CLINICAL STUDY PROTOCOL

A Placebo-controlled, Randomized, Multicenter, Double-blind, Parallel-group Trial to Confirm the Superiority of ETC-1002 in Patients With Hyper-LDL Cholesterolemia

A Confirmatory Trial of ETC-1002 in Patients With Hyper-LDL Cholesterolemia

NCT Number: NCT05683340

Protocol No. 346-102-00002

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

ETC-1002 (Nonproprietary name: Bempedoic acid)
Translation of Japanese Original
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CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	3
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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
apo B	Apolipoprotein B
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
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
eGFR	estimated glomerular filtration rate
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
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
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
MAR	Missing At Random
MMRM	Mixed-effects model repeated measures
non-HDL-C	Non-high-density lipoprotein-cholesterol
OC	Observed cases
PCSK9	Proprotein convertase subtilisin/kexin type 9
PPAR	Peroxisome proliferator-activated receptor
PQC	Product quality complaint
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid

Abbreviation	Definition
SAE	Serious adverse event
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
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.:

346-102-00002

Protocol Title:

A placebo-controlled, randomized, multicenter, double-blind, parallel-group trial to confirm the superiority of ETC-1002 in patients with hyper-LDL cholesterolemia

Protocol Lay Person Short Title:

A confirmatory trial of ETC-1002 in patients with hyper-LDL cholesterolemia

Clinical Phase/Trial Type:

Phase 3 trial/Confirmatory trial

Treatment/Indication:

Hyper-low-density lipoprotein (LDL) cholesterolemia

Objectives and Endpoints:

Objectives	Endpoints
Primary Objective: • To confirm the superiority of ETC-1002 after 12 weeks of administration at 180 mg/day to placebo in patients with hyper-LDL cholesterolemia who have inadequate control of low-density lipoprotein cholesterol (LDL-C).	Primary Endpoint: • Percent change in LDL-C from baseline to Week 12
Secondary Objectives: • To assess the effects of ETC-1002 on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (apo B), 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.	Efficacy Assessments: • Percent change in non-HDL-C, TC, apo B, hsCRP, and HbA1c from baseline to Week 12 • Proportion of subjects whose LDL-C value achieves the lipid management goals based on the 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]) at Week 12

Objectives	Endpoints
• To assess the safety of ETC-1002, when ETC-1002 at 180 mg/day is administered for 12 weeks.	Safety Assessments: • Adverse events (AEs), clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), 12-lead electrocardiogram (ECG), and body weight
Other Efficacy Assessments: • To assess the effects of ETC-1002 on high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG).	Other Efficacy Assessments: • Percent change in HDL-C and TG from baseline to Week 12

Trial Design:

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

Trial Population:

This trial will enroll subjects with hyper-LDL cholesterolemia between 18 and 85 years of age, inclusive, who are at risk for cardiovascular events and who have inadequate control of LDL-C with existing hyper-LDL cholesterolemia treatments.

The target number of subjects is 84 in total (42 in the ETC-1002 180-mg group and 42 in the placebo group) as randomized subjects.

Key Inclusion/Exclusion Criteria:

Inclusion Criteria

1) Patients who have the ability to provide informed consent, and who provide written informed consent prior to the start of the trial
2) Patients, either male or female, between 18 and 85 years of age, inclusive, at the time of informed consent
3) Patients with inadequate response to statins or statin intolerance as defined below

[Inadequate response to statins]

Patients with hyper-LDL cholesterolemia who have been taking statins and cannot achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)), meeting either of the following a) or b)

Category	LDL-C at Week −5 and Week −1	Background lipid-lowering drugs at screening		
		Type of drugs	Timing of the start of treatment: before informed consent	Dose and regimen
a)	The lipid management goals of LDL-C based on the risk assessment cannot be achieved (see inclusion criterion 4)).	Statins alone	From at least 4 weeks before	Same dose and regimen within the approved dose range
b)		Statins + nonstatins	• Fibrates, selective peroxisome proliferator-activated receptor (PPAR)α modulators: From at least 6 weeks before • Statins and drugs other than those above: From at least 4 weeks before	• Statins: Same dose and regimen within the approved dose range • Nonstatins: Same dose and regimen

[Statin intolerance]

Patients with hyper-LDL cholesterolemia for whom safety problems have occurred while taking at least one type of statin, and who experienced resolution of the problems after discontinuation or dose reduction, and who cannot achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)), meeting any of the following a) to c)

Category	LDL-C at Week −5 and Week −1	Background lipid-lowering drugs at screening		
		Type of drugs	Timing of the start of treatment: before informed consent	Dose and regimen
a)	The lipid management goals of LDL-C based on the risk assessment cannot be achieved (see inclusion criterion 4)).	Statins alone	From at least 4 weeks before	Same dose and regimen at (or below) the lowest approved dose
b)		Statins + nonstatins	• Fibrates, selective PPARα modulators: From at least 6 weeks before • Statins and drugs other than those above: From at least 4 weeks before	• Statins: Same dose and regimen at (or below) the lowest approved dose • Nonstatins: Same dose and regimen
c)		Only nonstatins	• Fibrates, selective PPARα modulators: From at least 6 weeks before • Drugs other than the above: From at least 4 weeks before	Same dose and regimen

4) Patients with a history or current condition meeting any of the following criteria 1) to 3)

Category	History or current condition	LDL-C at Week −5 and Week −1
1)	History of coronary artery disease	≥100 mg/dL
	Heterozygous familial hypercholesterolemia (HeFH)	
2)	Peripheral arterial disease	≥120 mg/dL
	History of non-cardiogenic cerebral infarction	
	Chronic kidney disease (Provided that it does not fall under exclusion criterion 12))	
	Type 2 diabetes mellitus (Diagnosed at least 3 months before Week −5, without falling under exclusion criterion 7))	
3)	The total score in the coronary artery disease risk prediction model using the Suita score specified by the Japan Atherosclerosis Society is ≥56 points (high risk)	≥120 mg/dL
	The 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)	≥140 mg/dL

5) Patients with fasting TG levels of <400 mg/dL at screening (Week −5)

Exclusion Criteria

1) Females who are pregnant or breast-feeding or who have a positive pregnancy test (urine) result at screening (Week −5) or on Day 1
2) Sexually active and reproductive males or sexually active females 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, or condom (all methods are approved or certified in Japan).
3) Patients with homozygous familial hypercholesterolemia (HoFH)
4) Patients who currently have or who have had within the past 3 months prior to screening (Week −5) any of the following cardiovascular diseases, or those who have developed any of these AEs during the screening and placebo run-in 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
- Patients with risk factors for torsade de pointes, such as unexplained syncope or long-QT syndrome, or a family history of long-QT syndrome

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 screening (Week −5)
6) Patients with uncontrolled and serious hematologic or coagulation disorders, or with hemoglobin of <10.0 g/dL at screening (Week −5)
7) Patients with uncontrolled diabetes with HbA1c of ≥9% at screening (Week −5)
8) Patients with uncontrolled hypothyroidism with thyroid-stimulating hormone (TSH) of >1.5 × the upper limit of normal (ULN) at screening (Week −5)
9) Patients with liver disease or dysfunction, including:

- Positive serology for hepatitis B surface antigen (HBsAg) or a positive hepatitis C virus (HCV) antibody test at screening (Week −5)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of ≥3 × ULN or total bilirubin of ≥2 × ULN at screening (Week −5)

10) Patients with a history or current chronic musculoskeletal symptoms that may be difficult to differentiate from myalgia
    (eg, fibromyalgia)
11) Patients with creatine kinase (CK) of >3 × ULN at screening (Week −5)
12) Patients with a history or current renal dysfunction, nephritic syndrome, or nephritis, and with estimated glomerular filtration rate (eGFR) of ≤30 mL/min/1.73 m^2 at screening (Week −5)

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 screening (Week −5)
15) Patients with a history of drug, alcohol, or cocaine abuse within the past 2 years prior to screening (Week −5)
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 screening (Week −5)
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 screening (Week −5)
18) Patients who took the IMP in Trial 346-102-00001 or patients who have used ETC-1002 in the past
19) Patients who used or received the following drugs (including food) or therapies within the specified period or who are planning to use or receive them by the end of the tests at Week 12

	Drugs (including food) or therapies	**Prohibition period**
1.	Systemic corticosteroids	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, the drug may be used concomitantly with no change in dose from 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable).
2.	Lomitapide	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors	From 4 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	[redacted]	[redacted]
5.	Red yeast rice and food containing red yeast rice	From 2 weeks prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
6.	LDL apheresis	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)

20) Patients in whom the following drugs (therapies) are changed prior to Day 1 or in whom initiation of the following drugs (therapies) is planned by the end of the tests at Week 12

	Drugs or therapies	Period in which the drug or therapy cannot be changed or newly started
1.	Female or male hormone replacement	From 6 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
2.	Thyroid replacement	From 6 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Diabetes medications	From 4 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Obesity medications	From 3 months prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)

21) Patients whose LDL-C level at Week −1 has changed by at least ±20% as compared with that at screening (Week −5)
22) Patients with <80% compliance with the single-blind placebo up to Day 1 during the placebo run-in period or who cannot continue drug administration due to safety issues
23) Patients in whom a muscle-related AE other than due to strain, trauma, or other obvious etiology newly occurs or is aggravated during the placebo run-in period
24) Patients otherwise judged inappropriate for participating in the trial in the opinion of the investigator or subinvestigator

Trial Sites:

Approximately 35 sites in Japan

Investigational Medicinal Product, Dose, Dosage Regimen, Treatment Duration, Formulation, and Mode of Administration:

