CLINICAL STUDY PROTOCOL

A Multicenter, Open-label, Uncontrolled, Long-term Trial to Assess the Safety and Efficacy of ETC-1002 in Patients With Hyper-LDL Cholesterolemia

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

NCT Number: NCT05687071
Protocol No. 346-102-00003
Version Date: 04 Oct 2022 (Version 1.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

ETC-1002 (Nonproprietary name: Bempedoic acid)
Translation of Japanese Original
CLINICAL PROTOCOL

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Protocol No. 346-102-00003

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	Office of PV Operations, Department of Pharmacovigilance, Otsuka Pharmaceutical Co., Ltd. [redacted]
Approval:	04 Oct 2022
Date of Translation:	16 Jan 2023

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
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
CSR	Clinical study report
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
eICF	Electronic informed consent form
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
MACE	Major adverse cardiac event
non-HDL-C	Non-high-density lipoprotein-cholesterol
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
SAE	Serious adverse event
TC	Total cholesterol

Abbreviation	Definition
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.:

346-102-00003

Protocol Title:

A multicenter, open-label, uncontrolled, long-term trial to assess the safety and efficacy of ETC-1002 in patients with hyper-LDL cholesterolemia

Protocol Lay Person Short Title:

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

Clinical Phase:

Phase 3 trial/Long-term trial

Treatment/Indication:

Hyper-low-density lipoprotein (LDL) cholesterolemia

Objectives and Endpoints:

Objectives	Endpoints
Primary Objective: • To assess the safety of ETC-1002 at 180 mg administered for 52 weeks in patients with hyper-LDL cholesterolemia	Safety Assessments: • Adverse events (AEs), clinical laboratory tests, vital signs (blood pressure, pulse rate, and body temperature), body weight, physical examination, and 12-lead electrocardiogram (ECG)
Secondary Objectives: • To assess the effects of ETC-1002 at 180 mg administered for 52 weeks on LDL-C in patients with hyper-LDL cholesterolemia • 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)	Efficacy Assessments: • Percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to Week 52 • Percent change in non-HDL-C, TC, apo B, hsCRP, and HbA1c from baseline to Week 52 • 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 52

Objectives	Endpoints
Other Efficacy Assessments: • To assess the effects of ETC-1002 at 180 mg administered for 52 weeks on HDL-C and triglycerides (TG) in patients with hyper-LDL cholesterolemia	Other Efficacy Assessments: • Percent change in HDL-C and TG from baseline to Week 52

Trial Design:

A multicenter, open-label, uncontrolled, long-term trial

Trial Population:

This is a multicenter, open-label, uncontrolled, long-term trial to assess the safety and efficacy of ETC-1002 long term administration in patients with hyper-LDL cholesterolemia, who are receiving treatment 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 who are determined to have difficulty in treatment with statins due to the occurrence of or potential for safety problems and cannot achieve the lipid management goals. Subjects who have completed the treatment period in the phase 3 confirmatory trial (Protocol No. 346-102-00002) can also be enrolled in this trial, as they are in the same population and their enrolment allows assessments of the occurrence of AEs over a longer period.

The number of subjects starting the treatment is set at 120 to ensure that at least 100 patients complete the treatment at Week 52. The number of patients who have difficulty in treatment with statins is planned to be at least 20% among the entire number in this trial.

Key Inclusion/Exclusion Criteria:

Inclusion Criteria

<Newly enrolled subjects >

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 who have difficulty in treatment with statins as defined below

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

- Inadequate response to statins: Patients with hyper-LDL cholesterolemia who are currently taking or have previously taken statins, and cannot achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)), meeting any of the following a), b), or c)
  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 for fibrates and selective peroxisome proliferator-activated receptor [PPAR]α modulators, and at least 3 months for proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors)
  c) Patients who have previously experienced failure to achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)) even after taking statins within the approved dose range for at least 4 weeks and currently, based on medical judgment, who are taking only nonstatins at the same dose and regimen from at least 4 weeks before informed consent (at least 6 weeks for fibrates and selective PPARα modulators and at least 3 months for PCSK9 inhibitors)
  An outline is presented below.

Category	LDL-C during the screening period	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 • PCSK9 inhibitors: From at least 3 months 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
c)		Only nonstatins	• Fibrates, selective PPARα modulators: From at least 6 weeks before • PCSK9 inhibitors: From at least 3 months before • Drugs other than the above: From at least 4 weeks before	Same dose and regimen

- Difficulty in treatment with statins:

  Of those 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, or of those patients who have a history of statin administration and who are judged to have concerns of safety problems associated with the administration or dose increase of statins, those who fail to achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)), meeting any of the following a), b), or 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 for fibrates and selective PPARα modulators, and at least 3 months for PCSK9 inhibitors)

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 for fibrates and selective PPARα modulators, and at least 3 months for PCSK9 inhibitors)

An outline is presented below.

