints:

Objectives	Endpoints
Primary Objectives: • To assess the low-density lipoprotein cholesterol (LDL-C)-lowering efficacy of ETC-1002 at 60 mg, 120 mg, and 180 mg versus placebo when administered for 12 weeks in combination with ongoing stable statin therapy and/or other lipid-modifying therapy in patients with hypercholesterolemia who have inadequate control of LDL-C • To characterize the dose-response of ETC-1002 and investigate the appropriate dosage for a phase 3 trial	<u>Primary Endpoint</u> • Percent change in LDL-C from baseline to Week 12

Secondary Objectives: • To assess the effect of ETC-1002 on high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), triglyceride (TG), apolipoprotein B (apoB), high-sensitivity C-reactive protein (hsCRP), and glycosylated hemoglobin (HbA1c) • To assess the proportion of subjects achieving the lipid management goals of LDL-C by treatment with ETC-1002. • To assess the pharmacokinetic plasma trough and near-peak concentrations of ETC-1002 and its active metabolite (ESP15228) • To characterize the safety and tolerability of ETC-1002 versus placebo in patients with hypercholesterolemia when administered in combination with ongoing stable statin therapy and/or other lipid-modifying therapy	<u>Secondary Endpoints</u> • Percent change in HDL-C, non-HDL-C, TC, TG, apo B, hsCRP and HbA1c from baseline to Week 12 • Proportion of subjects whose LDL-C value achieve the lipid management goals based on risk assessment (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk], or <140 mg/dL [intermediate risk]) and the proportion of subjects whose LDL-C value achieve <70 mg/dL at Week 12 <u>Other Assessments</u> • Time course of LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c at each time point during the treatment period <u>Pharmacokinetic Assessments</u> • Plasma concentrations of ETC-1002 and its active metabolite, ESP15228 <u>Safety Assessments</u> Adverse events (AEs), clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), body weight, and 12-lead electrocardiogram (ECG)

Trial Design:

A placebo-controlled, randomized, multicenter, double-blind, parallel-group trial

Trial Population:

This trial will enroll subjects with hypercholesterolemia aged 20 years or older and younger than 75 years who are at risk for cardiovascular events and who have inadequate control of LDL-C by the existing hypercholesterolemia drugs.

The target number of subjects is 176 in total (44 in the ETC-1002 60-mg/day group, 44 in the 120-mg/day group, 44 in the 180-mg/day group, and 44 in the placebo group) as randomized subjects.

Inclusion/Exclusion Criteria:

Inclusion Criteria

1) Patients from whom written informed consent is obtained prior to start of the trial
2) Patients, either male or female, age 20 years or older and younger than 75 years at the time of informed consent
3) Patients who meet the following criteria for inadequate response to statins (statin tolerance) or statin intolerance
   - Statin tolerance

     Patients with hypercholesterolemia who have been taking statins (atorvastatin, pitavastatin, rosuvastatin, pravastatin, simvastatin, or fluvastatin), and hypercholesterolemia drugs other than statins if necessary, at the same dose and regimen from at least 4 weeks prior to Week −5 (Visit S1) (at least 6 weeks, for fibrates and selective peroxisome proliferator-activated receptor [PPAR] α modulators) to Week −5 (Visit S1) according to the approved dosage regimen, but fail to achieve the lipid management goals of LDL-C based on risk assessment shown in the inclusion criteria 4) at both Week −5 (Visit S1) and Week −1 (Visit S3)
   - Statin intolerance
     Patients with hypercholesterolemia in whom safety problems occurred when administration of statins was started or increased in dose and were resolved after discontinuation or dose reduction of statin administration, and who have been taking statins at (or below) the lowest approved daily dose and/or who have been taking at least one hypercholesterolemia drug other than statins at the same dose and regimen from at least 4 weeks prior to Week −5 (Visit S1) (at least 6 weeks, for fibrates and selective PPAR α modulators) to Week −5 (Visit S1) according to the approved dosage regimen, but fail to achieve the lipid management goals of LDL-C based on risk assessment shown in the inclusion criteria 4) at both Week −5 (Visit S1) and Week −1 (Visit S3)
4) Patients considered to be at risk of developing cardiovascular events who meet any of the following conditions a), b), or c)
   a) Patients with either of the following medical histories or complications and in whom LDL-C at Week −5 (Visit S1) and Week −1 (Visit S3) is ≥100 mg/dL
      – History of coronary artery disease
      – Diagnosed with heterozygous familial hypercholesterolemia (HeFH)
   b) Patients with any of the following medical histories or complications and in whom LDL-C at Week −5 (Visit S1) and Week −1 (Visit S3) is ≥120 mg/dL
      – Diagnosed with peripheral arterial disease
      – History of non-cardiogenic cerebral infarction
      – Diagnosed with chronic kidney disease and does not fall under the exclusion criteria 12)

- Diagnosed with type 2 diabetes mellitus more than 3 months prior to Week −5 (Visit S1) and does not fall under the exclusion criteria 7)

c) Patients who do not meet inclusion criteria a) or b), but whose total score in the coronary artery disease risk prediction model using the Suita score specified by the Japan Atherosclerosis Society is ≥41 and ≤55 points (intermediate risk) and in whom each LDL-C level at Week −5 (Visit S1) and Week −1 (Visit S3) is ≥140 mg/dL, or whose total score is ≥56 (high risk) and in whom each LDL-C level at Week −5 (Visit S1) and Week −1 (Visit S3) is ≥120 mg/dL

5) Patients with fasting TG level of <400 mg/dL at Week −5 (Visit S1)
6) Patients with body mass index (BMI) of ≥18 kg/m^2 and <35 kg/m^2 at Week −5 (Visit S1)

Exclusion Criteria

1) Women who are pregnant or breastfeeding or who have a positive pregnancy test (urine) result at Week −5 (Visit S1) or Day 1 (Visit T1)
2) Sexually active male subjects or sexually active female subjects of childbearing potential who do not agree to practice 2 different approved methods of birth control or to maintain complete abstinence (the methods of periodic abstinence and withdrawal are not appropriate for contraception) during the trial and for 30 days after final Investigational Medicinal Product (IMP) administration. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, and condoms (all methods are approved or certified in Japan).
3) Patients with homozygous familial hypercholesterolemia (HoFH)
4) Patients with a history or current symptoms of any of the following cardiovascular diseases within 3 months prior to Week −5 (Visit S1)[redacted]
   - Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, symptomatic carotid artery stenosis, symptomatic peripheral arterial disease, or decompensated heart failure
   - Abdominal aortic aneurysm
   - Unexplained syncope or long-QT syndrome, family history of long-QT syndrome, or risk factors for Torsade de Pointes, such as persistent hypokalemia or second- or third-degree atrioventricular block (except when controlled by medication, etc)
5) Patients with uncontrolled hypertension, defined as follows: sitting systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥100 mmHg after resting 5 minutes at Week −5 (Visit S1)
6) Patients with uncontrolled and serious hematologic or coagulation disorders or with Hgb of <10.0 g/dL at Week −5 (Visit S1)

7) Patients with type 1 diabetes or uncontrolled type 2 diabetes with HbA1c of ≥9% at Week −5 (Visit S1)
8) Patients with uncontrolled hypothyroidism with thyroid-stimulating hormone (TSH) of >1.5 × the upper limit of normal (ULN) at Week −5 (Visit S1)
9) Patients with liver disease or dysfunction, including:
   - Positive serology for hepatitis B surface antigen (HBsAg) or hepatitis C (HCV) antibodies at Week −5 (Visit S1)
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of ≥3 × ULN or total bilirubin of ≥2 × ULN at Week −5 (Visit S1)
10) Patients with a history or complication of chronic musculoskeletal symptoms that may be difficult to differentiate from myalgia (eg, fibromyalgia)
11) Patients with creatine kinase (CK) of >3 × ULN at Week −5 (Visit S1)
12) Patients with renal dysfunction or nephritic syndrome or a history or complication of nephritis and with estimated glomerular filtration rate (eGFR) of ≤30 mL/min/1.73m^2 at Week −5 (Visit S1)
13) Patients who have had gastrointestinal surgery that may affect drug absorption (eg, Lap-Band® or gastric bypass)
14) Patients who have undergone surgery, chemotherapy, or radiation for active malignancy (excluding properly treated nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ) within the past 5 years prior to Week −5 (Visit S1)
15) Patients with a history of drug, alcohol, or cocaine abuse within the past 2 years prior to Week −5 (Visit S1)
16) Patients who have had blood collection (eg, blood donation) in a cumulative amount exceeding 200 mL within 4 weeks, 400 mL within 12 weeks, or 1200 mL within 1 year prior to Week −5 (Visit S1)
17) Patients who have used any investigational drug not approved in Japan within either 4 weeks or 5 times the half-life of the drug, whichever is longer, prior to Week −5 (Visit S1)
18) Patients who used or received the following drugs (including food) or therapies within the specified period or who are expected to use or receive them by the end of tests at Week 12 (Visit T6)

1.	Initiation of administration or change in dose of a systemic corticosteroid (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
2.	Lomitapide (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
3.	Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (from 4 weeks prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
4.	[redacted]
5.	Red yeast rice and food containing red yeast rice (from 2 weeks prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])

6.	LDL apheresis (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])

19) Patients in whom the following drugs (therapies) are changed prior to Day 1 (Visit T1) or in whom initiation of the following drugs (therapies) is planned by the end of tests at Week 12 (Visit T6)
    - Hormone replacement: Within 6 weeks prior to Day 1 (Visit T1)
    - Thyroid replacement: Within 6 weeks prior to Day 1 (Visit T1)
    - Diabetes medications: Within 4 weeks prior to Day 1 (Visit T1)
    - Obesity medications: Within 3 months prior to Day 1 (Visit T1)
20) Patients [redacted] who cannot continue drug administration due to safety issues
21) [redacted]
22) Patients otherwise judged inappropriate for participating in the trial in the opinion of the investigator or subinvestigator

Trial Sites:

Approximately 50 sites in Japan

Investigational Medicinal Products and Mandatory Concomitant Medications, Dose, Dosage Regimen, Treatment Duration, Formulation, and Mode of Administration:

[redacted]

[Treatment period (double-blind)]

1) Medications
   - Mandatory concomitant medications:
     Hypercholesterolemia drugs (statins and/or drugs other than statins) that have been taken from before informed consent
   - Investigational medicinal products:
     – ETC-1002 60 mg tablets
     – Placebo tablets
2) Dose and regimen
   - Mandatory concomitant medications:
     Hypercholesterolemia drugs [redacted] will be continued without changing the type and the dose and regimen during the treatment period.
   - Investigational medicinal products:
     – 180-mg/day group: Three ETC-1002 60-mg tablets will be administered orally once daily.
     – 120-mg/day group: Two ETC-1002 60-mg tablets and one placebo tablet will be administered orally once daily.
     – 60-mg/day group: One ETC-1002 60-mg tablet and two placebo tablets will be administered orally once daily.
     – Placebo group: Three placebo tablets will be administered orally once daily.
3) Treatment duration: 12 weeks

Trial Assessments:

Assessments for Efficacy: LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c

Assessments for Pharmacokinetics: Plasma concentrations of ETC-1002 and its active metabolite, ESP15228

Assessments for Safety: Adverse events, clinical laboratory tests, 12-lead ECG, vital signs, physical examination, body weight

Screening/Other: demographics, height, virus test (HBsAg and HCV antibodies), endocrine test (TSH), pregnancy test (urine, serum), deoxyribonucleic acid (DNA) storage (optional), biomarker storage (optional)

Data Monitoring Committee: No

Statistical Methods:

[Statistical methods for the primary efficacy endpoint]

The primary efficacy endpoint is the percent change in LDL-C from baseline to Week 12. Analysis of covariance will be performed using treatment group and the randomization stratification factor (statin tolerance or statin intolerance) as factors and baseline value of LDL-C as a covariate at a two-sided significance level of 0.05. Comparisons versus the placebo group will be performed starting from the highest ETC-1002 dose group. Baseline is defined as the mean of the LDL-C values for Day 1 (Visit T1) and Week −1 (Visits S3).