Description		Placebo Run-in Period	Treatment Period
Investigational medicinal products	Medications	Placebo tablets	ETC-1002 180-mg tablets/ Placebo tablets
	Dose and regimen/ Mode of administration	1 tablet once daily/oral	
Lipid-lowering drugs	Medications	Lipid-lowering drugs used before informed consent (Statins and/or nonstatins)	
	Dose and regimen	Continue treatment without changing the type or dose and regimen	
Treatment duration		4 weeks	12 weeks

Trial Assessments:

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

Trial Assessments for Future Biospecimen Research (FBR): DNA sample storage (optional) and serum sample storage for biomarker exploration (optional)

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

Screening/Other: Demographics, height, medical history, prior medications, virus test (HBsAg and HCV antibodies), endocrine test (TSH), and pregnancy test (urine, serum)

Data Monitoring Committee: No

Statistical Methods:

Primary Efficacy Endpoint Analysis

The primary endpoint is the percent change from baseline to Week 12 in LDL-C measured by the direct method. Baseline is defined as the mean of the LDL-C values for Day 1 and Week −1. A mixed models repeated measures (MMRM) analysis assuming missing at random (MAR) will be performed using observed case (OC) data. The treatment comparison will be based on the least-squares mean difference between the ETC-1002 group and the placebo group at Week 12. A two-sided significance level of 5% will be used. The model will include treatment group, stratification factor, time, and treatment-by-time interaction as factors, and baseline and baseline-by-time interaction as covariates. The error covariance structure will be unstructured. The Kenward-Roger method will be used for the approximate degrees of freedom.

Sample Size

In the phase 2 trial conducted in Japan, the difference in the percent change from baseline in LDL-C to Week 12, between the ETC-1002 180-mg group and the placebo group was −19%, and the standard deviation of the percent change from baseline in each group ranged from 9% to 17%. Since the between-group difference in the phase 2 trial in Japan was comparable to the results estimated from phase 3 trials conducted outside Japan, the between-group difference in this trial is assumed to be −19%. Also considering the standard deviation (14% to 25%) in the phase 3 trials conducted outside Japan, in which similar populations of subjects to this trial were enrolled, the standard deviation in this trial is conservatively assumed to be 25%. Under those assumptions, a total of 76 subjects

(38 subjects/group) will be required to ensure a power of 90%. Assuming a withdrawal rate of 10%, the total number of subjects in this trial is set at 84.

Trial Duration:

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

- Screening period (1 week)
- Placebo run-in period (single-blind, 4 weeks)
- 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 11 months.

1.2 Schema

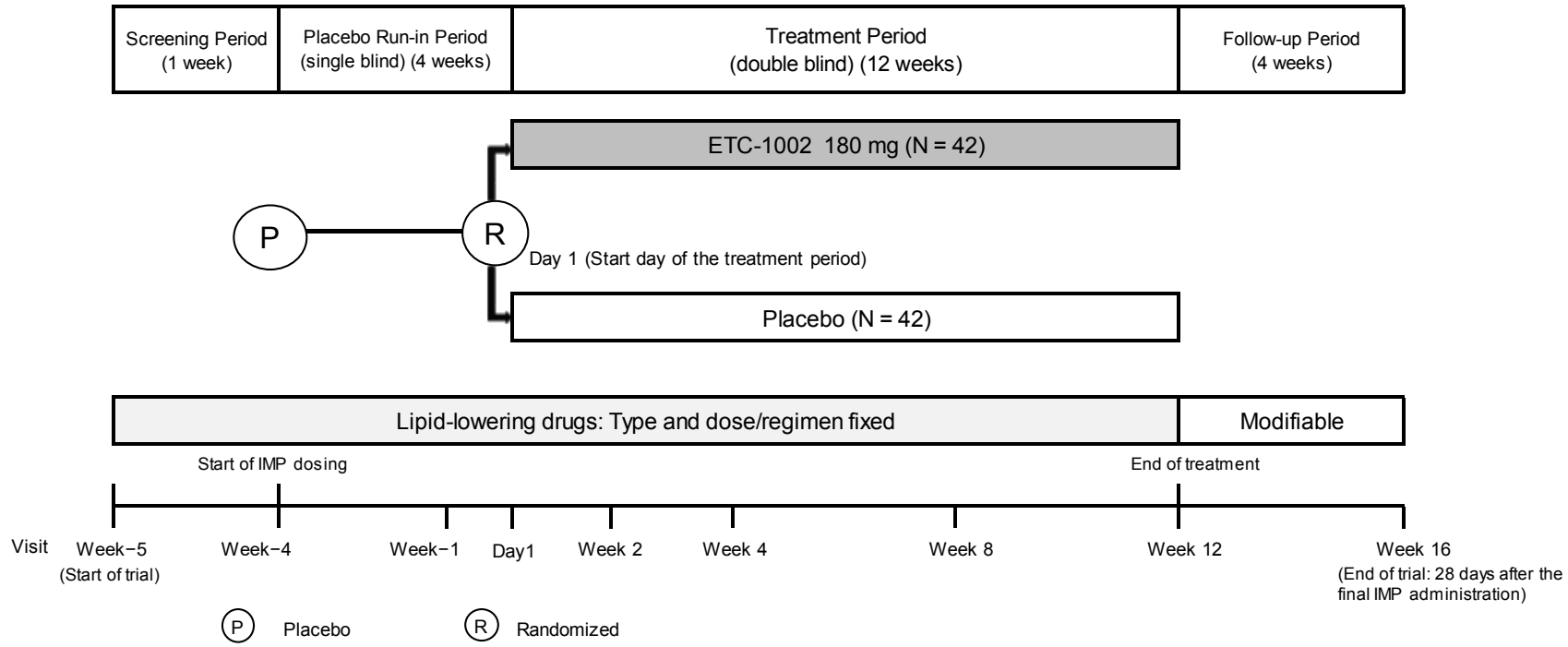


Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

	Screening Period	Placebo Run-in Period		Treatment Period					Follow-up Period
Visit (Week)	**Week −5**	**Week −4**	**Week −1**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12/ Discontinuation[a]**	**Week 16**
Trial Day	**Day −35 ± 3**	**Day −28 ± 3**	**Day −7 ± 2**		**Day 15 ± 3**	**Day 29 ± 3**	**Day 57 ± 3**	**Day 85 ± 3**	**28 days ±7 days after the final IMP administration**
Informed consent[b]	●								
Eligibility assessment	●	●	●	●					
Demographics	●								
Endocrine test (TSH) Virus test (HBsAg, HCV antibody)	●								
Placebo administration for the placebo run-in period		●	●						
Randomization				●					
IMP administration for the treatment period				●	●	●	●		
Fasting lipids[c, d]	●		●	●	●	●	●	●	●
HbA1c[d]	●			●				●	
hsCRP, apo B[d]				●				●	
Physical examination	●	●	●	●	●	●	●	●	●
Body weight	●		●	●		●	●	●	
Vital signs[e]	●	●	●	●	●	●	●	●	●
12-Lead ECG[f]	●			●		●		●	
Clinical laboratory tests[g]	●		●	●		●	●	●	●
Provision of subject diary		●	●	●	●	●	●		
Collection of subject diary			●	●	●	●	●	●	

Table 1.3-1 Schedule of Assessments

	Screening Period	Placebo Run-in Period		Treatment Period					Follow-up Period
Visit (Week)	**Week −5**	**Week −4**	**Week −1**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12/ Discontinuation[a]**	**Week 16**
Trial Day	**Day −35 ± 3**	**Day −28 ± 3**	**Day −7 ± 2**		**Day 15 ± 3**	**Day 29 ± 3**	**Day 57 ± 3**	**Day 85 ± 3**	**28 days ±7 days after the final IMP administration**
Confirmation of use of concomitant medications/therapies	◄								►
Adverse events	◄								►
Pregnancy test[h]	●			●				●	
Blood sampling for biomarker storage[i]				○	○	○		○	○
Blood sampling for DNA storage [i]				○					

● Mandatory; ○ Optional

[a]In cases of early discontinuation during the placebo run-in period or treatment period, "Discontinuation Visit" is to be performed within 2 days after the last dose of the IMP as far as possible. With regard to termination during the placebo run-in period, blood sampling for biomarker sample storage, DNA sample storage, hsCRP, and apo B measurement is not to be performed.

[b]Written informed consent will be obtained from the patient himself/herself prior to any trial-related assessments. Written consent will be obtained by Week −5.

[c]Fasting lipid assessments include LDL-C, HDL-C, non-HDL-C, TC, and TG.

[d]On scheduled visit days, subjects are to be instructed to come to the trial site without taking the IMP and reminded to take the IMP after tests are completed.

[e]Body temperature, blood pressure, and pulse measurements are to be performed after resting for at least 5 minutes and prior to blood sampling to the extent possible.

[f]12-Lead ECG is to be performed after resting for at least 10 minutes and prior to blood sampling whenever possible.

[g]Clinical laboratory tests include hematology, blood chemistry (except for HbA1c, fasting lipid assessments), and urinalysis.

[h]Pregnancy test is to be performed only for females of childbearing potential. If urine test is positive, the serum test will be performed (except Week −5).

[i]Blood sampling is to be performed only for subjects who provide written consent for DNA sample storage and biomarker sample storage. Blood sampling for DNA sample storage will be performed before IMP administration on Day 1 in principle. If blood sampling cannot be performed or needs to be performed again, it will be performed at a feasible time during the trial period.