Category	LDL-C during the screening period	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 • PCSK9 inhibitors: From at least 3 months 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 • PCSK9 inhibitors: From at least 3 months 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 during the screening period
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 −2, 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 Week −2

< Rollover subjects from the phase 3 confirmatory trial>

1) Patients who provide written informed consent prior to start of the trial
2) Subjects who have completed the 12-week treatment period in the phase 3 confirmatory trial (Protocol No. 346-102-00002), and do not meet the discontinuation criteria for the investigational medicinal product (IMP) at Week 12

Exclusion Criteria

<Newly enrolled subjects>

1) Females who are pregnant or breast-feeding or who have a positive pregnancy test (urine) result at screening (Week −2) 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 −2) any of the following cardiovascular diseases, or those who have developed any of these AEs during the screening 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 −2)
6) Patients with uncontrolled and serious hematologic or coagulation disorders, or with hemoglobin of <10.0 g/dL at screening (Week −2)
7) Patients with uncontrolled diabetes with HbA1c of ≥9% at screening (Week −2)
8) Patients with uncontrolled hypothyroidism with thyroid-stimulating hormone (TSH) of >1.5 × the upper limit of normal (ULN) at screening (Week −2)
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 −2)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of ≥3 × ULN or total bilirubin of ≥2 × ULN at screening (Week −2)

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 −2)
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 −2)
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 −2)
15) Patients with a history of drug, alcohol, or cocaine abuse within the past 2 years prior to screening (Week −2)
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 −2)
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 −2)

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 52

	Drugs (including food) or therapies	Prohibition period
1.	Systemic corticosteroids	From 3 months prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, if the drug has been used with the same dose and regimen since 3 months prior to Week −2, it may be used concomitantly with no change in dose until the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
2.	Lomitapide	From 3 months prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Probenecid	From Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Red yeast rice and food containing red yeast rice	From 2 weeks prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
5.	LDL apheresis	From 3 months prior to Week −2 to the end of the tests at Week 52 (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 52

	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 52 (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 52 (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 52 (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 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

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

<Rollover subjects from the phase 3 confirmatory trial>

1) Females who are pregnant or breast-feeding or who have a positive pregnancy test (urine) result 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, at least 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 any of the following AEs during the phase 3 confirmatory trial (Protocol No. 346-102-00002)

- Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, symptomatic carotid artery stenosis, symptomatic peripheral arterial disease, or decompensated heart failure
- Abdominal aortic aneurysm
- Unexplained syncope or torsade de pointes-type ventricular tachycardia

4) Patients with uncontrolled hypertension, defined as follows: sitting systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥100 mmHg after resting for 5 minutes on Day 1
5) Patients with uncontrolled and serious hematologic or coagulation disorders, or with hemoglobin of <10.0 g/dL at Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)
6) Patients with liver disease or dysfunction, including:

- Patients with positive serology for HBsAg or a positive HCV antibody test by Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)
- Patients with AST or ALT of ≥3 × ULN or total bilirubin of ≥2 × ULN by Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)

7) Patients with a history or current renal dysfunction, nephritic syndrome, or nephritis and with eGFR of ≤30 mL/min/1.73 m^2 at Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)
8) 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 52

	Drugs (including food) or therapies	Prohibition period
1.	Systemic corticosteroids	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, if the drug is being used with the same dose and regimen as before participation during the phase 3 confirmatory trial, it may be used concomitantly with no change in dose, until the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
2.	Lomitapide	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Probenecid	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Red yeast rice and food containing red yeast rice	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
5.	LDL apheresis	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

9) 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 52

	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 52 (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 52 (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 52 (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 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

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

Trial Sites:

Approximately 30 sites in Japan

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

Subjects who proceed to the treatment period will orally receive ETC-1002 180-mg tablets once daily for 52 weeks. Administration of lipid-lowering drugs used before informed consent should be continued without changing the type or dose and regimen.

Trial Assessments:

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

Trial Assessments for Future Biospecimen Research (FBR): DNA sample storage (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:

Safety Analysis

The incidence of treatment-emergent AEs will be calculated. Other safety assessments will be summarized using descriptive statistics, shift tables, etc.