[Sample size justification]

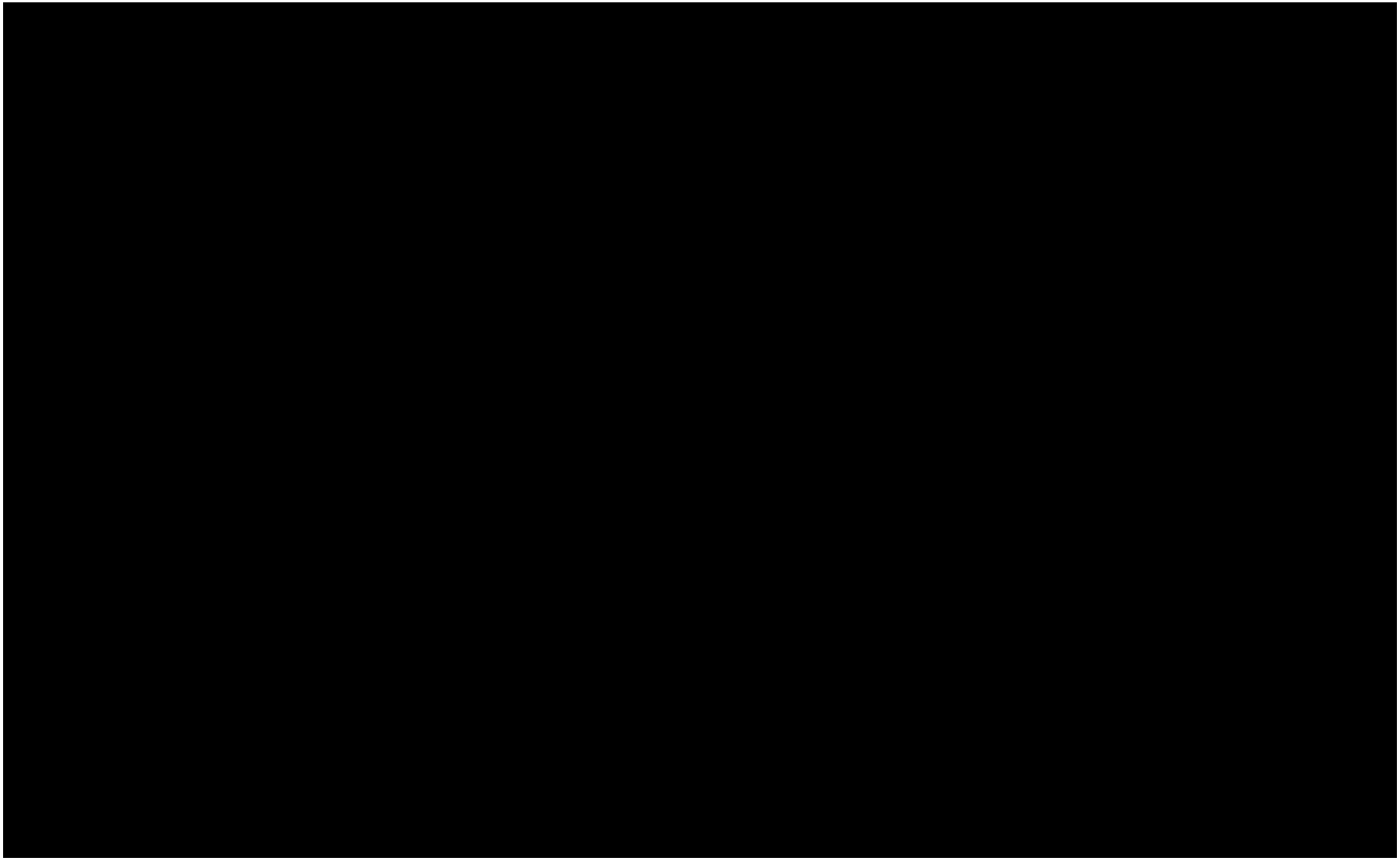
Differences in the percent change in LDL-C from baseline to Week 12 in the ETC-1002 group versus the placebo group in non-Japanese phase 3 trials were −18.1% and −17.42% in trials in statin tolerant subjects and −21.41% and −28.45% in trials in statin intolerant subjects. Base on the results, the difference between the ETC-1002 group and the placebo group in the subjects with statin tolerance was assumed to be 17%, and the difference between the ETC-1002 group and the placebo group in the subjects with statin intolerance was assumed to be 25%. For the present trial it was assumed that the percentage of statin intolerant subjects enrolled would be 20% and that the difference in the endpoint between the ETC-1002 group and the placebo group would be 19% in the overall trial population. Based on the results of the phase 3 trials, assuming a difference of 19% with standard deviation of 25% between the ETC-1002 groups and the placebo group in the percent change in LDL-C from baseline to Week 12, 38 subjects per group are required to achieve a power of 90% or higher in a two-tailed test with a 5% significance level. Assuming a withdrawal rate of 12.5%, the target number of subjects to be randomized was set at 44 per group.

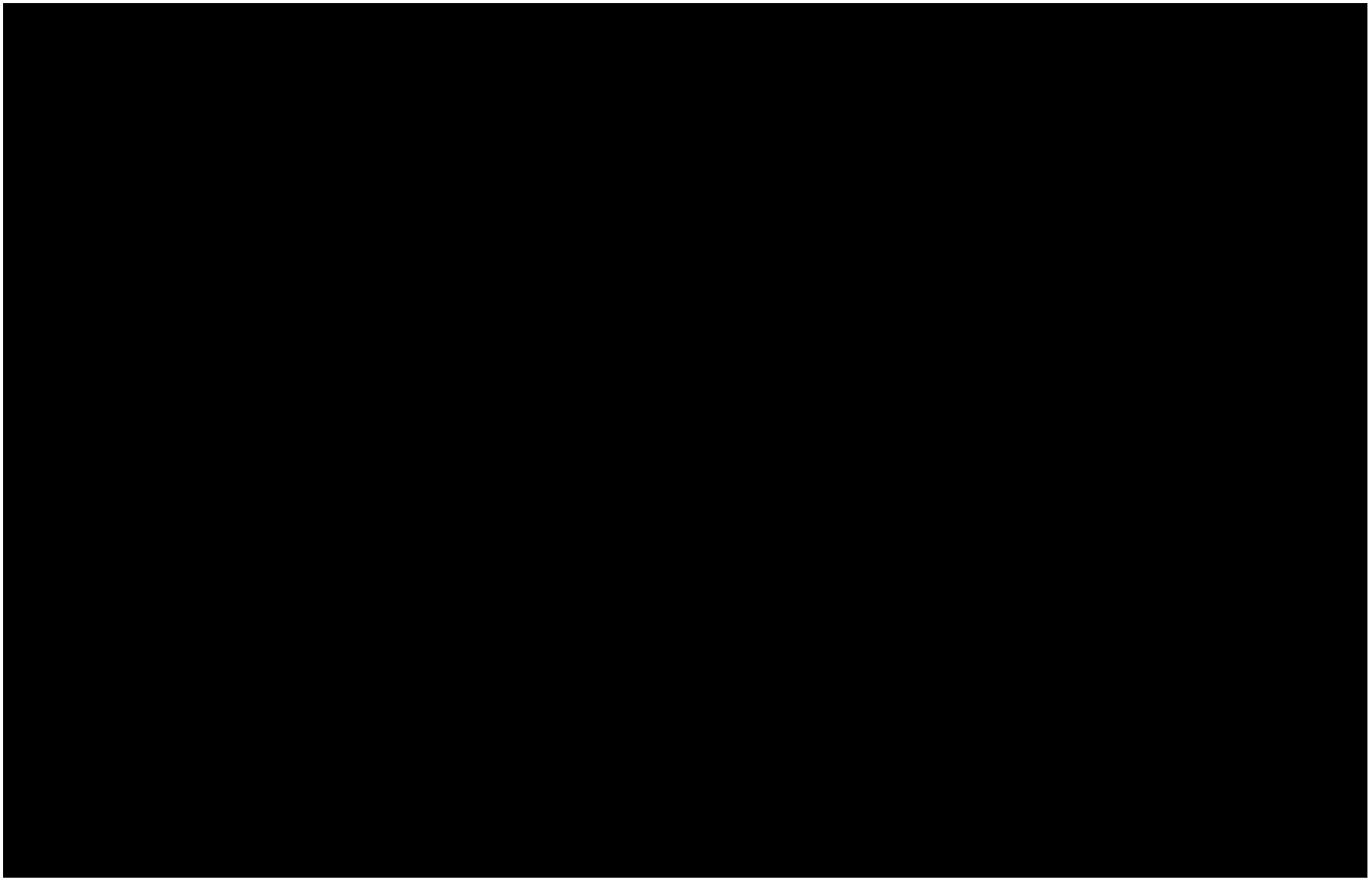
Trial Duration:

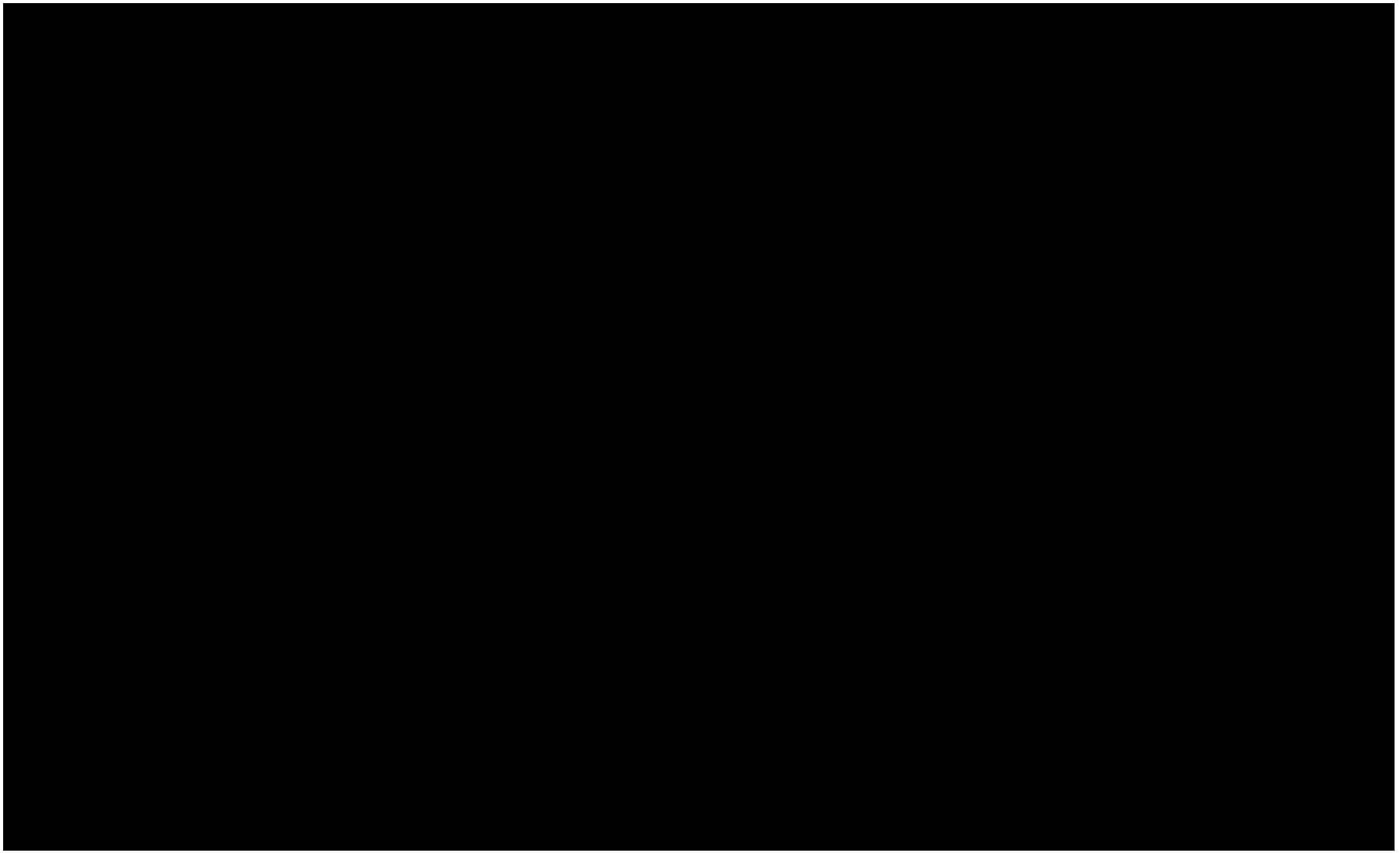
Each subject in this trial is expected to participate in the following periods of the trial:

- Screening period (1 week)
- [redacted]
- Treatment period (double-blind, 12 weeks)
- Follow-up period (4 weeks)

Overall, the trial duration from signing of the first informed consent form (ICF) to the end date of the follow-up period of the final subject assessment is expected to be approximately 15 months.