1.3.1 Screening Period

1.3.1.1 Informed Consent

Prior to starting any assessments at screening, written informed consent will be obtained from the patients themselves. After informed consent is obtained, each subject will be given a subject identification number and registered in the Interactive Web Response System (IWRS). 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 investigational medicinal product (IMP). The investigator or subinvestigator will enter 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 also be recorded in the source document and the electronic case report form (eCRF).

For DNA sample storage and biomarker sample storage, written informed consent will be obtained from the subjects themselves using a separate informed consent form (ICF), and the date of informed consent will be recorded in the source document and the eCRF. DNA and biomarker sample 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 sample storage.

1.3.1.2 Screening Visit: Week −5

After obtaining informed consent, the investigator or subinvestigator will perform the observation and assessments at Week −5 specified in Table 1.3-1, record the results in the source document and the eCRF with the visit date, and enter the required information in the IWRS. After judging the eligibility for participation in the trial, the investigator or subinvestigator will record the eligibility for enrollment, date of enrollment, and reasons in the 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, and country)
- Height (in units of 0.1 cm [if measured to the second decimal place or less, the second decimal place will be rounded.])
- Past medical history (within 1 year before informed consent, but this limitation is not applicable to those related to the inclusion and exclusion criteria)
- Current condition (at the time of informed consent)
- History of hypercholesterolemia

History of Hypercholesterolemia: Investigation Item
• Name of diagnosis • Date of diagnosis • Presence or absence of familial hypercholesterolemia • Classification and details of classification (according to the flowchart using the Suita score in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017,[1] and according to the flowchart using the score of the Hisayama Study in the Guidelines 2022[2]) • Statin response (inadequate response to statins, statin intolerance) • For patients with statin intolerance: Cause of statin intolerance and the name/daily dose of the statin

- Prior lipid-lowering drugs received within 6 weeks prior to informed consent
- Therapeutic drugs for diabetes mellitus used within 7 weeks prior to informed consent
- All prior medications and prior therapies received within 4 weeks prior to informed consent
- Result of eligibility assessment

1.3.2 Placebo Run-in Period

1.3.2.1 Placebo Run-in Period: Week −4

The investigator or subinvestigator will perform the observations and assessments at Week −4 at the start of the placebo run-in period specified in Table 1.3-1, record the results in the source document and the eCRF with the visit date. Subject eligibility will be determined, and the result of the determination will be recorded in the source document and the eCRF and entered in the IWRS. If the subject is judged to be eligible, the date of enrollment in the placebo run-in period will be recorded in the source document and the eCRF and entered in the IWRS.

1.3.2.2 Observations and Assessments During the Placebo Run-in Period: Week −1

Subjects who meet the eligibility criteria based on the observation and assessments at Week −4 will proceed to the 4-week placebo run-in period, continue taking any lipid-lowering drugs that they have been taking from before informed consent at the same dose and regimen, and receive placebo tablets for 4 weeks. The investigator or subinvestigator will perform the observation and assessments specified in Table 1.3-1, record the visit date in the source document and the eCRF, and enter the result of the determination in the IWRS. On and after Week −4, subjects not meeting the eligibility criteria based on the

observations and examinations at Week −1 will be withdrawn from the trial, as subjects withdrawn from the placebo run-in period.

1.3.3 Treatment Period

1.3.3.1 Day 1

The investigator or subinvestigator will determine whether or not a subject can proceed to the treatment period based on the results of the observations and assessments on Day 1 specified in Table 1.3-1, record the result in the source document and the eCRF, and enter the determination result in the IWRS. If the subject is judged to be eligible for proceeding to the treatment period, the subject will be randomly assigned to either the ETC-1002 180-mg group or the placebo group in a ratio of 1:1. The date and randomization number will be recorded in the source document and the eCRF.

1.3.3.2 Observations and Assessments During the Treatment Period: Week 2 to Week 12

If a subject who has been determined to be eligible for proceeding to the treatment period has received a lipid-lowering drug since before informed consent, the subject should continue to receive the drug at the same dose and regimen in addition to taking the IMP (ETC-1002 at 180 mg/day or placebo) for 12 weeks.

The observation and assessments specified in Table 1.3-1 will be performed during the treatment period, and the results will be recorded in the source document and the eCRF with the visit date. The investigator or subinvestigator will enter the required information in the IWRS at each visit for each subject.

1.3.4 Follow-up Period

The investigator or subinvestigator will perform the observation and assessments specified in Table 1.3-1 at the visit 28 days (±7 days) after the last IMP administration to all the subjects who proceed to the treatment period and record the results in the source document and the eCRF with the visit date. The investigator or subinvestigator will enter the required information in the IWRS at the end of the follow-up period for each subject. The tests during the follow-up period will not be performed for subjects who are proceeding to the treatment period in the 52-week (open-label) long-term trial. Proceeding to the long-term trial is optional.

1.3.5 Discontinuation Visit

When the subject discontinues during the placebo run-in period or the treatment period, the investigator or subinvestigator will perform the same assessments at Week 12 (see Table 1.3-1) at Discontinuation Visit within 2 days after the last dose of the IMP as much as possible and record the results in the source document and the eCRF with the visit date. The investigator or subinvestigator will enter the required information in the IWRS at the time of discontinuation for each subject.

2 Introduction

Dyslipidemia is defined as a condition in which low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) in the blood are outside the reference values. Since these abnormalities are primarily associated with the incidence of coronary artery disease, prophylaxis and subsequent treatment are considered critical. In addition, with the recent westernization of food, the number of patients with dyslipidemia is increasing each year in Japan, and currently stands at approximately 2.2 million.[3] Hyper-LDL cholesterolemia, which is one of the forms of dyslipidemia, refers to the state of having high LDL-C levels in the blood. If left untreated, this condition is considered as one of the most significant risk factors associated with the development and progression of arteriosclerosis. Drugs currently launched in Japan for the treatment of hyper-LDL cholesterolemia include 3 hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (various statins), small intestine cholesterol transporter inhibitors (ezetimibe), and human anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody formulations (evolocumab). Several large-scale clinical trials have demonstrated the usefulness of these drugs for the primary and secondary prevention of coronary artery disease.[4,5,6,7,8] Japanese and non-Japanese guidelines[1,9,10] place statins as the first-line drug, and statins have been used for the treatment of hyper-LDL cholesterolemia. LDL-C can be controlled with statins 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 the risk assessment for the primary and secondary prevention of coronary artery disease specified in Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017,[1] posing an issue with drug therapy for patients with inadequate control of LDL-C. In such cases, combination therapy using drugs with mechanisms of action different from statins is performed, the issue of drug therapy still remains. Statin intolerance, which requires a 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,[11] 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 nonstatins, 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 because of the inability of statin administration 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, 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 clinical trials conducted outside Japan in patients with hyper-LDL cholesterolemia, 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 hyper-LDL cholesterolemia compared with placebo. No particular safety concern has been identified in the clinical trials that have been conducted to date. Based on the results of clinical trials conducted outside Japan, the efficacy of ETC-1002 at 180 mg/day was confirmed in combination with statins and/or nonstatins in patients who are not able to achieve adequate control with their maximally tolerated statins in the US. As no particular safety concerns were identified, ETC-1002 was approved in February 2020 and has already been marketed. In Europe, since the efficacy and safety of ETC-1002 at 180 mg/day alone was demonstrated in patients with statin intolerance in addition to patients with an inadequate response to the maximally tolerated statins in whom ETC-1002 was used in combination with statins and/or nonstatins, ETC-1002 was approved in April 2020, and has already been marketed in some European countries. In addition, a large-scale cardiovascular outcome trial is currently ongoing to assess whether long-term treatment with ETC-1002 at 180 mg reduces the risk of major adverse cardiovascular events (MACE) in statin-intolerant patients with or at a high risk of atherosclerotic cardiovascular disease.

Otsuka Pharmaceutical Co., Ltd. (hereinafter referred to as “Otsuka”) considers that ETC-1002 can be a new treatment option for Japanese patients with hyper-LDL cholesterolemia in whom LDL-C values cannot be adequately controlled with existing statin-based therapy. Otsuka has obtained the development and marketing right in Japan from Esperion Therapeutics, Inc. and started development in Japan. A phase 2 dose-finding trial (Protocol No. 346-102-00001) conducted to assess the efficacy, dose-

response, and safety in Japanese patients and determine the dose used in the phase 3 trial has already been concluded.

For further information, please refer to the ETC-1002 Investigator's Brochure (IB).

2.1 Trial Rationale

Thus far, the efficacy of ETC-1002 on hyper-LDL cholesterolemia has been demonstrated in phase 3 placebo-controlled, double-blind trials conducted outside Japan in patients with hyper-LDL cholesterolemia (Trials 1002-040, 1002-046, 1002-047, and 1002-048), and it has been confirmed that there are no particular safety concerns. [redacted] Adverse events that occurred in 5% or more of subjects in the ETC-1002 group were pyrexia (7.1% [10/141 subjects]), malaise (5.0% [7/141 subjects]), hepatic function abnormal (5.0% [7/141 subjects]), arthralgia (5.0% [7/141 subjects]), and headache (5.0% [7/141 subjects]). [redacted]

[redacted]

The subgroup analysis by statin response (inadequate response to statins, statin intolerance) demonstrated that the percent change (least squares mean) in LDL-C from baseline to Week 12 was −5.48%, −18.13%, and −16.31% in the ETC-1002 60, 120, and 180-mg groups, respectively, versus −0.29% in the placebo group among subjects with inadequate response to statins; and −20.43%, −27.44%, and −31.25% in the ETC-1002 60, 120, and 180-mg groups, respectively, versus +1.00% in the placebo group among subjects with statin intolerance [redacted] There was no considerable difference in the tendency of the incidence of AEs between subjects with inadequate response to statins and those with statin intolerance.