Sample Size

The target number of subjects is set at 120 to ensure that 100 subjects will complete the 1-year treatment to assess the safety of ETC-1002 in long-term administration.

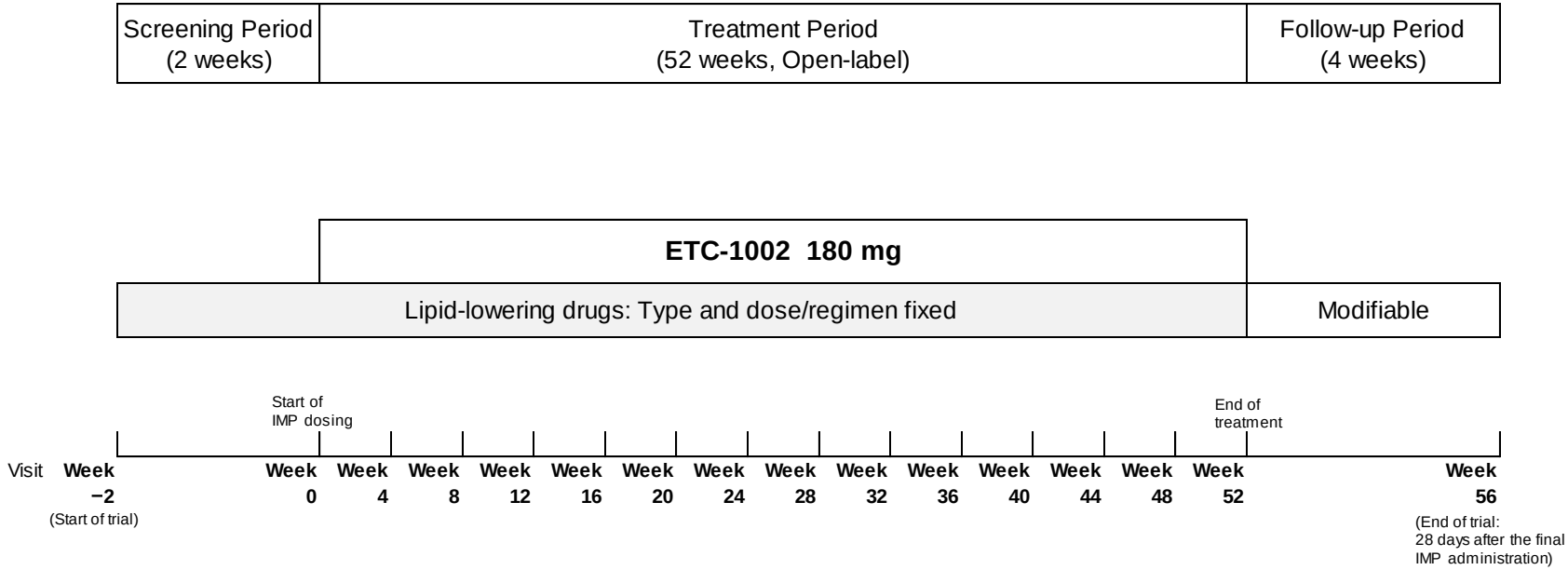
Trial Duration:

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

- Screening period (2 weeks)
- Treatment period (52 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 20 months.

1.2 Schema



[Rollover subjects from Trial 346-102-00002 will proceed directly to the treatment period of this trial (52 weeks, open-label) after completing the 12-week double-blind treatment period.]

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

	Screening Period		Treatment Period														Follow-up Period (28 days after the final IMP administration)
	Rollover Subjects	Newly Enrolled Subjects															
Visit (Week)	−4[a]	−2	0[b]	4	8	12	16	20	24	28	32	36	40	44	48	52/ Discontinuation[c]	56
Trial Day	−28 ± 3	−14 ±7	1	29 ± 7	57 ± 7	85 ± 7	113 ± 7	141 ± 7	169 ± 7	197 ± 7	225 ± 7	253 ± 7	281 ± 7	309 ± 7	337 ± 7	365 ± 7	393 ± 7
Informed consent[d]	●	●															
Eligibility assessment	●	●	●														
Demographics		●															
Physical examination	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Body weight		●	●	●		●		●	●	●		●		●		●	●
Endocrine test (TSH), virus test (HBsAg, HCV antibody)		●															
Vital signs[e]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
12-Lead ECG[f]		●	●			●			●			●				●	
Clinical laboratory tests[g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Fasting lipids[h, i]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
HbA1c[i]		●	●			●			●			●				●	
hsCRP, apo B[i]			●			●			●			●				●	
Confirmation of use of concomitant medications/therapies	◄																►
Adverse events	◄																►
Pregnancy test[j]		●	●			●			●			●				●	
Blood sampling for DNA storage[k]			○														
Dispensing of IMP			●	●	●	●	●	●	●	●	●	●	●	●	●		
Provision of subject diary			●	●	●	●	●	●	●	●	●	●	●	●	●		
Collection of unused IMP and subject diary				●	●	●	●	●	●	●	●	●	●	●	●	●	

● Mandatory; ○ Optional

[a]The results of the scheduled tests performed at Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002) will be used.