1.3.1 Informed Consent

Prior to all screening tests, written informed consent will be obtained from subjects himself/herself. After informed consent is obtained, each subject will be registered in the Interactive Web Response System (IWRS), given a subject identification number, and recorded. Operation of the IWRS after the initial registration will be separately specified in the procedure as a system to manage the registration status of subjects and the IMP. The investigator or subinvestigator enters the subject identification number and the date of informed consent in the subject screening log. The subject identification number and the date of informed consent will be also recorded in the source document and the electronic case report form (eCRF).

For DNA storage and biomarker storage, written informed consent will be obtained from subjects himself/herself using a separate ICF, and the date of informed consent will be recorded in the source document and the eCRF. DNA and biomarker storage are optional and will not impact the subject's participation in the trial if the subject does not consent to DNA and/or biomarker storage.

1.3.2 Screening

After obtaining informed consent, the investigator or subinvestigator will perform the observation and examinations at Week −5 (Visit S1) specified in Table 1.3-1, record them in the source document and the eCRF with the visit date, and register the visit date in the IWRS. After judging the eligibility for participation in the trial, the investigator or subinvestigator will describe the eligibility for enrollment, date of enrollment, and reasons in case of non-enrollment in the subject screening log.

The investigator or subinvestigator will investigate the following information and record it in the source document and the eCRF.

- Demographics (collection date, birth date, sex, possibility of pregnancy, race, ethnicity, country)
- Medical history (within 1 year before informed consent, but this limitation is not applicable to those related to the inclusion and exclusion criteria)
- Complications (at informed consent)
- History of hypercholesterolemia (name of diagnosis, date of diagnosis, presence or absence of familial hypercholesterolemia, classification and details of classification according to the flowchart using Suita score in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017,[1] statin response [statin tolerance/statin intolerance], cause of statin intolerance and name/daily dose of statin, if statin intolerance)

- Prior medications for hypercholesterolemia received within 6 weeks prior to informed consent
- All prior medications and prior therapies received within 4 weeks prior to informed consent
- Result of eligibility assessment

[redacted]

1.3.5 Observation and Examinations During the Treatment Period

Subjects who are judged to be eligible for proceeding to the treatment period based on the assessment on Day 1 (Visit T1) [redacted]

[redacted] and receive the IMP (ETC-1002 60 mg/day, 120 mg/day, 180 mg/day, or placebo) for 12 weeks. After each subject proceeds to the treatment period, the investigator or subinvestigator performs the observation and examinations specified in Table 1.3-1 and records them in the source document and the eCRF with the visit date. The investigator or subinvestigator will register necessary items in the IWRS at each visit for each subject.

1.3.6 Observation and Examinations During the Follow-up Period

The investigator or subinvestigator will perform the observation and examinations specified in Table 1.3-1 at the visit 28 days (±7 days) after the last date of IMP administration to all the subjects who proceed to the treatment period, and record them in the source document and the eCRF with the visit date. The investigator or subinvestigator will register necessary items in the IWRS at the end of the follow-up period for each subject.

1.3.7 Withdrawal Examination

When the subject is withdrawn during [redacted] the treatment period, the investigator or subinvestigator will perform the withdrawal examination specified in Table 1.3-1 and record them in the source document and the eCRF with the visit date. The investigator or subinvestigator will register necessary items in the IWRS at the time of withdrawal for each subject.

2 Introduction

Hypercholesterolemia is one of key risk factors associated with the development and progression of arteriosclerosis, and several large-scale clinical trials have demonstrated the usefulness of drug therapy for primary and secondary prevention of coronary artery disease.[2,3,4,5,6] Drugs currently launched in Japan and overseas for the treatment of hypercholesterolemia include 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (various statins), small intestine cholesterol transporter inhibitors (ezetimibe), and human anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody formulations (evolocumab). Among these drugs, Japanese and overseas guidelines[1,7,8] place statins as the first-line drug. Statins have been used for the treatment of hypercholesterolemia and have become able to control low-density lipoprotein cholesterol (LDL-C) in many patients. However, in some patients with a history of coronary artery disease or patients with familial hypercholesterolemia who require strict control of LDL-C, treatment with statins alone is often not able to achieve

the lipid management goals of LDL-C based on risk assessment (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk] or <140 mg/dL [intermediate risk]) specified in Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017.[1] In such cases, combination therapy using drugs with mechanisms of action different from statins is performed. However, the fact that there are patients who have inadequate control of LDL-C by combination therapy of statins and other drugs remains an issue of drug therapy for patients with hypercholesterolemia. Statin intolerance, which requires dose reduction or interruption of statins due to myopathy or hepatic impairment caused by statin therapy, is observed in some patients. According to the Statin Intolerance Clinical Guide 2018,[9] statin intolerance is defined as "in the individual case treated with statins for the first time, in whom statin continuation becomes difficult due to an adverse event upon initial statin administration, and those adverse events were again observed by at least one another statin". The guideline recommends dose reduction or discontinuation of statins, switching to other statins, or administration of other drugs other than statins, depending on the severity of adverse events (AEs), if myopathy (subjective symptoms such as myalgia, twitching, stiffness, discomfort, or muscle weakness, laboratory abnormalities such as creatine kinase (CK) elevation, or rarely rhabdomyolysis), or hepatic impairment such as transaminase elevations occurs during statin therapy. Thus, there is a need for a therapeutic drug with a new mechanism of action for patients whose LDL-C cannot be adequately controlled by drug therapy mainly with statin alone or in combination with other drugs or patients whose LDL-C cannot be adequately controlled due to statin intolerance.

ETC-1002 (nonproprietary name: bempedoic acid) is a drug with a new mechanism of action that inhibits cholesterol and fatty acid synthetic pathways by acting on adenosine triphosphate citrate lyase (ACL), an enzyme degrading citric acid, in the cholesterol biosynthetic pathway in the liver. Esperion Therapeutics, Inc. has been developing the drug in countries other than Japan. In non-Japanese clinical trials in patients with hypercholesterolemia, administration of add-on ETC-1002 to patients who are not adequately controlled with their maximally tolerated statins resulted in a significant decrease in LDL-C levels compared with the placebo group. Treatment with ETC-1002 also significantly reduced LDL-C levels in patients with statin-intolerant hypercholesterolemia compared with placebo. No particular safety concern has been identified in the clinical trials conducted to date. Based on the results of non-Japanese clinical trials, ETC-1002 was approved for the treatment of hypercholesterolemia in the US in February 2020 and in Europe in April 2020.

Otsuka Pharmaceutical Co., Ltd. (hereinafter referred to as “Otsuka”) considers that ETC-1002 can be a new treatment option for Japanese patients with hypercholesterolemia in whom LDL-C values cannot be adequately controlled by existing statin-based therapy. Otsuka has obtained the development and marketing right in Japan from Esperion Therapeutics, Inc. and started development in Japan.

For further information on results from the nonclinical and clinical trials of ETC-1002, please refer to the ETC-1002 Investigator’s Brochure. The outline is described below.

2.1 Non-clinical Study Results

[redacted]

[redacted]

2.2 Clinical Trial Results

[redacted]

[redacted]

2.3 Trial Rationale

Statins are recommended as the first-line drug for the treatment of hypercholesterolemia in Japanese and overseas guidelines.[1,7,8] Although statins enabled control in accordance with the lipid management goals in many patients, some patients with a history of coronary artery disease or patients with familial hypercholesterolemia who require strict control of LDL-C have not often achieved the target LDL-C level by treatment with statins alone. Despite the concomitant use of statins and drugs with other mechanisms of action in such patients, the fact that there are patients who cannot achieve the lipid management goals remains an issue of drug therapy. In addition, some patients are intolerant to statins and dose reduction or interruption of statins is required due to myopathy or hepatic impairment caused by statins. The guidelines recommend dose reduction or discontinuation of statins, switching to other statins, or administration of other drugs other than statins depending on the severity of AEs. Thus, there is a need for

a therapeutic drug with a new mechanism of action for patients whose LDL-C cannot be adequately controlled by drug therapy mainly with statin alone or in combination with other drugs or patients whose LDL-C cannot be adequately controlled due to statin intolerance.

The efficacy of ETC-1002 has been verified in several phase 3 placebo-controlled, double-blind trials in patients with hypercholesterolemia conducted in non-Japanese countries (Trials 1002-040, 1002-046, 1002-047, and 1002-048), and it has been confirmed that there was no particular safety concern. [redacted] It has also been confirmed that there is no safety problem and that ETC-1002 is well tolerated when administered to healthy Japanese adults. Therefore, there is a high possibility that treatment with ETC-1002 is also effective in Japanese patients with hypercholesterolemia.

This trial has been planned to confirm the efficacy and dose-response of ETC-1002 and determine the dose of ETC-1002 to be used in the phase 3 trial, as well as to assess the safety in Japanese patients with hypercholesterolemia who have had inadequate responses to statins and/or hypercholesterolemia drugs other than statins. [redacted] The type, dose and regimen of concomitant hypercholesterolemia drugs will be unchanged from at least 4 weeks before Week −5 (Visit S1) (at least 6 weeks before, for fibrates and selective PPARα modulators). The duration of the treatment period to compare with the placebo group is 12 weeks as with the period to evaluate the primary endpoint in non-Japanese trials.

The primary endpoint is the percent change from baseline in LDL-C to Week 12, as in the non-Japanese trials. A total of 4 treatment groups, ETC-1002 60-mg/day group, 120-mg/day group, 180-mg/day group, and placebo group, are set to investigate the efficacy and dose-response of ETC-1002.

[redacted]

Based on the above, it is judged to be scientifically and ethically appropriate to investigate the efficacy and safety of ETC-1002 by the combination of hypercholesterolemia drugs with ETC-1002 or placebo once daily for 12 weeks in Japanese patients with hypercholesterolemia.

2.4 Background

For patients in whom the onset risk of the cardiovascular event is high and who require strict control of LDL-C but cannot achieve the management goal with monotherapy of statins, the first-line drug for hypercholesterolemia, combination therapy of statins and drugs with other mechanism of action has been performed. In addition, in patients who have to reduce the dose of statins or interrupt statins due to statin intolerance, there are many cases in which LDL-C cannot be adequately controlled by combination therapy of the reduced statins and drugs of other mechanism of action, or by treatment with drugs other than statins. Therefore, a drug with a new mechanism of action is required for patients who cannot adequately control LDL-C by the existing hypercholesterolemia drugs, primarily statins.