[redacted] Meanwhile, a large-scale cardiovascular outcomes trial is currently ongoing to evaluate the effect of ETC-1002 at 180 mg on lowering the risk of MACE in patients with hyper-LDL cholesterolemia, and the results will be available in the future.

[redacted]

[redacted]

The primary endpoint is the percent change from baseline to Week 12 in LDL-C. The duration of the treatment period for the evaluation in this trial is set at 12 weeks, because the evaluation time point for the primary endpoint in the phase 2 trial is at 12 weeks after the start of administration, and also because the trial duration should persist for at least 3 months according to the Guidelines on Clinical Evaluation of Medicinal Products for Treatment of Dyslipidemia.[12] In addition, this trial will include patients who cannot achieve the lipid management goals specified in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017,[1] even after taking existing therapeutics for hyper-LDL cholesterolemia. [redacted] The concomitant lipid-lowering drugs will be continued without changing the type, dose, and regimen from at least 4 weeks before informed consent (at least 6 weeks before, for fibrates and selective peroxisome proliferator-activated receptor [PPAR]α modulators).

[redacted]

Taken together, it is judged to be ethically appropriate to conduct this trial to confirm the superiority of ETC-1002 at 180 mg/day to placebo in patients with hyper-LDL cholesterolemia.

2.2 Background

Efficacy data supporting the indication of LDL-C reduction have been obtained from 4 phase 3 [redacted] trials of ETC-1002 in clinical trials conducted outside Japan. In these trials, the once-daily administration of ETC-1002, added to a maximum tolerated

dose of statins (including no statin) and/or other therapeutics for hyper-LDL cholesterolemia (ezetimibe or PCSK9 inhibitors) resulted in a significant reduction of LDL-C from baseline in patients with hyper-LDL cholesterolemia (including those at high cardiovascular risk). [redacted] Overall, ETC-1002 has an acceptable safety profile in combination with other LDL-C lowering therapies (including statins, ezetimibe, or PCSK9 inhibitors) in a variety of patient populations. [redacted]

In Japan, a dose-finding trial (Protocol No. 346-102-00001) of ETC-1002 as a phase 2 trial was conducted in patients with hyper-LDL cholesterolemia to investigate the efficacy and safety of ETC-1002 at 60 mg/day, 120 mg/day, 180 mg/day, and placebo. The results verified the efficacy and safety of ETC-1002 at up to 180 mg/day in Japanese patients with hyper-LDL cholesterolemia.

Therefore, this clinical trial has been planned to confirm the superiority of ETC-1002 to placebo in patients with inadequate response to statins or statin intolerance in whom the target LDL-C level cannot be achieved by drug therapy with statin alone or in combination with other drugs. (See Section 2.1 for details.)

2.3 Known and Potential Risks and Benefits

[redacted]

[redacted]

The results of the clinical trials conducted outside Japan and the Japanese phase 2 trial have demonstrated that ETC-1002 at 180 mg/day was effective in patients with inadequate response to statins or statin intolerance. For safety, ETC-1002 was tolerated at up to 180 mg/day with no tendency for an increased incidence of AEs in a dose-dependent manner in the Japanese phase 2 trial.[redacted]

[redacted] ETC-1002 can be a useful treatment for patients with hyper-LDL cholesterolemia who need to continue long-term therapy for hyper-LDL cholesterolemia.

Once the IB 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 below.

Table 3-1 Objectives and Endpoints of This Trial (Primary and Secondary)

Objectives	Endpoints
Primary Objective: • To confirm the superiority of ETC-1002 after 12-week of administration at 180 mg/day to placebo in patients with hyper-LDL cholesterolemia who have inadequate control of low-density lipoprotein cholesterol (LDL-C).	Primary Endpoint: • Percent change in LDL-C from baseline to Week 12
Secondary Objectives: • To assess the effects of ETC-1002 on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (apo B), 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 safety of ETC-1002, when ETC-1002 at 180 mg/day is administered for 12 weeks.	Efficacy Assessments: • Percent change in non-HDL-C, TC, apo B, hsCRP, and HbA1c from baseline to Week 12 • Proportion of subjects whose LDL-C value achieves the lipid management goals based on the 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]) at Week 12 Safety Assessments: • Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), 12-lead ECG, and body weight
Other Efficacy Assessments: • To assess the effects of ETC-1002 on high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG).	Other Efficacy Assessments: • Percent change in HDL-C and TG from baseline to Week 12

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 confirm the efficacy and assess the safety of 12-week administration of ETC-1002 at 180 mg/day in patients with hyper-LDL cholesterolemia who are being treated for hyper-LDL cholesterolemia but have inadequate control and cannot achieve the lipid management goals. The trial population will include patients with an inadequate response to statins who cannot achieve the lipid management goals despite statin therapy, and patients with statin intolerance who cannot achieve the lipid management goals because they have experienced safety problems caused by statin administration which resolved after discontinuation or dose reduction.

A schematic of the trial design is presented in Figure 1.2-1.

This trial consists of the screening period, the placebo run-in period, the treatment period, and the follow-up period. Subjects determined to be eligible in the screening period will proceed to the placebo run-in period, continue the treatment without changing the type or dose and regimen of lipid-lowering drugs that have been taken from before informed consent, and receive placebo in a single-blind manner. Subjects with noncompliance with less than 80% compliance with the single-blind placebo during the 4-week placebo run-in period will be withdrawn at the end of the placebo run-in period. Subjects who do not have safety problems or muscle-related AEs in the 4-week placebo run-in period, or who do not fall under the exclusion criteria as judged by the investigator or subinvestigator, will be assigned to either the ETC-1002 180-mg group or the placebo group, and proceed to the treatment period. Statin response (inadequate response to statins/statin intolerance) is set as a randomization stratification factor so that subjects with inadequate response to statins and statin intolerance will be equally allocated to each treatment group.

During the treatment period, subjects should continue to take the lipid-lowering drugs that they have taken from before informed consent and receive either ETC-1002 at 180 mg or placebo for 12 weeks. The medications to be administered in the placebo run-in period and the treatment period are as follows:

Description		Placebo Run-in Period	Treatment Period
Investigational medicinal products	Medications	Placebo tablets	ETC-1002 180-mg tablets/ Placebo tablets
	Dose and regimen/ Mode of administration	1 tablet once daily/oral	
Lipid-lowering drugs	Medications	Lipid-lowering drugs used before informed consent (Statins and/or nonstatins)	
	Dose and regimen	Continue treatment without changing the type or dose and regimen	
Treatment duration		4 weeks	12 weeks

4.2 Scientific Rationale for Trial Design

This clinical trial has been planned to confirm the superiority of ETC-1002 to placebo in patients with inadequate response to statins or statin intolerance who cannot achieve the lipid management goals specified in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017.[1] The primary endpoint is the percent change from baseline to Week 12 in LDL-C. This trial consists of the screening period, the placebo run-in period, the treatment period, and the follow-up period. Subjects who are determined to meet the inclusion criteria and do not fall under the exclusion criteria in the screening period are to proceed to the placebo run-in period from 4 weeks before randomization and receive placebo for 4 weeks in a single-blind manner. 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.[11,13] Some patients have been reported to experience a reverse placebo effect (nocebo effect) and complain of events such as muscle symptoms, even with nonstatin drugs such as placebo.[14,15] To evaluate the safety of ETC-1002 more appropriately, a placebo run-in period is set in the same manner as in the Japanese phase 2 trial and the clinical trials conducted outside Japan of ETC-1002. Subjects who show the nocebo effect during the placebo run-in period will be excluded.

In the treatment period, the lipid-lowering drugs will be continued without changing the type or dose and regimen from at least 4 weeks before informed consent (at least 6 weeks before, for fibrates and selective PPARα modulators), and ETC-1002 or placebo will be added in a double-blind manner. As described above, placebo is selected as a comparator to appropriately assess the efficacy in this trial.

As for the treatment duration, the percent change in LDL-C from baseline to 12 weeks after the start of administration was selected as the primary endpoint in all 4 phase 3 trials conducted outside Japan as well as in the Japanese phase 2 trial. [redacted]

[redacted] In addition, a period of 12 weeks is set as the duration necessary to evaluate the efficacy of ETC-1002, because the trial duration should persist for at least 3 months according to the Guidelines on Clinical Evaluation of Medicinal Products for Treatment of Dyslipidemia.[12] The primary endpoint is set as the percent change in LDL-C from baseline to Week 12.

4.3 Dosing Rationale

[redacted]

4.4 End of Trial Definition

The “end of trial date” is defined as the “last date of visit/contact” or the “date of final contact attempt” recorded on the page of the post-treatment follow-up in the eCRF for the last subject completing or withdrawing from the trial. For subjects who will proceed to the long-term trial (Trial 346-102-00003), the end of trial date in this trial is defined as the date of the Week 12 assessment.

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for the 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 complete the Week 12 assessment will be defined as trial completers.