[b]Body weight and 12-lead ECG will not be required on Day 1 if they have been performed within 7 days prior to Day 1 in the screening period. The results of the scheduled tests performed at Week 12 in the phase 3 confirmatory trial (Protocol No. 346-102-00002) will be used for rollover subjects.

[c]In cases of early discontinuation during the treatment period, the same assessments as in Week 52 are to be performed at Discontinuation Visit within 2 days after the last dose of the IMP as far as possible.

[d]Written informed consent will be obtained from the patient himself/herself prior to any trial-related assessments. Written informed consent will be obtained by Week −2 for newly enrolled subjects, and by Week 12, but on or after Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002) for rollover subjects (before the start of Day 1 of this trial).

[e]Body temperature, blood pressure, and pulse rate measurements are to be performed after resting for at least 5 minutes. Vital signs should be measured before blood collection whenever possible to minimize effects on the assessment.

[f]12-Lead ECG is to be performed after resting for at least 10 minutes. The 12-lead ECG should be performed before blood collection whenever possible to minimize effects on the assessment.

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

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

[i]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.

[j]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 −2).

[k] Blood sampling for DNA storage will only be performed for subjects who provide written consent for sample collection. Blood sampling for DNA 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, 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 sample storage is optional and will not impact the subject's participation in the trial if the subject does not consent.

For rollover subjects, written informed consent will be obtained from the patients themselves by Week 12, but on or after Week 8 of the phase 3 confirmatory trial (Protocol No. 346-102-00002). The rollover subjects participating in DNA sample storage in the confirmatory trial will not be able to provide informed consent for DNA sample storage in this trial.

1.3.1.2 Screening Visit

After obtaining informed consent, the investigator or subinvestigator will perform the observation and assessments at Week −4 (rollover subjects) or Week −2 (newly enrolled subjects) 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. Re-testing during the screening period will be permitted in terms of eligibility assessment.

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)
- 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/difficulties in treatment with statins) • For patients with difficulties in treatment with statins: Reasons for judging that treatment with statins is difficult and the name/daily dose of the statin

<Information obtained during the screening period>

- Prior lipid-lowering drugs received within 6 weeks prior to informed consent
- Therapeutic drugs for diabetes mellitus used within 10 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 Treatment Period

The investigator or subinvestigator will determine whether or not a subject can proceed to the treatment period based on the results of the observation 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 a subject who is determined to be eligible for proceeding to the treatment period has been receiving a lipid-lowering drug since before informed consent, the subject should continue the drug at the same dose and regimen in addition to taking ETC-1002 at 180 mg/day for 52 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.

For subjects who are concomitantly using proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, all scheduled visits during the treatment period will be set within 48 hours before the scheduled date and time for subsequent doses of PCSK9 inhibitor.

1.3.3 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.

1.3.4 Discontinuation Visit

When the subject discontinues during the treatment period, the investigator or subinvestigator will perform the same assessments as performed at Week 52 (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] In such cases, combination therapy using drugs with mechanisms of action different from statins is performed. However, the fact that there are a certain number of patients with poorly controlled LDL-C who cannot achieve the lipid management goals remains an issue for current drug therapy. 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 2018,[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 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, ETC-1002 has already been approved and marketed for the treatment of hyper-LDL cholesterolemia in the US in February 2020 and in Europe in April 2020. 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") has obtained the development and marketing rights in Japan from Esperion Therapeutics, Inc. and started development in Japan, in the expectation 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. 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 has been demonstrated in several phase 3 placebo-controlled, double-blind trials and long-term 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. In addition, the results of the phase 1 trial in healthy Japanese and non-Japanese adults living outside Japan showed that C_{max} and AUC in Japanese subjects were approximately 1.2 fold and 1.4 fold those in white subjects, respectively. Although the C_{max} and AUC in Japanese subjects were slightly higher than those in white subjects, it has been demonstrated that there was no safety problem and that ETC-1002 was well-tolerated when administered at up to 180 mg/day to healthy Japanese adults.