ETC-1002 is a compound with a new mechanism of action different from that of existing hypercholesterolemia drugs and can become a new therapeutic option for patients who have inadequate control of LDL-C with these existing hypercholesterolemia drugs. On the basis of the results of non-Japanese clinical trials in patients with hypercholesterolemia, the efficacy of ETC-1002 at 180 mg/day was confirmed in combination of statins and/or hypercholesterolemia drugs other than statins. As no particular safety concerns have been identified, ETC-1002 was approved in the US in February, 2020 and in Europe in April, 2020. Based on the above, ETC-1002 is considered to be a promising therapeutic drug for Japanese patients with hypercholesterolemia and therefore this clinical trial is planned.

2.5 Known and Potential Risks and Benefits

[redacted]

In the non-Japanese clinical trials of ETC-1002, efficacy was confirmed in patients with statin tolerance or statin intolerance, and there were no AEs with significantly different incidence from those in the placebo group in terms of safety. [redacted]

ETC-1002 can be a useful treatment for patients with hypercholesterolemia who need to continue long-term therapy with hypercholesterolemia drugs.

Once the Investigator's Brochure is revised, the revised version will be provided to the trial sites. The trial sites should refer to the most current version provided as needed.

3 Objectives and Endpoints

The objectives and endpoints of this trial are shown in Table 3-1.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary Objectives: • To assess the LDL-C-lowering efficacy of ETC-1002 at 60 mg, 120 mg, and 180 mg versus placebo when administered for 12 weeks in combination with ongoing stable statin therapy and/or other lipid-modifying therapy in patients with hypercholesterolemia who have inadequate control of LDL-C • To characterize the dose-response of ETC-1002 and investigate the appropriate dosage for a phase 3 trial	Primary Endpoint • Percent change in LDL-C from baseline to Week 12
Secondary Objectives: • To assess the effect of ETC-1002 on HDL-C, non-HDL-C, TC, TG, apo B, hsCRP and HbA1c • To assess the proportion of subjects achieving the lipid management goals of LDL-C by treatment with ETC-1002. • To assess the pharmacokinetic plasma trough and near-peak concentrations of ETC-1002 and its active metabolite (ESP15228) • To characterize the safety and tolerability of ETC-1002 versus placebo in patients with hypercholesterolemia when administered in combination with ongoing stable statin therapy and/or other lipid-modifying therapy	Secondary Endpoints • Percent change in HDL-C, non-HDL-C, TC, TG, apo B, hsCRP and HbA1c from baseline to Week 12 • Proportion of subjects whose LDL-C value achieve the lipid management goals based on risk assessment (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk], or <140 mg/dL [intermediate risk]) and the proportion of subjects whose LDL-C value achieve <70 mg/dL at Week 12 Other Assessments • Time course of LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c at each time point during the treatment period Pharmacokinetic Assessments • Plasma concentrations of ETC-1002 and its active metabolite, ESP15228 Safety Assessments

	Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), body weight, and 12-lead electrocardiogram (ECG)

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

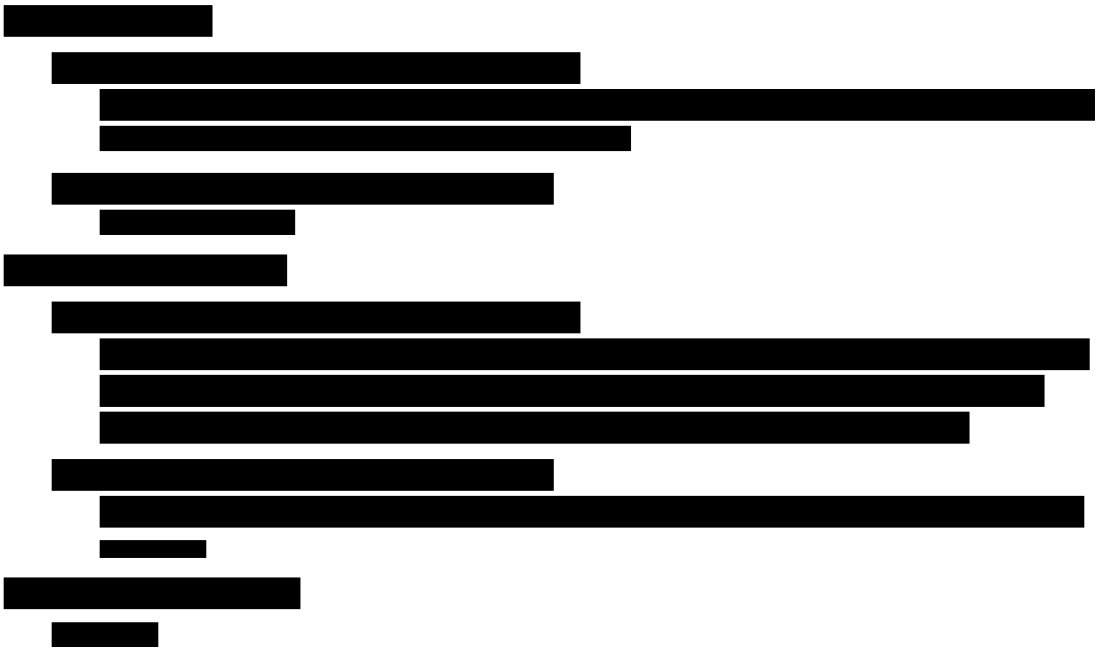
4.1 Type/Design of Trial

This is a placebo-controlled, randomized, multi-center, double-blind, parallel-group trial to assess the efficacy and safety of ETC-1002 in patients with hypercholesterolemia who are being treated with hypercholesterolemia drugs but have inadequate control and cannot achieve the lipid management goals. The trial population will include patients with statin tolerance who do not sufficiently respond to statins and cannot achieve the lipid management goals despite being treated with statins, and patients with statin intolerance who have experienced safety problems at the time of starting or increasing the dose of statins, have been successfully resolved after stopping or reducing the dose of statins, and cannot achieve the lipid management goals in spite of taking statins at (or below) the lowest approved daily dose and/or hypercholesterolemia drugs other than statins.

A schematic of the trial design is presented in Figure 1.2-1. This trial consists of the screening period, [redacted] the treatment period, and the follow-up period.

Subjects determined to be eligible in the screening period will proceed to [redacted] the treatment without changing the type and the dose and regimen of hypercholesterolemia drugs that have been taken from before informed consent, and receive placebo tablets in a single-blind manner. [redacted] Subjects who do not have safety problems and muscle-related AEs [redacted] and who do not fall under the exclusion criteria as judged by the investigator or subinvestigator will be assigned either to the ETC-1002 60-mg/day, 120-mg/day, 180-mg/day, or placebo group and proceed to the treatment period. Statin response (statin tolerance/statin intolerance) is set as a randomization stratification factor so that subjects with statin intolerance will be equally allocated to each treatment group.

During the treatment period, subjects will continue to take the hypercholesterolemia drugs that have been taken from before informed consent and receive either placebo or ETC-1002 (60 mg/day, 120 mg/day, or 180 mg/day) for 12 weeks. [redacted]



4.1.2 Treatment Period

1) Medications
   - Mandatory concomitant medications:
     Hypercholesterolemia drugs (statins and/or drugs other than statins) that have been taken from before informed consent
   - Investigational medicinal products:
     – ETC-1002 60 mg tablets
     – Placebo tablets
2) Dose and regimen
   - Mandatory concomitant medications:
     Hypercholesterolemia drugs [redacted] will be continued without changing the type and the dose and regimen during the treatment period.
   - Investigational medicinal products:
     – 180-mg/day group: Three ETC-1002 60-mg tablets will be administered orally once daily.

- 120-mg/day group: Two ETC-1002 60-mg tablets and one placebo tablet will be administered orally once daily.
- 60-mg/day group: One ETC-1002 60-mg tablet and two placebo tablets will be administered orally once daily.
- Placebo group: Three placebo tablets will be administered orally once daily.

3) Treatment duration
   12 weeks

4.2 Scientific Rationale for Trial Design

[redacted] Patients with statin intolerance are known to experience muscle-related AEs such as muscle pain, or AEs associated with hepatic impairment when treated with statins.[9,10] Some patients have been reported to experience a reverse placebo effect (nocebo effect) to complain of events such as muscle symptoms, even with non-statin drugs such as placebo.[11,12] [redacted]

In the treatment period, the hypercholesterolemia drugs will be continued without changing the type and the dose and regimen from at least 4 weeks before Week −5 (Visit S1) (at least 6 weeks before, for fibrates and selective PPARα modulators), and ETC-1002 or placebo will be added in a double-blind manner. Since the primary objective of this trial is to confirm the efficacy of ETC-1002 and determine the dose used in the phase 3 trial, placebo is considered to be an appropriate comparator to be administered in the treatment period.

As for the treatment duration, the percent change in LDL-C from baseline to Week 12 was selected as the primary endpoint in all 4 non-Japanese phase 3 trials, and LDL-C decreased from baseline at Week 2 to 4 after start of administration. Therefore, a period of 12 weeks is set as the duration necessary to evaluate the efficacy of ETC-1002. The primary endpoint is set as the percent change in LDL-C from baseline to Week 12, as in the non-Japanese trials.

4.3 Rationale for Dosage Regimen

[redacted]

4.4 End of Trial Definition

The end of trial date is defined as the following date from the eCRF page for the last subject completing or withdrawing from the trial: the "completion of trial date or withdrawal date" from the page of trial completion, or the "last date of visit/contact" or the "date of final contact attempt" from the page of the post-treatment observation or follow-up.

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject was administered all doses of the IMP. For purposes of this trial, subjects who compete the Week 12 (Visit T6) assessment will be defined as trial completers.

5 Trial Population

This trial will be conducted in Japanese patients with hypercholesterolemia who are aged 20 years or older and younger than 75 years at the time of informed consent and who are being treated with hypercholesterolemia drugs but have inadequate control and cannot achieve the lipid management goals. [redacted] The target number of subjects is 176 in total (44 in the ETC-1002 60-mg/day group, 44 in the 120-mg/day group, 44 in the 180-mg/day group, and 44 in the placebo group) as randomized subjects. In addition to patients with statin tolerance, patients with statin intolerance will be enrolled at ≥20% of the total. Statin response (statin tolerance/statin intolerance) is set as a randomization stratification factor so that subjects with statin intolerance will be equally allocated to each treatment group.

5.1 Subject Selection and Numbering

[redacted]

[redacted]

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the subinvestigator.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria when assessed:

1) Patients from whom written informed consent is obtained prior to start of the trial
2) Patients, either male or female, age 20 years or older and younger than 75 years at the time of informed consent
3) Patients who meet the following criteria for statin tolerance or statin intolerance
   - Statin tolerance
     Patients with hypercholesterolemia who have been taking statins (atorvastatin, pitavastatin, rosuvastatin, pravastatin, simvastatin, or fluvastatin) and hypercholesterolemia drugs other than statins if necessary, at the same dose and regimen from at least 4 weeks prior to Week −5 (Visit S1) (at least 6 weeks, for fibrates and selective PPAR α modulators) to Week −5 (Visit S1) according to the approved regimen, but fail to achieve the lipid management goals of LDL-C based on risk assessment shown in the inclusion criteria 4) at both Week −5 (Visit S1) and Week −1 (Visit S3)
   - Statin intolerance
     Patients with hypercholesterolemia in whom safety problems occurred when administration of statins was started or increased in dose and were resolved after discontinuation or dose reduction of statin administration, and who have been taking statins at (or below) the lowest approved daily dose and/or who have been taking at least one hypercholesterolemia drug other than statins at the same dose and regimen from at least 4 weeks prior to Week −5 (Visit S1) (at least 6 weeks, for fibrates and selective PPAR α modulators) to Week −5 (Visit S1) according to the approved dosage regimen, but fail to achieve the lipid management goals of LDL-C based on risk assessment shown in the inclusion criteria 4) at both Week −5 (Visit S1) and Week −1 (Visit S3)
4) Patients considered to be at risk of developing cardiovascular events who meet any of the following conditions a), b), or c)
   a) Patients with either of the following medical histories or complications and in whom LDL-C at Week −5 (Visit S1) and Week-1 (Visit S3) is ≥100 mg/dL
      – History of coronary artery disease
      – Diagnosed with heterozygous familial hypercholesterolemia (HeFH)

b) Patients with any of the following medical histories or complications and in whom LDL-C at Week −5 (Visit S1) and Week-1 (Visit S3) is ≥120 mg/dL
   - Diagnosed with peripheral arterial disease
   - History of non-cardiogenic cerebral infarction
   - Diagnosed with chronic kidney disease and does not fall under the exclusion criteria 12)
   - Diagnosed with type 2 diabetes mellitus more than 3 months prior to Week −5 (Visit S1) and does not fall under the exclusion criteria 7)

c) Patients who do not meet inclusion criteria a) or b), but whose total score in the coronary artery disease risk prediction model using the Suita score specified by the Japan Atherosclerosis Society is ≥41 and ≤55 points (intermediate risk) and in whom each LDL-C level at Week −5 (Visit S1) and Week −1 (Visit S3) is ≥140 mg/dL, or whose total score is ≥56 (high risk) and in whom each LDL-C level at Week −5 (Visit S1) and Week −1 (Visit S3) is ≥120 mg/dL