5 Trial Population

This trial will include Japanese patients with hyper-LDL cholesterolemia between 18 and 85 years of age, inclusive, at the time of informed consent and with an inadequate response to statins or statin intolerance, who cannot achieve the lipid management goals specified in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017.[1] Subjects who are determined to be eligible by the investigator or subinvestigator in the screening period will proceed to the placebo run-in period. Among the subjects with no safety problems and no muscle-related AEs in the placebo run-in period, those confirmed by the investigator or subinvestigator not to fall under the exclusion criteria will be randomized. The target number of subjects is 84 in total (42 in the ETC-1002 180-mg group and 42 in the placebo group) as randomized subjects. In addition to patients with inadequate response to statins, patients with statin intolerance is planned to be enrolled at ≥20% of the total population in this trial. Statin response (inadequate response to statins/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 who have the ability to provide informed consent and who provide written informed consent prior to the start of the trial
2) Patients, either male or female, between 18 and 85 years of age, inclusive, at the time of informed consent
3) Patients with inadequate response to statins or statin intolerance as defined below

Statins refer to atorvastatin, pitavastatin, rosuvastatin, pravastatin, simvastatin, or fluvastatin.

- Inadequate response to statins: Patients with hyper-LDL cholesterolemia who have been taking statins and cannot achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)), meeting either of the following a) or b)
  a) Patients who have been taking statins (within the approved dose range) alone at the same dose and regimen from at least 4 weeks before informed consent
  b) Patients who have been taking statins (within the approved dose range) and nonstatins at the same dose and regimen from at least 4 weeks before informed consent (at least 6 weeks before, for fibrates and selective PPARα modulators)

[Inadequate response to statins]

Category	LDL-C at Week −5 and Week −1	Background lipid-lowering drugs at screening		
		Type of drugs	Timing of the start of treatment: before informed consent	Dose and regimen
a)	The lipid management goals of LDL-C based on the risk assessment cannot be achieved (see inclusion criterion 4)).	Statins alone	From at least 4 weeks before	Same dose and regimen within the approved dose range
b)		Statins + nonstatins	• Fibrates, selective PPARα modulators: From at least 6 weeks before • Statins and drugs other than those above: From at least 4 weeks before	• Statins: Same dose and regimen within the approved dose range • Nonstatins: Same dose and regimen

- Statin intolerance: Patients with hyper-LDL cholesterolemia for whom safety problems occurred while taking at least one type of statin, and who experienced resolution of problems after discontinuation or dose reduction, and who cannot achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)), meeting any of the following a) to c)
  a) Patients who have been taking statins (at or below the lowest approved dose) alone at the same dose and regimen from at least 4 weeks before informed consent
  b) Patients who have been taking statins (at or below the lowest approved dose) and nonstatins at the same dose and regimen from at least 4 weeks before informed consent (at least 6 weeks before, for fibrates and selective PPARα modulators)
  c) Patients who have been taking only nonstatins at the same dose and regimen, from at least 4 weeks before informed consent (at least 6 weeks before, for fibrates and selective PPARα modulators)

[Statin intolerance]

Category	LDL-C at Week −5 and Week −1	Background lipid-lowering drugs at screening		
		Type of drugs	Timing of the start of treatment: before informed consent	Dose and regimen
a)	The lipid management goals of LDL-C based on the risk assessment cannot be achieved (see inclusion criterion 4)).	Statins alone	From at least 4 weeks before	Same dose and regimen at (or below) the lowest approved dose
b)		Statins + nonstatins	• Fibrates, selective PPARα modulators: From at least 6 weeks before • Statins and drugs other than those above: From at least 4 weeks before	• Statins: Same dose and regimen at (or below) the lowest approved dose • Nonstatins: Same dose and regimen
c)		Only nonstatins	• Fibrates, selective PPARα modulators: From at least 6 weeks before • Drugs other than the above: From at least 4 weeks before	Same dose and regimen

4) Patients with a history or current condition meeting any of the following criteria 1) to 3)

Category	History or current condition	LDL-C at Week −5 and Week −1
1)	History of coronary artery disease	≥100 mg/dL
	Heterozygous familial hypercholesterolemia (HeFH)	
2)	Peripheral arterial disease	≥120 mg/dL
	History of non-cardiogenic cerebral infarction	
	Chronic kidney disease (Provided that it does not fall under exclusion criterion 12))	
	Type 2 diabetes mellitus (Diagnosed at least 3 months before Week −5, without falling under exclusion criterion 7))	
3)	The total score in the coronary artery disease risk prediction model using the Suita score specified by the Japan Atherosclerosis Society is ≥56 points (high risk)	≥120 mg/dL
	The 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)	≥140 mg/dL

5) Patients with fasting TG level of <400 mg/dL at screening (Week −5)

[Rationale for the inclusion criteria]

1) This criterion is set based on ethical considerations.
2) The lower limit of age is set as adults with sufficient ability to provide informed consent. The upper limit of age is set at 85 years in consideration of safety.

3) to 4) These criteria are set to appropriately evaluate the efficacy.

5) This criterion is set in consideration of safety. It is also considered that it will be difficult to appropriately calculate LDL-C values using the Friedewald formula.

5.2.2 Exclusion Criteria

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

1) Females who are pregnant or breast-feeding or who have a positive pregnancy test (urine) result at screening (Week −5) or on Day 1
2) Sexually active and reproductive males or sexually active females 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, or condom (all methods are approved or certified in Japan).
3) Patients with homozygous familial hypercholesterolemia (HoFH)
4) Patients who currently have or who have had within the past 3 months prior to screening (Week −5) any of the following cardiovascular diseases, or those who had developed any of these AEs during the screening and placebo run-in 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
- Patients with risk factors for torsade de pointes, such as unexplained syncope, or long-QT syndrome or a family history of long-QT syndrome

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 screening (Week −5)
6) Patients with uncontrolled and serious hematologic or coagulation disorders or with hemoglobin of <10.0 g/dL at screening (Week −5)
7) Patients with uncontrolled diabetes with HbA1c of ≥9% at screening (Week −5)
8) Patients with uncontrolled hypothyroidism with thyroid-stimulating hormone (TSH) of >1.5 × the upper limit of normal (ULN) at screening (Week −5)
9) Patients with a liver disease or dysfunction, including:

- Positive serology for hepatitis B surface antigen (HBsAg) or a positive hepatitis C virus (HCV) antibody test at screening (Week −5)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of ≥3 × ULN or total bilirubin of ≥2 × ULN at screening (Week −5)

10) Patients with a history or current chronic musculoskeletal symptoms that may be difficult to differentiate from myalgia
    (eg, fibromyalgia)
11) Patients with CK of >3 × ULN at screening (Week −5)
12) Patients with a history or current renal dysfunction, nephritic syndrome, or nephritis and with estimated glomerular filtration rate (eGFR) of ≤30 mL/min/1.73 m^2 at screening (Week −5)
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 therapy 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 screening (Week −5)
15) Patients with a history of drug, alcohol, or cocaine abuse within the past 2 years prior to screening (Week −5)
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 screening (Week −5)
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 screening (Week −5)
18) Patients who took the IMP in Trial 346-102-00001, or patients who have used ETC-1002 in the past
19) Patients who used or received the following drugs (including food) or therapies within the specified period or who are planning to use or receive them by the end of the tests at Week 12

	Drugs (including food) or therapies	**Prohibited period**
1.	Systemic corticosteroids	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, the drug may be used concomitantly with no change in dose from 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable).
2.	Lomitapide	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	PCSK9 Inhibitors	From 4 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)

	Drugs (including food) or therapies	Prohibited period
4.	[redacted]	[redacted]
5.	Red yeast rice and food containing red yeast rice	From 2 weeks prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
6.	LDL apheresis	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)

20) Patients in whom the following drugs (therapies) are changed prior to Day 1 or in whom initiation of the following drugs (therapies) is planned by the end of the tests at Week 12

	Drugs or therapies	Period in which the drug or therapy cannot be changed or newly started
1.	Female or male hormone replacement	From 6 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
2.	Thyroid replacement	From 6 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Diabetes medications	From 4 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Obesity medications	From 3 months prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)

21) Patients whose LDL-C level at Week −1 has changed by at least ±20% as compared with that at screening (Week −5)

22) Patients with <80% compliance with the single-blind placebo up to Day 1 during the placebo run-in period or who cannot continue drug administration due to safety issues

23) Patients in whom a muscle-related AE other than due to strain, trauma, or other obvious etiology newly occurs or is aggravated during the placebo run-in period

24) Patients otherwise judged inappropriate for participating in the trial in the opinion of the investigator or subinvestigator

A definition of childbearing potential can be found in Section 10.3.

Subjects must agree to the restrictions on medications and lifestyle described in Section 6.5.1 and Section 5.3, respectively.

[Rationale for the 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 breast-feeding has not been established.

3) to 9), 12), 15), 24) These criteria are set in consideration of safety.

10) to 11), 14), 18), 22) to 23) These criteria are set to appropriately evaluate the safety of ETC-1002.

13) This criterion is set to avoid the influence of such a surgery on ETC-1002 absorption, etc.

16) This criterion is set according to the Blood Sampling Criteria of the New Blood Program Advisory Committee to ensure the safety of subjects.

17), 19) to 20) These criteria are set to appropriately evaluate the efficacy and safety of ETC-1002.

21) This criterion is set to appropriately evaluate the efficacy of ETC-1002.

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 should not be changed from Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable). For dietary supplements that may affect cholesterol levels including LDL-C, the investigator or subinvestigator will explain to the subjects at each visit so that the intake status will not change from Week −4 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable), and record the intake status in the source document.