5) Patients with fasting TG level of <400 mg/dL at Week −5 (Visit S1)
6) Patients with body mass index (BMI) of ≥18 kg/m^2 and <35 kg/m^2 at Week −5 (Visit S1)

[Rationale for inclusion criteria]

1) This criterion is set from ethical considerations.
2) Since elderly patients generally have reduced physiological function and ETC-1002 is administered to Japanese patients with hypercholesterolemia for the first time, the trial is to be conducted in patients aged <75 years in consideration of safety. The lower limit of age is set at 20 years from ethical considerations.
3) to 4) These criteria are set to appropriately evaluate the efficacy.
5) This criterion is set in consideration of the difficulty in accurate calculation of LDL-C using the Friedewald formula and subject safety.
6) This is set to minimize the inter-individual variation in pharmacokinetics due to body size.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria when assessed:

1) Women who are pregnant or breastfeeding or who have a positive pregnancy test (urine) result at Week −5 (Visit S1) or Day 1 (Visit T1)
2) Sexually active male subjects or sexually active female subjects of childbearing potential who do not agree to practice 2 different approved methods of birth

control or to maintain complete abstinence (the methods of periodic abstinence and withdrawal are not appropriate for contraception) during the trial and for 30 days after final IMP administration. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, and condoms (all methods are approved or certified in Japan). A definition of childbearing potential can be found in Section 10.3.

3) Patients with homozygous familial hypercholesterolemia (HoFH)
4) Patients with a history or current symptoms of any of the following cardiovascular diseases within 3 months prior to Week −5 (Visit S1), or with any of the following AEs during the screening [redacted] period
   - Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, symptomatic carotid artery stenosis, symptomatic peripheral arterial disease, or decompensated heart failure
   - Abdominal aortic aneurysm
   - Unexplained syncope or long-QT syndrome, family history of long-QT syndrome, or risk factors for Torsade de Pointes, such as persistent hypokalemia or second- or third-degree atrioventricular block (except when controlled by medication, etc)
5) Patients with uncontrolled hypertension, defined as follows: sitting systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥100 mmHg after resting 5 minutes at Week −5 (Visit S1)
6) Patients with uncontrolled and serious hematologic or coagulation disorders or with Hgb of <10.0 g/dL at Week −5 (Visit S1)
7) Patients with type 1 diabetes or uncontrolled type 2 diabetes with HbA1c of ≥9% at Week −5 (Visit S1)
8) Patients with uncontrolled hypothyroidism with thyroid-stimulating hormone (TSH) of >1.5 × the upper limit of normal (ULN) at Week −5 (Visit S1)
9) Patients with liver disease or dysfunction, including:
   - Positive serology for hepatitis B surface antigen (HBsAg) or hepatitis C (HCV) antibodies at Week −5 (Visit S1)
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of ≥3 × ULN or total bilirubin of ≥2 × ULN at Week −5 (Visit S1)
10) Patients with a history or complication of chronic musculoskeletal symptoms that may be difficult to differentiate from myalgia (eg, fibromyalgia)
11) Patients with CK of >3 × ULN at Week −5 (Visit S1)
12) Patients with renal dysfunction or nephritic syndrome or a history or complication of nephritis and with estimated glomerular filtration rate (eGFR) of ≤30 mL/min/1.73m^2 at Week −5 (Visit S1)
13) Patients who have had gastrointestinal surgery that may affect drug absorption (eg, Lap-Band® or gastric bypass)

14) Patients who have undergone surgery, chemotherapy, or radiation for active malignancy (excluding properly treated nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ) within the past 5 years prior to Week −5 (Visit S1)
15) Patients with a history of drug, alcohol, or cocaine abuse within the past 2 years prior to Week −5 (Visit S1)
16) Patients who have had blood collection (eg, blood donation) in a cumulative amount exceeding 200 mL within 4 weeks, 400 mL within 12 weeks, or 1200 mL within 1 year prior to Week −5 (Visit S1)
17) Patients who have used any investigational drug not approved in Japan within either 4 weeks or 5 times the half-life of the drug, whichever is longer, prior to Week −5 (Visit S1)
18) Patients who used or received the following drugs (including food) or therapies within the specified period or who are expected to use or receive them by the end of tests at Week 12 (Visit T6)

1.	Initiation of administration or change in dose of a systemic corticosteroid (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
2.	Lomitapide (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
3.	PCSK9 inhibitors (from 4 weeks prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
4.	[redacted]
5.	Red yeast rice and food containing red yeast rice (from 2 weeks prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
6.	LDL apheresis (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])

19) Patients in whom the following drugs (therapies) are changed prior to Day 1 (Visit T1) or in whom initiation of the following drugs (therapies) is planned by the end of tests at Week 12 (Visit T6)
    - Hormone replacement: Within 6 weeks prior to Day 1 (Visit T1)
    - Thyroid replacement: Within 6 weeks prior to Day 1 (Visit T1)
    - Diabetes medications: Within 4 weeks prior to Day 1 (Visit T1)
    - Obesity medications: Within 3 months prior to Day 1 (Visit T1)
20) Patients [redacted] who cannot continue drug administration due to safety issues
21) [redacted]
22) Patients otherwise judged inappropriate for participating in the trial in the opinion of the investigator or subinvestigator

[Rationale for exclusion criteria]

1) to 2) These criteria are set in consideration of the safety because the safety of administration of ETC-1002 during pregnancy and breastfeeding has not been established.
3) to 9) These criteria are set in consideration of the safety.
10) to 11) These criteria are set to appropriately evaluate the safety of ETC-1002.
12) This criterion is set in consideration of the safety.
13) This criterion is set to avoid influence on pharmacokinetics.
14) This criterion is set to appropriately evaluate the safety of ETC-1002.
15) This criterion is set in consideration of the safety.
16) This criterion is set according to the Blood Sampling Criteria of New Blood Program Advisory Committee to ensure the safety of subjects.
17) to 19) These criteria are set to appropriately evaluate the efficacy and safety of ETC-1002.
20) to 21) These criteria are set to appropriately evaluate the safety of ETC-1002.
22) This criterion is set in consideration of the safety.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

To properly evaluate the efficacy and safety of ETC-1002, diet therapy receiving since before informed consent will not be changed during the trial period. For supplements and dietary supplements that may affect cholesterol levels including LDL-C, the investigator or subinvestigator will explain the subjects at each visit so that the intake status will not change from Week −4 (Visit S2) to the end of tests at Week 12 (Visit T6), and record the intake status in the source document.

5.3.2 Caffeine, Alcohol, and Tobacco

For alcohol and tobacco, the amount of alcohol consumed and the number of cigarettes smoked will be checked with the subject prior to participation in the trial and documented in the source document. The investigator or subinvestigator will instruct subjects not to significantly increase the amount of alcohol consumption or the number of cigarettes smoked during the trial period. Subjects will be monitored at each visit for any significant changes during the trial to record the results in the source document. No caffeine restrictions will be applied.

5.3.3 Activity

To properly evaluate the efficacy and safety of ETC-1002, exercise therapy for hypercholesterolemia since before informed consent will not be changed during the trial period. In addition, the investigator or subinvestigator will instruct subjects at each visit to refrain from strenuous exercise during the trial period to avoid influence on laboratory values such as CK.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF)[redacted]. All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespectively of IMP administration.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in the eCRF:

- Date of informed consent
- Visit date (screening visit)
- Demographics (collection date, birth date, sex, race, ethnicity, country)
- History of hypercholesterolemia (name of diagnosis, date of diagnosis, presence or absence of familial hypercholesterolemia, classification and details of classification according to the flowchart using Suita score in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017,[1] statin response [statin tolerance/statin intolerance], cause of statin intolerance and name/daily dose of statin, if statin intolerance)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure
- Adverse Events

Subjects who sign ICF [redacted] (screen failure) will be allowed to rescreen. In the event that the subject is re-screened for trial participation, a new ICF must be signed.

6 Trial Treatments

6.1 Trial Treatments Administered

[redacted]

6.1.2 Treatment Period

Subjects who are randomized and proceed to the treatment period will continue to receive hypercholesterolemia drugs that have been taken from before informed consent without changing the type or the dose and regimen [redacted]. Subjects will also orally receive ETC-1002 60 mg/day, 120 mg/day, 180 mg/day, or placebo. The time of IMP administration should be same to the extent possible. The following information will be recorded in the eCRF: number of tablets taken per day, start and end dates of administration as for the IMP; and name of the drug, route of administration, dose and frequency, daily dose, start and end dates of administration as for hypercholesterolemia drugs. Subjects with less than 80% compliance with IMP between scheduled visits will be withdrawn from the trial. The IMP compliance rate will be calculated using the

following formula. For information regarding the dose regimen and treatment period for each treatment group of the trial, see Section 4.1.

$$\text{IMP compliance rate (\%)} = \frac{\text{Actual number of days of taking 3 tablets of the IMP}}{\text{Number of days from the previous visit to the day before the current visit}} \times 100$$

6.1.3 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the ETC-1002 Investigator's Brochure and the separate procedures.

6.2.1 Packaging and Labeling

Investigational medicinal product will be provided by the sponsor or designated agent to the IMP storage manager. The IMP will be supplied as the blister cards. Each blister card used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP storage manager.

The IMP will be stored according to the conditions indicated on the IMP label.

The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The IMP storage manager must maintain an inventory record of IMP (including investigational, or placebo) received, dispensed, administered, and returned. The IMP storage manager must not provide IMP to any subject not participating in this protocol.

6.2.4 Returns and Destruction

Upon completion or termination of the trial, all unused IMP and partially used IMP must be returned to the sponsor or a designated agent. All IMP returned to the sponsor must be accompanied by inventory record, etc. and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return of used IMP containers, unused IMP, and partially-used IMP.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, subject, medical representative, regulatory agency, Partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Medical Device or Medicinal Product or a falsified, tampered, or diverted product after it is released for distribution to a clinical trial. Examples include, but are not limited to:

- Failure/malfunction of IMPs to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Product defects (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator or designee must record each PQC identified through any means from the receipt of the IMP from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator, subinvestigator or designee must notify the sponsor (or sponsor's designee) by e-mail [redacted] of the information specified in Section 6.2.5.2 immediately after becoming aware of the PQC.

Identification of a PQC by the subject should be reported to the site investigator or subinvestigator, who should then follow the reporting procedure above.

6.2.5.2 Information Required for Reporting Product Quality Complaints

- Description of complaint

- Reporter identification (eg, subject, investigator, subinvestigator, trial site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, IMP number)
- Clinical protocol reference (protocol number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return

6.2.5.3 Return Process in Case of Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide return instructions, when applicable.