5.3.2 Caffeine, Alcohol, and Tobacco

For alcohol and tobacco, the usual amount of alcohol consumed and the number of cigarettes smoked prior to participation in the trial will be checked with the subject and documented in the source document. The investigator or subinvestigator will instruct subjects not to significantly increase the amount of alcohol consumed or the number of cigarettes smoked from Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable). 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 that has been received since before informed consent should not be changed from Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable). 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), but who is not enrolled in the placebo run-in period. All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespective 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

History of Hypercholesterolemia: Investigation Item
• Name of diagnosis • Date of diagnosis • Presence or absence of familial hypercholesterolemia • Classification and details of classification (according to the flowchart using the Suita score in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017,[1] and according to the flowchart using the score of the Hisayama Study in the Guidelines 2022[2]) • Statin response (inadequate response to statins, statin intolerance) • For patients with statin intolerance: Cause of statin intolerance and the name/daily dose of the statin

- Result of eligibility assessment
- Screen failure date
- Reason for screen failure
- Adverse events

Subjects who sign an ICF but do not enter the placebo run-in period (screen failure) will be allowed to re-screen. In the event that the subject is re-screened for trial participation, a new ICF must be signed.

6 Trial Treatments

Trial interventions used in this trial are a test product and a placebo. No trial interventions are used in this trial other than the IMP.

6.1 Trial Treatments Administered

6.1.1 Placebo Run-in Period

Subjects who are judged to be eligible at screening will proceed to the placebo run-in period, continue the treatment without changing the type or dose and regimen of lipid-lowering drugs that have been taken from before informed consent, and receive placebo once daily orally in a single-blind manner. The time of IMP administration should be same to the extent possible. The following information will be recorded in the eCRF: for the IMP, the number of tablets taken per day, start and end dates of administration; for lipid-lowering drugs, the name of the drug, route of administration, dose and frequency, daily dose, start and end dates of administration.

Subjects who are unable to fix the type or dose and regimen of lipid-lowering drugs will be withdrawn from the trial. Subjects with noncompliance with less than 80% compliance with the single-blind placebo throughout the placebo run-in period will be withdrawn from the trial. The IMP compliance rate will be calculated using the following formula. See Section 7.3.2 for treatment discontinuation.

$$\text{IMP compliance rate (\%)} = \frac{\text{Actual number of days of taking single-blind placebo tablets}}{\text{Number of days specified to take single-blind placebo tablets throughout the placebo run-in period}^{a}} \times 100$$

[a]Number of days from the start day of administration of the single-blind placebo (on the day of Week −4) to the day before Day 1

6.1.2 Treatment Period

Subjects who are randomized and proceed to the treatment period should continue to receive the lipid-lowering drugs that have been taken from before informed consent without changing the type or dose and regimen as in the placebo run-in period, and will

also receive ETC-1002 at 180 mg or placebo once daily orally. The time of IMP administration should be same to the extent possible. The following information will be recorded in the eCRF: for the IMP, the number of tablets taken per day, start and end dates of administration; for lipid-lowering drugs, the name of the drug, route of administration, dose and frequency, daily dose, start and end dates of administration. For information regarding the dose regimen and treatment period, see Section 4.1.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the IB and the separate procedures.

6.2.1 Packaging and Labeling

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

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

6.2.6 Investigational Medicinal Product Reserve Sample Requirements

Not applicable.

6.3 Measures to Minimize/Avoid Bias

In this trial, the placebo run-in period will be conducted in a single-blind manner while the treatment period will be conducted in a double-blind manner. In the treatment period, stratified randomization by statin response (inadequate response to statins/statin intolerance) will be performed to minimize the influence on the evaluation. Subjects will be randomized to each group in a ratio of 1:1. Details of randomization will be provided in a separate procedure. Neither the subjects 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) cannot know the IMP randomization code during the trial.

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.

Procedures for breaking the blind can be found in Section 8.8.7.

Maintenance of blinding for the efficacy endpoints is described 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 or to the completion of the assessments at Discontinuation Visit.
- Comply with the dosage regimen, duration, and frequency of administration of the IMP and, if any, concomitant lipid-lowering drugs taken since before informed consent. Subjects with less than 80% compliance with the single-blind placebo tablets throughout the placebo run-in period will be withdrawn from the trial.
- Use appropriate contraceptive methods.
- Note the lifestyle considerations (see Section 5.3).
- Fill in the subject diary (see Section 8.10.1) every day while taking the IMP, and bring it to the visit.

6.5 Concomitant Medications or Therapies

The investigator or subinvestigator will record all of the following drugs (therapies) in the eCRF during the specified collection period.

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.

Drug (therapy)	Collection period
Lipid-lowering drugs	From 6 weeks prior to the date of informed consent to Week 12 or discontinuation

Drug (therapy)	Collection period
Diabetes medications	From 7 weeks prior to the date of informed consent to Week 12 or discontinuation
All concomitant medications other than lipid-lowering drugs and diabetes medications or concomitant therapies	From 4 weeks prior to the date of informed consent to Week 12 or discontinuation
Concomitant medications or therapies that have caused AEs or been used for the treatment of AEs	From the first day of use to the final observation day of the subject

6.5.1 Prohibited Medications or Therapies

6.5.1.1 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		
	Drugs (including food)	**Prohibited period**
1.	Systemic corticosteroids	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, the drug may be used concomitantly without a change in dose from 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable).
2.	Lomitapide	From 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	PCSK9 Inhibitors	From 4 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	[redacted]	[redacted]
5.	Red yeast rice and food containing red yeast rice	From 2 weeks prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)

6.5.1.2 Prohibited Therapies

LDL apheresis is prohibited from 3 months prior to Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable). If performed, the subject will discontinue the trial.

6.5.2 Permitted Medications or Therapies

Lipid-lowering drugs (excluding PCSK9 inhibitors) used from before informed consent should be continued without changing the type or dose and regimen until the end of tests at Week 12 of the treatment period (or to the completion of the assessments at Discontinuation Visit, if applicable). If any medication or therapy shown in Table 6.5.2-1 has been taken or used from before informed consent, the type or 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 6.5.2-1 List of Medications or Therapies Permitted Before and During the Trial

	Drugs or therapies	Period in which the drug or therapy cannot be changed or newly started
1.	Female or male hormone replacement	From 6 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
2.	Thyroid replacement	From 6 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Diabetes medications	From 4 weeks prior to Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Obesity medications	From 3 months prior t Day 1 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
5.	Diet therapy	From Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)
6.	Exercise therapy	From Week −5 to the end of the tests at Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable)

6.5.3 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

At sites that are conducting a separately planned long-term trial (Trial 346-102-00003), subjects who complete this trial may be allowed to participate in the long-term trial. When participating in the long-term trial, the subjects must meet the eligibility requirements specified in the protocol, and provide a new written informed consent based on their voluntary decision during the enrollment period of the long-term trial. The subjects should be enrolled in the long-term trial after the completion of all observations, tests, and assessments at Week 12, and their records in the source document and the eCRF must be completed within 5 days after the completion of Week 12 in principle and by the day before the next visit date after Day 1 of the long-term trial, at the latest.

7 Discontinuation of Trial/Treatment and Subject Discontinuation/Withdrawal

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 trial discontinuation to be necessary during the placebo run-in period or the treatment period, the assessments at Discontinuation Visit specified in Table 1.3-1 will be performed within 2 days after the last dose of IMP to the extent possible. In the case of the trial discontinuation of subjects who have proceeded to the treatment period, such subjects should additionally receive the same tests as in the follow-up period (Week 16).

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 entered 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 the eligibility criteria
  - Assessed as ineligible based on the eligibility assessment at Week −1 and Day 1
- Significant 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 or dose and regimen of lipid-lowering drugs concomitantly used with the IMP (including adding a new lipid-lowering drug)
- Lost to follow-up
- Pregnancy (see Section 10.3)
- Site terminated by the sponsor
- Trial terminated by the sponsor
- Withdrawal by the subject's request
- 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 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 in some follow-up procedures refused by the subject).
- 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 for 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 at Week 12, 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?", "Date of contact/Date of final contact attempt" and "Contact method" will be recorded in the eCRF.

8 Trial Procedures

The 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 for LDL-C, non-HDL-C, TC, HDL-C, TG, apo B, hsCRP, and HbA1c will be collected.

- Blind items: LDL-C, non-HDL-C, TC, apo B, and hsCRP

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. If a subject cannot visit the trial site in a fasting state, the subject should not undergo blood sampling but 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 again 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 measured using the direct method and calculated using the Friedewald formula (TC−HDL-C−TG/5). 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 of the blind items obtained from the start of IMP administration on Day 1 to Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable) will not be reported to the trial

site and the sponsor. The test results will be stored strictly by the central laboratory, disclosed to the trial site after unblinding, and provided to the sponsor in electronic files. In addition, the measurement of the blind items at the laboratory of trial sites is not allowed for the samples obtained from the start of IMP administration on Day 1 to Week 12 (or to the completion of the assessments at Discontinuation Visit, if applicable).

8.2 Pharmacokinetic Assessments

Not applicable.

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

Future Biospecimen Research (FBR) samples will be collected at the time points described in the Schedule of Assessments (Table 1.3-1).

[Rationale of sample storage for FBR]

Storage of DNA will be done to perform genomic/genetic analysis for cases in which additional explanation about the pharmacokinetics of ETC-1002 is required or new findings on genes and pharmacokinetics are obtained, and/or genomic/genetic analysis related to drug response (efficacy or safety) to the IMP or disease is judged to be useful. Regarding the collection and storage of DNA samples during the trial period, the Ministry of Health, Labour and Welfare states in the Q&A 1 of “Clinical Trials That Use Pharmacogenomics (PFSB/ELD Notification No. 0930007 dated 30 Sep 2008)” that it is possible to collect samples for genomic/genetic analysis related to the evaluation of the IMP (pharmacokinetics, efficacy, safety, etc.) from subjects in either of following cases:

1) the samples for which the targets and timing of genomic/genetic analysis have been specifically identified at the time of the trial, 2) the samples for which the targets and timing of genomic/genetic analysis have not been specifically identified at the time of the trial and analysis related to the evaluation of the IMP will be conducted in the future. In the same Q&A 2, it is stated that samples for genomic/genetic analysis with the objectives including the search for disease-related genes unrelated to the evaluation of the IMP can be obtained from subjects.[16] In addition, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) states in Section 1.4. General Principles of ICH E18 Guideline on Genomic Sampling and Management of Genomic Data, "With advances in science and increased awareness of the impact of genomics, there is a need and an opportunity to maximize the value of the collected samples and the data generated from them. Therefore, genomic sample acquisition is strongly encouraged in all phases and studies of clinical development."[17] In addition to the above, since the sample will be collected at the same timing as other tests to reduce the burden on subjects as much as possible, it is considered appropriate to collect and store optional DNA samples.

Serum samples for biomarker exploration will be also stored to conduct a biomarker exploration study when biomarker discovery related with drug response (eg, efficacy and safety) to the IMP or with disease is considered useful. The sample collection will be performed only at trial sites that have agreed in advance to store samples for biomarker exploration and only for subjects who have provided written consent for biomarker sample storage. Since biomarkers are expected to improve the R&D productivity of drugs and the sample will be collected at the same timing as other tests to reduce the burden on subjects as much as possible, it is judged appropriate to collect optional samples for biomarker exploration and store them.

8.6.1 Scope of Future Biospecimen Research

Future Biospecimen Research samples will be collected from subjects who consent to this sample collection. Research performed on these samples may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics, and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from subjects who have provided appropriate consent. The objective of collecting specimens for FBR is to explore and

identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

8.6.2 Summary of Procedures for Future Biospecimen Research Samples

All subjects enrolled in the clinical trial will be considered for enrollment in the optional FBR substudy.

After obtaining informed consent, the following FBR specimens will be obtained:

- Blood for DNA analysis (2 mL whole blood; includes ethylenediaminetetraacetic acid as an anticoagulant)
- Serum for measurements of proteins, sugars, and other molecules (volume of blood sampling: 2 mL)

The presence or absence of blood collection for DNA sample storage and the date of the sample collection will be recorded in the eCRF. The date and time of collecting samples for biomarker exploration will be recorded in the eCRF. Additional information will be provided in a manual prepared separately. If an FBR substudy is planned, a separate document describing the analysis may be prepared, and the results may be reported separately from the clinical study report (CSR).

8.6.3 Storage of Future Biospecimen Research Samples

Biospecimen research samples will be retained in the biorepository for potential analysis until: 1) genomic/genetic analysis and biomarker exploration are deemed unnecessary; 2) 15 years (DNA samples) or 5 years (biomarker samples) have passed since the informed consent of the first subject; or 3) the subject withdraws consent to storage of FBR samples, whichever comes first.

8.6.4 Genomic/Genetic Analysis and Biomarker Exploration

Genomic/genetic analysis will be conducted only if it is considered useful as an exploratory investigation regarding variations in DNA characteristics related to individual differences in drug response (including efficacy, safety, or PK) to the IMP and/or variations in disease-related DNA characteristics, or as a basic investigation for development to treat disease or promote health. Biomarker exploration will be conducted

only if it is considered useful to explore a biomarker related to drug response (including efficacy and safety) to the IMP and/or a disease-related biomarker.

If the conduct of the research is determined, a protocol will be separately prepared and approved by the sponsor's research review committee. Then, the research will be conducted in accordance with the local regulations to be followed for analysis. Results will not be included in the CSR, but will be reported separately.

The target of genomic/genetic analysis cannot be identified at present, and genome-wide association analysis using DNA chip, microarray, or next-generation sequencer may be performed. Biomarkers for measurement and analyses may include proteins, lipids, or RNA in the samples, but cannot be identified at this time, including any analytical methods. However, the results will not be used for purposes other than the above.

8.6.5 Acquisition and Withdrawal of Informed Consent for Future Biospecimen Research

Written information for the storage of FBR samples and exploratory research using the samples will be prepared separately from that for the trial, and the informed consent form will be signed. The date of informed consent will be recorded in the source document and the eCRF.

If the subject withdraws consent to storage of FBR samples during the storage period, the sponsor will request the biorepository to destroy the samples and the biorepository will destroy the samples in such a way that the subject cannot be identified. However, if any personal sample cannot be identified, for example, in the case where the information that links the sample with the subject's information (such as the code list) is discarded, the sample of the subject who withdrew the consent may not be destroyed as a result.

Even if the participation in the trial is withdrawn, it does not mean that the storage of FBR samples is canceled unless the subject separately withdraws consent to the storage of FBR samples. If the results of genomic/genetic analysis and/or biomarker exploration have already been obtained by the time of withdrawal of consent, the results will not be discarded.

8.6.6 Disclosure of Results of Genomic/Genetic Analysis and Biomarker Exploration to Subjects

Even if some findings are obtained as a result of analyses, the results are exploratory or at an early stage of research, and therefore scientific reliability such as precision and

certainty cannot be sufficiently confirmed. In principle, the sponsor will not disclose the results of genomic/genetic analysis and biomarker exploration to subjects because disclosure of information that has not been established the reliability of scientific evaluation will not be beneficial to subjects.

8.7 Safety Assessments

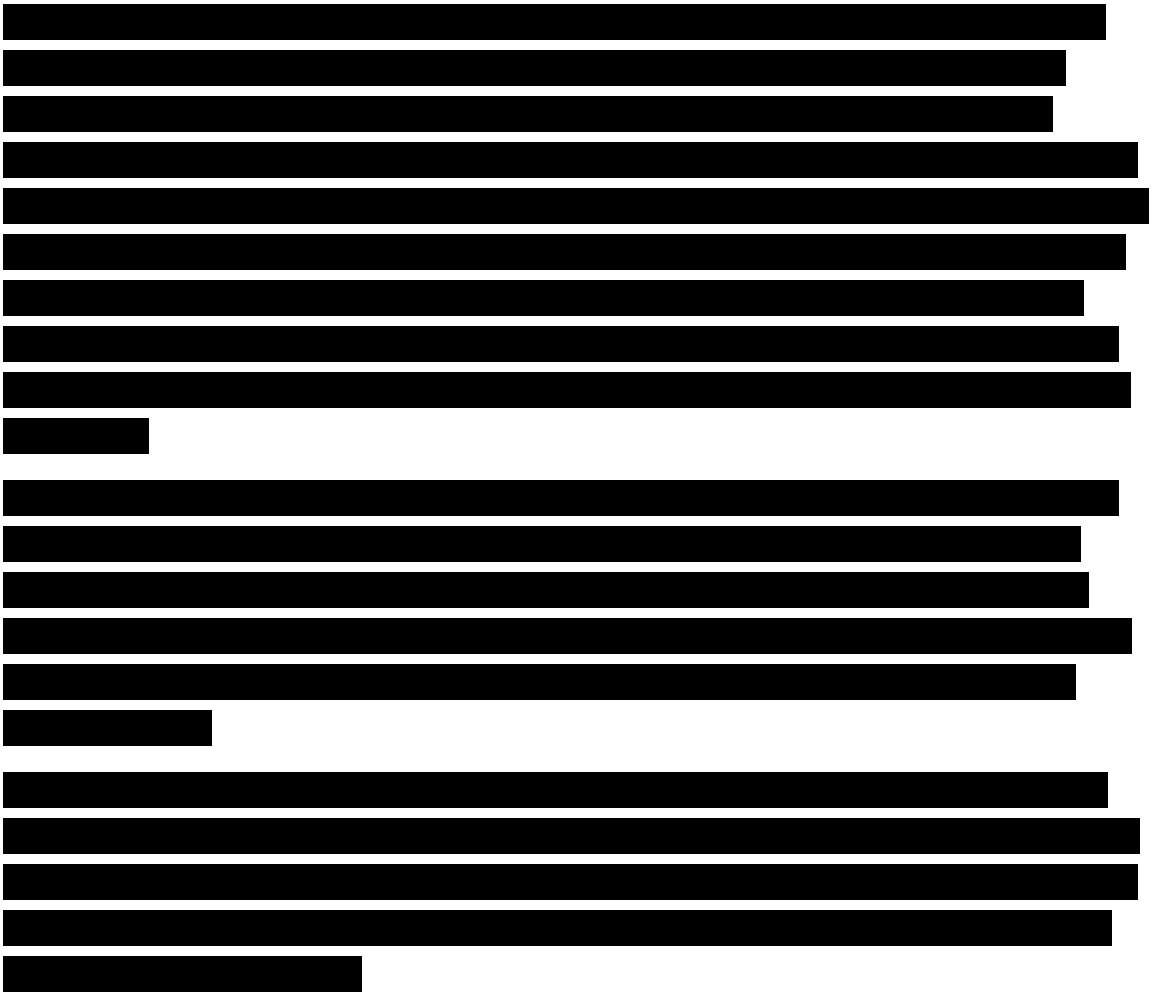
If a “new abnormality” or “exacerbation” is observed in the observation/examination items shown in the following sections after the start of the IMP administration which is judged to be clinically significant for the subject by the investigator or subinvestigator as compared to before administration, 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 Schedule 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 Schedule 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 not undergo blood sampling but 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 again 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.