It must be documented in the site accountability record that the complaint sample has been forwarded to the sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

6.3 Measures to Minimize/Avoid Bias

In this trial [redacted] the treatment period will be conducted in a double-blind manner. [redacted]

In the treatment period, stratified randomization by statin response (statin tolerance /statin intolerance) will be performed to minimize influence on evaluation. Subjects will be randomized to each group in a ratio of 1:1:1:1. Details of randomization will be provided in a separate procedure. Neither the subject nor the investigator/subinvestigator will be informed of the IMP randomization code. The persons involved in the trial of the sponsor, including the contract research organization (CRO) (except the bioanalytical laboratory), cannot know the IMP randomization code during the trial period.

Indistinguishability of the IMP will be confirmed by the IMP packaging company and the sponsor before the start of the trial.

The randomization table will be stored securely until unblinding after all eCRFs and database lock.

The emergency code will be managed by the Interactive Web Response System (IWRS) until the end of the trial. If a medical emergency occurs to a subject and it is determined that knowledge of the IMP randomization code is important for the treatment of the subject, emergency code will be obtained according to Section 8.8.7.

Plasma drug concentrations will not be disclosed until unblinding at the end of the trial. These measurements will be performed at a specific bioanalytical laboratory and will not be performed at the clinical laboratory of the trial site.

Maintenance of blinding for efficacy endpoints will be found in Section 8.1.

6.4 Subject Compliance

To ensure compliance with the protocol, the investigator or subinvestigator will instruct subjects to:

- Visit the trial site in a fasting state (fasting for at least 10 hours) without taking the IMP on the days specified in the protocol.
- Not take any prohibited concomitant medications or therapies during the period from informed consent to the completion of the tests at Week 12 (Visit T6) or to the completion of the withdrawal examination.
- Comply with the dosage regimen, duration, and frequency of administration of the IMP and mandatory concomitant medications for hypercholesterolemia. A subject will be withdrawn from the trial if the compliance rate [redacted] is less than 80% between the scheduled visits in the treatment period.
- Use appropriate contraceptive methods.
- Note the lifestyle considerations (see Section 5.3).

6.5 Concomitant Medications or Therapies

The investigator or subinvestigator will record hypercholesterolemia drugs from 6 weeks before the day of informed consent to Week 12 (Visit T6) or at withdrawal, and all drugs other than those for hypercholesterolemia (including Chinese herbal medicines that affect cholesterol levels such as LDL-C) and therapies from 4 weeks before the day of informed consent to Week 12 (Visit T6) or at withdrawal in the eCRF. The investigator or subinvestigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the final observation day for that individual subject in the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in the eCRF: therapy, indication, start date and end date.

6.5.1 Prohibited Medications

The use or intake of medications, food, and preference products listed in Table 6.5.1-1 is prohibited during the applicable period. The subject will be withdrawn from the trial if any of these medications, food, and preference products are used or taken.

Table 6.5.1-1 List of Prohibited Medications, Food, and Preference Products

1.	Initiation of administration or change in dose of a systemic corticosteroid (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
2.	Lomitapide (from 3 months prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
3.	PCSK9 inhibitors (from 4 weeks prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
4.	[redacted]
5.	Red yeast rice and food containing red yeast rice (from 2 weeks prior to Week −5 [Visit S1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])

6.5.2 Prohibited Therapies

LDL apheresis is prohibited from 3 months prior to Week −5 (Visit S1) to the end of tests at Week 12 (Visit T6) (or to the completion of the withdrawal examination, if applicable). If performed, the subject will be withdrawn from the trial.

6.5.3 Permitted Medications or Therapies

Hypercholesterolemia drugs (excluding PCSK9 inhibitors) used from before informed consent will be continued without changing the type and the dose and regimen until the end of tests at Week 12 (Visit T6) (or to the completion of the withdrawal examination, if applicable). If any medication or therapy shown in Table 6.5.3-1 has been taken or used from before informed consent, the type and the dose and regimen of the concomitant medications or the details of the concomitant therapy should not be changed during the applicable period. These medications or therapies cannot be newly started during the applicable period.

Table 6.5.3-1	List of Medications or Therapies Permitted Before and During the Trial
1.	Hormone replacement (from 6 weeks before Day 1 [Visit T1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
2.	Thyroid replacement (from 6 weeks before Day 1 [Visit T1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
3.	Diabetes medications (from 4 weeks before Day 1 [Visit T1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
4.	Obesity medications (from 3 months before Day 1 [Visit T1] to the end of tests at Week 12 [Visit T6] [or to the completion of the withdrawal examination, if applicable])
5.	Diet therapy (during the trial)
6.	Exercise therapy (during the trial)

6.5.4 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

7 Withdrawal Criteria and Procedures

7.1 Entire Trial or Treatment Discontinuation

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to the head of the trial site and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site Discontinuation

Individual trial site participation may be discontinued by the sponsor, investigator, or Institutional Review Board (IRB) if judged necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and the Good Clinical Practice (GCP). The head of the trial site will notify the sponsor promptly if the trial is terminated by the investigator or IRB at the site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

Not applicable.

7.3.2 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator or subinvestigator. However, each investigator or subinvestigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 7.3.5.

When the investigator or subinvestigator considers the trial discontinuation necessary during [redacted] the treatment period, the withdrawal examination specified in Table 1.3-1 will be performed to the extent possible. In case of the trial discontinuation of subjects who proceed to the treatment period, the same tests as at Week 16 (Visit FU) will be performed as the tests in the follow-up period.

7.3.3 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for the reasons listed below: Only one reason for treatment discontinuation (primary reason) will be recorded in the source document and eCRF with the date of discontinuation and registered in the IWRS.

- Adverse event
  - Death
  - Worsening of underlying disease
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator or subinvestigator (eg, a safety concern that is related to IMP)
    - Serious adverse event
    - Other potentially IMP-related safety concerns or AEs
- Failure to meet randomization criteria
  - Assessed as ineligible based on the eligibility assessment at Week −1 (Visit S3) and Day 1 (Visit T1)

- Non-compliance with IMP (subjects with an IMP compliance rate of <80% between scheduled visits during the treatment period will be withdrawn from the trial. See Section 6.1.2 for calculation of the IMP compliance rate.)
- Protocol deviations
  - Randomized by mistake
  - Revealed to have not met the inclusion criteria or fall under the exclusion criteria
  - Use of prohibited medications (including food and preference products) or prohibited therapies
  - Changes in the type and the dose and regimen of hypercholesterolemia drugs concomitantly used with the IMP (except for worsening of the underlying disease)
- Lost to follow-up
- Pregnancy (see Section 10.3)
- Site terminated by sponsor
- Trial terminated by sponsor
- Withdrawal by subject's request (including withdrawal of consent by subject)
- Judgment by the investigator
- Other

If the subject discontinues IMP due to an AE, the investigator/subinvestigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.2 must be followed.

7.3.4 Withdrawal of Consent

Each subject has the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects can withdraw consent for use of data which has not previously been anonymously transferred into trial data sets collected as part of the trial and can only withdraw consent for future participation. The investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator or subinvestigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).

- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, though this is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator or subinvestigator should follow the procedures outlined in Section 7.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

Details on the withdrawal of consent from the optional storage of DNA and biomarker samples are provided in the ICF for the storage of DNA and biomarker samples.

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators or subinvestigators will be instructed to meet and discuss (without undue coercion) with the subject their options of continuing in the trial, preferably on therapy. The investigator or subinvestigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the tests on Visit 12 (Visit T6), who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as “lost to follow-up”. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a “lost to follow-up” status.

If the subject was classified as “lost to follow-up”, “Were you able to contact the subject?”, “presence/absence of AEs”, “Date of contact/Date of final contact attempt” and “Contact method” will be recorded in eCRF.

8 Trial Procedures

The schedule of tests and assessments to be conducted during the trial are summarized in Table 1.3-1. The investigator or subinvestigator will perform observation, examinations and assessments according to the schedule. The clinical trial associates are allowed to perform the tests under the supervision of the investigator, such as investigation of subject demographics and laboratory tests.

8.1 Efficacy Assessments

To evaluate the efficacy of ETC-1002, blood samples will be collected for the following fasting lipid assessments of 1) to 5) and assessments of 6) to 8).

The investigator or subinvestigator will instruct subjects to visit the trial site according to the schedule specified in Table 1.3-1 under fasting conditions and collect blood samples. The investigator or subinvestigator will record the date and time of blood sampling and the fasting state at the time of blood sampling in the source document and the eCRF. The test results will be directly reported to the sponsor by the central laboratory selected by

the sponsor in electronic files. Therefore, it is not necessary to record the results in the source document and eCRF. The fasting state is defined as a state in which a subject has fasted (including abstaining from sugar-containing beverages such as juice) for 10 hours or more from the night before. If a subject cannot visit the trial site in a fasting state, the subject should visit the trial site again in a fasting state for blood sampling within the visit window for the same evaluation time point. If the subject cannot visit in the fasting state within the visit window for the same evaluation time point, this case will be recorded as a protocol deviation and the blood sample will be submitted as a sample in a fed state to the central laboratory. Each subject will visit the trial site without taking the IMP on the visit day.

Samples will be sent to the central laboratory, the results of which will be used for analysis. LDL-C values will be calculated using the Friedewald formula (TC−HDL-C−TG/5) and measured using the LDL-C direct method. Proper sample collection, handling, and shipping procedures will be provided to the trial sites in a separate manual prior to the start of the trial.

To maintain the blind of the trial, the results of the assessments 1) to 7) will not be reported to the trial site and the sponsor from the start of IMP administration on Day 1 (Visit T1) to Week 12 (Visit T6) (or to the completion of the withdrawal examination, if applicable). The test results will be stored strictly by the central laboratory, submitted to the trial site after unblinding, and provided to the sponsor in electronic files. In addition, measurement at the laboratory of trial sites is not allowed from the start of IMP administration on Day 1 (Visit T1) to Week 12 (Visit T6) (or to the completion of the withdrawal examination, if applicable).

1) LDL-C
2) HDL-C
3) non-HDL-C
4) TC
5) TG
6) apo B
7) hsCRP
8) HbA1c

8.2 Pharmacokinetic Assessments

The investigator or subinvestigator will instruct subjects to visit the trial site according to the schedule specified in Table 1.3-1 without taking the IMP and blood sampling will be performed before IMP administration. On Day 1 (Visit T1) and Week 4 (Visit T3),

subjects will take the IMP at the trial site and blood sampling will be performed 2 to 4 hours after IMP administration in addition to pre-dose blood sampling.

8.2.1 Pharmacokinetic Plasma Samples

Blood samples (3 mL) will be collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA) and processed into plasma to determine the concentrations of ETC-1002 and its active metabolite ESP15228. Additional metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of analytical methods, if needed.

The actual date and time of the PK sample collection and the date and time of IMP administration immediately before the sample collection will be recorded in the eCRF. The results of measurement will be reported directly from the bioanalytical laboratory to the sponsor, and therefore, recording in the eCRF is not required.

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C or −20°C, unless otherwise instructed in the Operations.

All plasma samples will be shipped to the bioanalytical laboratory. Additional information will be provided in the manuals.

The bioanalytical laboratory will measure drug concentrations only in the samples of the ETC-1002 group after keeping a record of the use of the allocation table. The contents of the allocation table will not be disclosed to any persons other than those who are considered necessary for the duties by the bioanalytical study director and strictly store it. The bioanalytical laboratory will retain the results strictly and submit the electronic file to the sponsor after unblinding.

[redacted]

[redacted]

8.3 Pharmacodynamic Assessments

Pharmacodynamic assessments other than those described for efficacy assessments are not planned.

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Biomarker assessments other than those described for efficacy and pharmacodynamic assessments are not planned.

[redacted]

[redacted]

[redacted]

[redacted]

8.7 Safety Assessments

If a “new abnormality” or “exacerbation” is observed in the following observation/examination items after the start of the IMP administration which are judged to be clinically significant by the investigator or subinvestigator as compared to before administration, appropriate measures will be taken as necessary.

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the Schedules of Assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2. The total volume of blood to be collected during the trial will be documented in the ICF.

On the day of the tests shown in the Schedules of Assessments (Table 1.3-1), subjects will be asked to visit the trial site in a fasting state (at least 10 hours of fasting [including abstaining from sugar-containing beverages such as juice]) without taking the IMP, and blood and urine samples will be collected from each subject. If a subject cannot visit the trial site in a fasting state, the subject should visit the trial site again in a fasting state for blood sampling within the visit window for the same evaluation time point. If the subject cannot visit in the fasting state within the visit window for the same evaluation time point, this case will be recorded as a protocol deviation and the blood sample will be submitted as a sample in a fed state to the central laboratory. The date and time of blood sampling, date of urine sampling, and the fasting state at the time of blood sampling will be recorded in the source document and the eCRF. The sponsor will select a central laboratory for this trial. The test results measured by the central laboratory will be used to confirm the eligibility. Proper sample collection, handling, and shipping procedures will be provided to the trial sites in a separate manual prior to the start of the trial. The central laboratory will report the test results to the investigator or subinvestigator who confirms the results. The laboratory report will be officially documented by entering the date of confirmation and signing the report by the investigator or subinvestigator. The test results will be directly reported to the sponsor by the central laboratory in electronic files. Therefore, it is not necessary to record the results in the source document and the eCRF.

[redacted]

[redacted]

8.7.2 Physical Examination

Physical examinations will be performed at the time points described in the Schedules of Assessments (Table 1.3-1). The investigator or subinvestigator will perform physical examinations for the following test items by methods such as interview and record the results in the source document. For consistency of assessments, it is recommended that all physical examinations for individual subjects be performed by the same physician throughout the trial. At Week −5 (Visit S1) and Day 1 (Visit T1), the dates and results of the examinations will be recorded in the source document and the eCRF. At other time points, only the date of the examination will be recorded. If clinically significant physical findings, which are compared with Week −5 (Visit S1) during the screening [redacted] and compared with Day 1 (Visit T1) during the treatment and follow-up periods, are observed, those findings will be recorded as AEs.

Test items: HEENT (head, eyes, ears, nose, throat), chest, abdomen, genitourinary, extremities, nerves, skin/mucosae

8.7.3 Vital Signs

Vital signs will be collected at the time points described in the Schedules of Assessments (Table 1.3-1) after resting for at least 5 minutes and before blood sampling. Subjects should be monitored for potentially clinically significant vital signs values. Body temperature, systolic and diastolic blood pressure, and pulse rate will be measured in the sitting position after resting for at least 5 minutes according to the procedures specified by the trial site. The date, time, and results of body temperature, systolic and diastolic blood pressure, and pulse rate measurements will be recorded in the source document and the eCRF.

8.7.4 Electrocardiogram

Electrocardiograms will be performed at the time points described in the Schedules of Assessments (Table 1.3-1) after resting for at least 10 minutes and before blood sampling. Subjects should be monitored for potentially clinically significant ECG results.

The investigator or subinvestigator will record the 12-lead ECG using the 12-lead ECG monitor provided by the central ECG measurement facility and record the date and time of the measurement in the source document and the eCRF. The original 12-lead ECG tracing will be retained in the medical record or investigator file. The central ECG measurement facility will collect the 12-lead ECG data, and measure the heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval [QTcF = QT interval/(RR interval)$^{1/3}$] to be judged by physician in the central ECG measurement facility. The central ECG measurement facility will report the analysis results to the investigator or subinvestigator who confirms the results. The report on analysis results will be officially documented by entering the date of confirmation and signing by the investigator or subinvestigator. The investigator or subinvestigator will assess the results with reference to the “Report on Analysis Results” prepared by the central ECG measurement facility and record the results of normal/abnormal assessment and abnormal findings in the source document and the eCRF. The analysis results will be directly reported to the sponsor by the central ECG measurement facility in electronic files. Therefore, it is not necessary to record the results in the source document and the eCRF.

8.7.5 Suicidality Monitoring

Not applicable.

8.7.6 Other Safety Variables

8.7.6.1 Height/body Weight

Body weight and height will be measured at the time points described in the Schedules of Assessments (Table 1.3-1), and the dates and results of measurements will be recorded in the source document and the eCRF (body weight in units of 0.1 kg and height in units of 0.1 cm). Body weight will be measured using a calibrated and reliable scale. The same scale should be used for the same subject as much as possible, and the measurement will be done using the standard method (without shoes and with normal clothing). Height will be measured only at Week −5 (Visit S1). Body mass index {BMI = body weight [kg]/(height [m]) ^{2}} will be calculated using the body weight measured at Week −5 (Visit S1) to confirm that the subject meets the inclusion criteria.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. In this trial, any untoward medical occurrence in a subject not receiving the IMP will be included. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of IMP treatment during the treatment period. In more detail, TEAEs are defined as all AEs which newly started after the start of IMP treatment during the treatment period; or if the AE was continuous at the start of the treatment period and was worsening.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator or subinvestigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.

- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 8.8.6).
- Pregnancies are also defined as immediately reportable events (IREs). Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the subject or the partner of the subject. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a female subject and there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator/subinvestigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator/subinvestigator's dated signature on the laboratory report. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. However, the central laboratory should not report the results of any repeated or additional tests for fasting lipid assessments, apo B, and hsCRP between Day 1 (Visit T1) and Week 12 (Visit T6) to the trial site and the sponsor to maintain the blind. As for LDL-C and TG, an alert email will be sent from the central laboratory to the investigator, subinvestigator, or their staff if an abnormality exceeding a certain reference value is

observed (details will be specified in a separate procedure). If this laboratory test value is considered medically relevant (ie, clinically significant) by the investigator or subinvestigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory test value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale below:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal relationship between the IMP and the AE.

8.8.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRF provided by the sponsor. Adverse event collection will begin after a subject signs the ICF and will continue until the final observation day. All AEs must be recorded in the eCRF after subject informed consent has been obtained, including screening failures due to AEs, irrespective of IMP administration. In this trial, AEs during the screening [redacted] will be assessed compared to Week −5 (Visit S1), and those during the treatment and follow-up periods will be assessed compared to Day 1 (Visit T1).

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition. A reported AE that undergoes worsening in severity or seriousness should be reported as a new AE in the eCRF. However, if worsening of the

condition is observed on Day 1 (Visit 1) or later, the AE should be reported as a new AE in the eCRF without limiting to worsening in severity or seriousness.

In addition, the sponsor must be notified immediately by e-mail in principle of any IREs according to the procedure outlined below, in Section 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

The adverse event, start date, end date, seriousness, severity, relationship to trial treatment (IMP causality), action taken with trial treatment, and outcome will be recorded on the source documents and in the eCRF.

8.8.3 Immediately Reportable Events

The investigator/subinvestigator or designee must immediately report (within 24 hours), using forms including an IRE form, after he/she or site personnel become aware of any IRE (SAE, AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy), by e-mail in principle to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the entry column for AEs in the eCRF). Patient confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.8.8.2.

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

Not applicable.

8.8.6 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥2 times the ULN, complete an IRE form or other documentation with all values listed and also report as an AE in the eCRF.

8.8.7 Procedure for Breaking the Blind

When the investigator or subinvestigator determines that emergency code breaking is necessary to ensure the subject's safety in the case of a SAE or other events, the investigator or subinvestigator can obtain the emergency code of the subject from the IWRS in accordance with the separately specified procedure.

The investigator or subinvestigator is encouraged to contact the sponsor/CRO medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator/subinvestigator, or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator or subinvestigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator or subinvestigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Global Pharmacovigilance Department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

8.8.8 Follow-up of Adverse Events

8.8.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 28 days after the last dose of IMP is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form or other documentation. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form or other documentation, according to the appropriate reporting procedures described in Section 8.8.3.

It is expected that the investigator or subinvestigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor. The investigator or subinvestigator will follow IREs until the events are:

- Resolved,
- Stabilized,
- The subject is lost to follow-up, or
- Has died.

Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition. The investigator or subinvestigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the duration of follow-up for subjects that become pregnant or for pregnant partners of male subjects.

8.8.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator or subinvestigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.9 Treatment of Overdose

For treatment of overdose, refer to the overdose section of the Investigator's Brochure. There is no specific treatment for overdose with ETC-1002. In the event of overdose, symptomatic and supportive therapies should be provided as appropriate.

8.10 Subject Assessment Recording

8.10.1 Completion of Subject Diary

The investigator or subinvestigator will instruct the subjects who are able to receive the IMP to enter the status of compliance with the IMP and hypercholesterolemia drugs, status of diet/exercise therapy and lifestyle (alcohol intake, smoking), presence or absence of subjective symptoms, and the date and time of the IMP administration immediately before the visit in the subject diary and bring it to the visit. The investigator or subinvestigator will record the status of compliance with the IMP and hypercholesterolemia drugs and the date and time of the IMP administration immediately before the visit for blood sampling for pharmacokinetic evaluation in the eCRF based on the contents entered in the subject diary, and also check the status of diet/exercise therapy and lifestyle (alcohol intake, smoking) and changes in subjective symptoms. If any subjective symptom is observed between visits, the investigator or subinvestigator will ask the subject about the symptom, date and time of onset, etc. to determine whether it is an AE.

8.11 Other Assessments

8.11.1 Pregnancy Test

A urine test will be performed for female subjects of childbearing potential according to the schedule specified in Table 1.3-1, and the date and result of the test will be recorded in the source document and the eCRF. A definition of childbearing potential can be found in Section 10.3. [redacted] any positive urine test will lead to re-test using serum and the date of blood sampling will be recorded in the source document and the eCRF. The serum test will be performed by the central laboratory selected by the sponsor. Proper sample collection, handling, and shipping procedures will be provided to the trial sites in a separate manual prior to the start of the trial. The central laboratory will report the test results to the investigator or subinvestigator who confirms the test results. The laboratory report will be officially documented by entering the date

of confirmation and signing the report by the investigator or subinvestigator. The results of the serum test will be directly reported to the sponsor by the central laboratory in electronic files. Therefore, it is not necessary to record the results in the source document and the eCRF.

8.11.2 Endocrine Test and Virus Test

Samples for the endocrine test (of TSH) and the virus test (of HBsAg and HCV antibodies) will be collected at Week −5 (Visit S1) to confirm eligibility of subjects regarding thyroid and liver function. The date and time of blood sampling will be recorded in the source document and the eCRF. Samples will be shipped to the central laboratory selected by the sponsor, and eligibility will be confirmed based on the test results measured by the central laboratory. Proper sample collection, handling, and shipping procedures will be provided to the trial sites in a separate manual prior to the start of the trial. The central laboratory will report the test results to the investigator or subinvestigator who confirms the results. The laboratory report will be officially documented by entering the date of confirmation and signing the report by the investigator or subinvestigator. The test results will be directly reported to the sponsor by the central laboratory in electronic files. Therefore, it is not necessary to record the results in the source document and the eCRF.

9 Statistical Considerations

The definitions of the analysis set and the statistical methods for the endpoints in the treatment period are described below. Details of the analysis plan for the treatment period [redacted] will be described in the statistical analysis plan (SAP).

9.1 Sample Size

Differences in the percent change in LDL-C from baseline to Week 12 in the ETC-1002 group versus the placebo group in non-Japanese phase 3 trials were −18.1% and −17.42% in trials in statin tolerant subjects and −21.41% and −28.45% in trials in statin intolerant subjects. Base on the results, the difference between the ETC-1002 group and the placebo group in the subjects with statin tolerance was assumed to be 17%, and the difference between the ETC-1002 group and the placebo group in the subjects with statin intolerance was assumed to be 25%. For the present trial it was assumed that the

percentage of statin intolerant subjects enrolled would be 20% and that the difference in the endpoint between the ETC-1002 group and the placebo group would be 19% in the overall trial population. Based on the results of the phase 3 trials, assuming a difference of 19% with standard deviation of 25% between the ETC-1002 groups and the placebo group in the percent change in LDL-C from baseline to Week 12, 38 subjects per group are required to achieve a power of 90% or higher in a two-tailed test with a 5% significance level. Assuming a withdrawal rate of 12.5%, the target number of subjects to be randomized was set at 44 per group.