8.7.2 Physical Examination

Physical examinations will be performed at the time points described in the Schedule of Assessments (Table 1.3-1). The investigator or subinvestigator will perform physical examinations for the following assessments by methods such as interview and record the date and results of the assessment 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 and Day 1, the dates and results of the examinations will be recorded in the source document and the eCRF. At the other time points, only the date of the examination will be recorded. If clinically significant physical findings, which are compared with Week −5 during the screening and

placebo run-in periods and compared with Day 1 during the treatment and follow-up periods, are observed, those findings will be recorded as AEs.

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

8.7.3 Vital Signs

Vital signs will be measured at the time points described in the Schedule of Assessments (Table 1.3-1) after resting for at least 5 minutes. The vital signs should be measured before blood collection whenever possible to minimize the effects on the assessment. 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 a sitting position after resting for at least 5 minutes according to the procedures specified by the trial site. The date 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 Schedule of Assessments (Table 1.3-1) after resting for at least 10 minutes. The 12-lead ECG should be performed before blood collection whenever possible to minimize the effects on the assessment. Subjects should be monitored for potentially clinically significant ECG results.

The investigator or subinvestigator will perform the ECG according to the procedures specified at each trial site and record the date of measurement, heart rate, PR interval, RR interval, QRS width, QT interval, and QTcF in the source document and the eCRF. The investigator or subinvestigator will determine normality/abnormality by the assessment of the measurements, and record the determinations in the source document and the eCRF. Any abnormal findings will be recorded in the source document and the eCRF.

The sponsor may request to provide a copy of the ECG chart for any reason, including additional safety analysis.

8.7.5 Suicidality Monitoring

Not applicable.

8.7.6 Other Safety Variables

8.7.6.1 Body Weight

Body weight will be measured at the time points described in the Schedule of Assessments (Table 1.3-1), and the dates and results of the measurements will be recorded in the source document and the eCRF (in units of 0.1 kg [if measured to the second decimal place or less, the second decimal place will be rounded.]). 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).

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a trial intervention* and does not necessarily have a causal relationship with this treatment. In this trial, any untoward medical occurrence in a subject not receiving the trial intervention 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 a trial intervention related to any dose administered.

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

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of IMP treatment. In more detail, TEAEs are all AEs which started after the start of IMP treatment; or if the event was continuous from baseline and worsened after the start of IMP treatment.

* Refer to the guidance in Article 2 of the revised GCP. No trial interventions other than the IMP will be used in this clinical trial.

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 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 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 and there is an abnormality or medical problem.

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 confirm the results of the original

laboratory tests. However, the central laboratory should not report the results of any repeated or additional tests for the blind items (see Section 8.1) obtained between Day 1 (the start of IMP treatment) and Week 12 to the trial site and the sponsor to maintain the blind. As for LDL-C, 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. However, if an abnormal result is found in a test performed at the central laboratory and is considered an AE, the course should be confirmed with the test results of the central laboratory in principle.

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 the 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 end of the follow-up period. All AEs must be recorded in the eCRF after subject informed consent has been obtained, including screening failures due to AEs, irrespective of trial intervention. In this trial, AEs during the screening and placebo

run-in periods will be assessed compared to Week −5, and those during the treatment and follow-up periods will be assessed compared to Day 1.

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 or later, the AE should be reported as a new AE in the eCRF without limiting to worsening in severity or seriousness. If a subject is suspected to have COVID-19 during the trial, the investigator or subinvestigator will confirm the results of an antigen test, etc., and take necessary measures such as a determination on the necessity for discontinuation of the IMP, in consideration of the safety of the subjects. A positive result will be reported as an AE in the eCRF.

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 AE, 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 the last scheduled contact (Week 16, 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 have resolved,
- The events have stabilized,
- The subject is lost to follow-up, or
- The subject 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 or subinvestigator to be reasonably associated with the use of the trial intervention, 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 IB. 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 judged able to receive the IMP to enter the status of compliance with the IMP and lipid-lowering drugs, status of diet/exercise therapy and lifestyle (alcohol intake, smoking), and presence or absence of subjective symptoms in the subject diary, and bring it to the visit. The investigator or subinvestigator will record the status of compliance with the IMP and lipid-lowering drugs 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 females 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. Subjects with a positive urine test will be withdrawn from the trial. However, any positive urine test on or after the placebo run-in period will lead to a re-test using serum to confirm the diagnosis, and the date of blood sampling will be recorded in the source document and the eCRF. If the serum test is positive, the investigator or subinvestigator will report it to the sponsor as an IRE.

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 to confirm eligibility of subjects regarding thyroid and liver function. The date 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

9.1 Sample Size

[redacted]

9.2 Datasets for Analysis

The safety analysis set will include subjects who receive at least one dose of the IMP during the treatment period.

The full analysis set will include subjects who receive at least one dose of the IMP during the treatment period, and who have LDL-C measurements at baseline and at one or more time points after administration of the IMP during the treatment period.

9.3 Handling of Missing Data for Primary Endpoint Analysis

In the primary analysis of the primary endpoint, a mixed-effects model repeated measures (MMRM) analysis assuming missing at random (MAR) will be performed using observed cases (OC) data set without imputation of missing data. Placebo multiple imputation, etc. assuming missing not at random will be performed as a sensitivity analysis for the handling of missing data. Details will be described in the statistical analysis plan.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary endpoint is the percent change from baseline to Week 12 in LDL-C measured by the direct method. Baseline is defined as the mean of the LDL-C values for Day 1 and Week −1. The MMRM analysis assuming MAR will be performed using OC data. The treatment comparison will be based on differences in the least-squares mean between the ETC-1002 group and the placebo group at Week 12. A two-sided significance level of 5% will be used. The model will include the treatment group, randomization stratification factor, time, and treatment-by-time interaction as factors, and baseline and baseline-by-time interaction as covariates. The error covariance structure will be unstructured. The Kenward-Roger method will be used for the degrees of freedom approximation. If any problem occurs in the convergence status in the estimation of the variance components, the following structure will be used in the order of heterogeneous toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry, and the first error covariance structure that converges will be used. If a structure other than unstructured is selected, a sandwich estimator of the standard error will be used.

9.4.1.2 Key Secondary Efficacy Endpoint Analysis

Not applicable.

9.4.1.3 Secondary Efficacy Endpoint Analysis

The same MMRM analysis as used for the primary endpoint will be performed for non-HDL-C and TC. The baseline is defined as the mean of Day 1 and Week −1 for both non-HDL-C and TC.

For apo B, hsCRP, and HbA1c, an analysis of covariance will be performed using OC data. The model will include the treatment group and the randomization stratification factor of statin response (inadequate response to statins/statin intolerance) as factors, and the baseline for each endpoint as a covariate.

The proportion of subjects whose LDL-C value achieves the lipid management goals (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk], or <140 mg/dL [intermediate risk]) at

Week 12 will be analyzed by the Cochran-Mantel-Haenszel test, stratified by statin response (inadequate response to statins/statin intolerance), and the difference in proportions between the ETC-1002 group and the placebo group, and the two-sided 95% confidence intervals (based on the Cochran-Mantel-Haenszel test) will be calculated. In cases where the LDL-C at Week 12 is missing, it will be handled as not achieving the lipid management goals.

9.4.1.4 Control of Experiment-wise Type 1 Error

Not applicable.

9.4.1.5 Other Efficacy Endpoint Analysis

The same MMRM analysis as used for the primary endpoint will be performed for HDL-C and TG.

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 (inadequate response to statins, statin intolerance)

9.4.2 Safety Analysis

Safety analyses will be performed using the safety analysis set. The same summarization will also be performed by randomization stratification factors (statin response).

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 by treatment group:

- Treatment-emergent AEs
- TEAEs by severity
- TEAEs causally related to the IMP
- TEAEs with an outcome of death

- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- [redacted]

9.4.2.2 Clinical Laboratory Data

For parameters other than qualitative urinalysis, descriptive statistics of the actual value and change from baseline will be calculated by treatment group at each time point. For qualitative urinalysis parameters, shift tables at each time point from baseline will be prepared by treatment group. 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 by treatment group.

The number and percentage of subjects meeting Criteria for Identifying Laboratory Values of Potential Clinical Relevance will be calculated by treatment group.

9.4.2.3 Physical Examination and Vital Signs Data

Physical examination results will be tabulated.

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 by treatment group.

The number and percentage of subjects meeting Criteria for Identifying Vital Signs of Potential Clinical Relevance will be calculated by treatment group.

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 by treatment group. The number and percentage of subjects with an actual value of QTcF of >450 msec, >480 msec, or >500 msec at any postdose time point will be calculated by treatment group. In addition, the number and percentage of subjects with a change from baseline in QTcF of >30 msec or >60 msec at any postdose time point will be calculated by treatment group. Similarly, the number and

percentage of subjects meeting these criteria at each postdose time point will also be calculated by treatment group.

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

The number and percentage of subjects meeting Criteria for Identifying ECG Measurements of Potential Clinical Relevance will be calculated by treatment group.

9.4.2.5 Other Safety Data

Descriptive statistics of the actual value and change from baseline will be calculated at each time point for body weight by treatment group.

The number and percentage of subjects meeting Criteria for Identifying Body Weight of Potential Clinical Relevance will be calculated by treatment group.

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 in each analysis set by treatment group.

9.4.3.2 Pharmacokinetic Analysis

No pharmacokinetic analysis is planned.

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.

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), as well as by any other parties required by the IRB. 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 and standard operating procedures.

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 (excluding FBR documents) 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.

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, 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
- The period of FBR sample storage.

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 or his/her partner 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, or 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. 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
- The 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.

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ADDITIONAL RISK TO THE SUBJECT:

No further risk is imposed on 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	DD Mon YYYY Date

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