9.2 Datasets for Analysis

The full analysis set (FAS) will include all subjects who receive at least one dose of IMP during the treatment period and for whom LDL-C values at baseline and at least one post-dose (up to 2 days after final IMP administration) are observed. The safety analysis set will include subjects who receive at least one dose of IMP during the treatment period. The pharmacokinetic analysis set will include subjects who receive ETC-1002 and for whom the measured result of plasma drug concentration after ETC-1002 administration is observed.

9.3 Handling of Missing Data for Primary Endpoint Analysis

In the primary analysis of the primary endpoint, when LDL-C at Week 12 is missing, the missing value will be imputed using the last value observed from after initial IMP administration until 2 days after final IMP administration (last observation carried forward: LOCF).

A mixed-effects model repeated measures analysis assuming missing at random will be performed using observed case data as sensitivity analyses.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

The following analyses will be performed on the FAS using the values measured by the central laboratory.

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the percent change in LDL-C from baseline to Week 12. Analysis of covariance will be performed using treatment group and the randomization stratification factor (statin tolerance/statin intolerance) as factors and baseline value of LDL-C as a covariate at a two-sided significance level of 0.05. Comparisons versus the placebo group will be performed starting from the highest ETC-1002 dose group. Baseline is defined as the mean of the LDL-C values for Day 1 (Visit T1) and Week −1 (Visits S3). If only one value is observed, the observed value will be used as the baseline.

The percent change in LDL-C from baseline to Week 12 will be tested using a contrast between low-dose saturation, medium-dose saturation, and linear to investigate the dose-response relationship among placebo, low-dose, medium-dose, and high-dose.

9.4.1.2 Key Secondary Efficacy Endpoint Analysis

Not applicable.

9.4.1.3 Secondary Efficacy Endpoint Analysis

Secondary efficacy endpoints are the percent change from baseline to Week 12 in each assessment (HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c), the proportion of subjects whose LDL-C value achieve the lipid management goals based on risk assessment at Week 12, and the proportion of subjects whose LDL-C value achieve <70 mg/dL at Week 12.

For the percent change from baseline to Week 12 in each assessment (HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c), analysis of covariance will be performed using treatment group and the randomization stratification factor (statin tolerance/statin intolerance) as factors and the baseline value of each assessment as a covariate. The least squares mean of each treatment group and differences in mean of least squares between each ETC-1002 group and the placebo group as well as their two-sided 95% confidence intervals will be calculated. The proportion of subjects whose LDL-C value achieve the lipid management goals based on risk assessment at Week 12, and the proportion of subjects whose LDL-C value achieve <70 mg/dL at Week 12 will be analyzed by the Cochran-Mantel-Haenszel test stratified by statin response (statin tolerance/statin intolerance). The proportion in each treatment group and its two-sided 95% interval, as well as the differences of proportion between each ETC-1002 group and the placebo group and their two-sided 95% confidence intervals will be calculated.

9.4.1.4 Control of Experiment-wise Type 1 Error

In the primary analysis of the primary endpoint, type 1 error will be controlled by the comparative test versus the placebo group using a closed testing procedure, starting from the highest dose group.

9.4.1.5 Other Efficacy Endpoint Analysis

Other efficacy endpoints include the actual value, change and percent change from baseline at each time point of each assessment (LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c). Their descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) by treatment group will be calculated at each time point.

9.4.1.6 Subgroup Analyses

Subgroup analyses will be performed for the percent change in LDL-C from baseline to Week 12, which is the primary endpoint. The analyses will be performed by the following items:

- Statin response (statin tolerance, statin intolerance)
- Sex (male, female)
- Familial hypercholesterolemia (yes, no)
- Diabetes mellitus (yes, no)
- Age (<65 years, ≥65 years)

9.4.2 Safety Analysis

Tabulation by treatment group (by dose and overall for ETC-1002) will be performed in the safety analysis set. Baseline is defined as the last data before the start of IMP administration in the treatment period.

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized: If a subject experiences the same event more than once, the more severe event will be used.

- Treatment-emergent AEs
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- [redacted]

TEAEs potentially causally related to the IMP will be summarized in the same manner.

9.4.2.2 Clinical Laboratory Data

Among parameters of the urinalysis in the laboratory tests, the qualitative urinalysis includes parameters other than pH and specific gravity.

For parameters other than qualitative urinalysis, descriptive statistics of the actual value and change from baseline will be calculated at each time point. For qualitative urinalysis parameters, shift tables at each time point from baseline will be prepared. For parameters other than qualitative urinalysis, measured values will be categorized using the reference range to “below the lower limit of reference range”, “within the reference range” and “above the upper limit of reference range”, and shift tables at each time point from baseline will be prepared.

The number and percentage of subjects meeting Criteria for Identifying Laboratory Values of Potential Clinical Relevance will be calculated (the criteria will be specified in the SAP).

9.4.2.3 Vital Signs Data

For vital signs (blood pressure, pulse rate, and body temperature), descriptive statistics of the actual value and change from baseline will be calculated at each time point.

The number and percentage of subjects meeting Criteria for Identifying Vital Signs of Potential Clinical Relevance will be calculated (the criteria will be specified in the SAP).

9.4.2.4 Electrocardiogram Data

For ECG parameters (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF), descriptive statistics of the actual value and change from baseline will be calculated at each time point.

The number and percentage of subjects with a QTcF of >450 msec, >480 msec, or >500 msec at any postdose time point will be calculated. In addition, the number and percentage of subjects who have a change in QTcF from baseline of >30 msec or >60 msec at any postdose time point will be calculated. The number and percentage of subjects meeting these criteria at baseline or each postdose time point will also be calculated.

For assessment of normality/abnormality, shift tables at baseline and each time point will be prepared.

The number and percentage of subjects meeting Criteria for Identifying ECG Measurements of Potential Clinical Relevance will be calculated (the criteria will be specified in the SAP).

9.4.2.5 Other Safety Data

9.4.2.5.1 Body weight

Descriptive statistics of the actual value and change from baseline will be calculated at each time point.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Frequency distributions or descriptive statistics of each item for demographic and other baseline characteristics will be calculated by treatment group (by dose and overall for ETC-1002) in each analysis set.

9.4.3.2 Pharmacokinetic Analysis

In the PK analysis set, descriptive statistics (number of subjects, mean, standard deviation, coefficient of variation, minimum, median, and maximum) will be calculated for the plasma concentrations of ETC-1002 and its active metabolite ESP15228 at each dose, visit, and post-dose time point. Population pharmacokinetic analysis of ETC-1002 will be performed separately.

9.4.3.3 Pharmacodynamic Analysis

No pharmacodynamic analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No pharmacokinetic/pharmacodynamic analysis is planned.

9.4.3.5 Pharmacogenomic Analysis

No pharmacogenomic analysis is planned.

9.4.3.6 Exploratory Endpoint Analysis

Not applicable.

9.5 Interim Analysis and Adaptive Design

Not applicable for interim analysis or adaptive design.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, applicable ICH (International Council for Harmonisation) GCP guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval by an IRB according to regional requirements, and the trial site will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the eCRF, IRE and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject.

Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the trial site.

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH GCP Guidelines, and local regulatory requirements.

Investigators or subinvestigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman’s terms to the subject by the investigator/subinvestigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB approved written ICF will be signed and dated by both the subject and

the person obtaining consent (investigator/subinvestigator or designee). The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator. Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the non-subject partner and fetus.

A separate and similar consent process will be followed for the optional blood samples for FBR. Consent must be obtained before the blood sample is collected. Sample storage for FBR is optional and will not affect the subject's participation in the trial if the subject does not consent to the FBR sample storage.

10.1.3 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject ID in the eCRF. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

10.1.4 Quality Control and Quality Assurance

The sponsor will perform quality management activities for this trial in accordance with the ICH GCP guidance. The details of quality management activities are described separately in the quality management plan.

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators/subinvestigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, site operations, delegation of authority and training, and a review of the eCRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

Regulatory authorities may inspect the trial site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator/subinvestigator or designee will contact the sponsor at the earliest possible time by telephone or via e-mail. The investigator/subinvestigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator/subinvestigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the trial sites and made available for direct inspection by authorized persons.

Investigators/trial sites will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

During each subject's visit to the site, an investigator/subinvestigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator/subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator/subinvestigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and IMP compliance;
- The signature (or initials) and date of the investigator/subinvestigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in the medical records and other source documents will be initialed and dated on the day the change is made by a trial site staff member authorized

to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or subinvestigator. If electronic data systems are used, a full audit trail of the change must be maintained.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is 21 CFR Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on eCRF, such as data received from central laboratories and central ECG measurement facilities, will be reconciled using key data fields by the sponsor or designee with the eCRF data to ensure consistency.

10.1.6.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site file is maintained in accordance with applicable ICH guidance and as required by applicable local regulations. The trial site will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

The trial site will retain all documents and records related to this trial for the longest of the following 3 periods. However, if the sponsor requires a longer storage period, the storage period and method will be discussed with the sponsor.

- A period of at least 2 years after the date on which approval to market the IMP is obtained; However, in the case that development is discontinued or a notification to inform that the trial results will not be attached to the approval application is received, a period of at least 3 years after the decision date of stopping development, or the receiving date of the notification informing that the trial results will not be attached to the approval application.
- A period of at least 3 years after date of trial discontinuation/completion; OR
- Date of decision to terminate storage of FBR samples.

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The trial site will be responsible for maintaining adequate and

accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities.

10.1.6.5 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial subjects who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial subjects consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Red blood cell count Hemoglobin Hematocrit Mean corpuscular hemoglobin concentration Mean corpuscular volume White blood cell (WBC) count WBC count with differential (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) Platelets Urinalysis (parameters other than pH and specific gravity will be included in the qualitative urinalysis) pH Protein Glucose Occult blood Bilirubin Urobilinogen Specific gravity Ketones	Serum Chemistry: Alkaline phosphatase ALT AST Total bilirubin Gamma glutamyl transferase Total protein Albumin Lactate dehydrogenase Blood urea nitrogen Creatinine Uric acid CK Serum electrolytes (sodium, potassium, chloride, calcium, bicarbonate) Glucose

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Females of nonchildbearing potential do not meet definition of FOCBP.

For males and FOCBP, or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) or remains abstinent during the trial and for 30 days after the last dose of IMP, 2 of the following approved methods of birth control must be used: (vasectomy, tubal ligation, intrauterine device, birth control pill, and condom [all methods are approved or certificated in Japan]). Any single method of birth control,

including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the source document. Male subjects must agree not to donate sperm from the time of screening through the trial and until 30 days after the last dose of IMP.

Before enrolling males and females in this clinical trial, investigators or subinvestigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, males and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine pregnancy test will be performed on all FOCBP. If a urine test is performed and is positive, the investigator or subinvestigator will follow-up with a confirmatory serum test (for human chorionic gonadotropin) (except at screening).

During the trial, all FOCBP should be instructed to contact the investigator or subinvestigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator or subinvestigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 30 days after the last dose of IMP, and record the event on the IRE form or other documentation and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator or subinvestigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator or subinvestigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Protocol Amendments

The investigator or subinvestigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators or subinvestigator will wait for IRB approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMPs used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, followed by IRB notification within local applicable timelines. If required, the sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval of the new ICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

[redacted]

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, ETC-1002, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where ETC-1002 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me or subinvestigator, and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, I do not comply with the protocol to avoid an immediate hazard to subjects, I will provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____
Principal Investigator Print Name	Name of the Trial Site
_____	_____
Signature	Date

The sponsor's signature on this agreement has been electronically signed. The electronic signature page is attached to this agreement.