In Japan, a phase 2 dose-finding trial (Protocol No. 346-102-00001) was conducted in 188 patients with hyper-LDL cholesterolemia to investigate the efficacy, dose-response,

and safety of ETC-1002 at 60 mg/day, 120 mg/day, 180 mg/day, and placebo. The percent change (least squares mean) in LDL-C from baseline to Week 12, which was the primary endpoint, was −10.59% in the ETC-1002 60-mg group, −21.85% in the 120-mg group, and −21.26% in the 180-mg group versus −1.92% in the placebo group. The percent changes were significantly high in all of the ETC-1002 groups ($p < 0.001$ in the 120-mg and 180-mg groups, and $p = 0.002$ in the 60-mg group). The incidence of AEs was 56.7% (80/141 subjects) in the ETC-1002 group versus 38.3% (18/47 subjects) in the placebo group. 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]). All of these events had already been observed in the phase 3 trials conducted outside Japan. All AEs were mild or moderate in severity with no severe events. Serious adverse events (SAEs) were reported in 2 subjects (in the 180-mg group [calculus urinary] and the placebo group [dental cyst]). However, both events were considered to be unrelated to the IMPs. The incidence of AEs in the ETC-1002 group was 58.3% (28/48 subjects) in the 180-mg group, 54.3% (25/46 subjects) in the 120-mg group, and 57.4% (27/47 subjects) in the 60-mg group, showing comparable incidences in all groups. There were no events whose incidence increased markedly in a dose-dependent manner. There were no clinically significant changes in clinical laboratory test values, vital signs, or 12-lead electrocardiogram (ECG) parameters in any of the treatment groups.

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. These results showed higher efficacy in the ETC-1002 120 and 180-mg groups than in the 60-mg group in both subject populations. The incidence of AEs was 54.5% (61/112 subjects) in the ETC-1002 group versus 35.1% (13/37 subjects) in the placebo group among subjects with inadequate response to statins, and 65.5% (19/29 subjects) in the ETC-1002 group versus 50.0% (5/10 subjects) in the placebo group among subjects with statin intolerance. 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]

[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]

Based on the above results, ETC-1002 was considered to be a treatment option with a new mechanism of action for patients with hyper-LDL cholesterolemia who are receiving treatment for hyper-LDL cholesterolemia but cannot achieve the lipid management goals due to inadequate control. Therefore, this clinical protocol has been planned as a phase 3 long-term trial to evaluate the safety and efficacy of ETC-1002 at 180 mg/day administered for 52 weeks in Japanese patients with hyper-LDL cholesterolemia.

2.2 Background

Efficacy data supporting the indication of LDL-C reduction have been obtained from 4 phase 3 and 10 phase 2 trials of ETC-1002 in 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. Available data thus far also show that ETC-1002 can be safely administered over a prolonged period in patients on statin treatment of the maximum tolerated dose.

Single-dose and multiple-dose trials were conducted in Japanese and non-Japanese (white and Chinese) healthy adult subjects living outside Japan to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of ETC-1002, and to determine whether there were differences in pharmacokinetics and pharmacodynamics between Japanese, white, and Chinese races. The results showed no significant differences in the mean plasma concentration over time between Japanese and white subjects following repeated administration of 180 mg of ETC-1002. The geometric mean C_{max} and AUC in Japanese subjects were approximately 1.2 fold and 1.4 fold those in white subjects, respectively. Although the geometric mean C_{max} and AUC in Japanese subjects were slightly higher than those in white subjects, no significant difference was observed. There were no SAEs or AEs leading to discontinuation and all AEs were mild in severity. It was demonstrated that there was no significant safety problem and that ETC-1002 at 180 mg/day was well-tolerated when administered to healthy Japanese adults.

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.

While a phase 3 confirmatory trial (Protocol No. 346-102-00002) has been designed based on the results of the phase 2 dose-finding trial, the present clinical trial has been planned to assess the safety and efficacy of ETC-1002 at 180 mg/day administered for 52 weeks in Japanese patients.

2.3 Known and Potential Risks and Benefits

In a drug-interaction trial conducted outside Japan, administration of ETC-1002 at 180 mg/day increased the exposure to simvastatin lactone approximately 1.2 to 1.3 fold and the exposure to simvastatin hydroxy acid approximately 2 fold. [redacted]

[redacted]

Serum uric acid increased was observed in the clinical trials conducted outside Japan. In pooled data from the phase 3 placebo-controlled trials, mean uric acid levels increased within the first 1 month, and then remained stable and returned to baseline in subjects who discontinued ETC-1002 for any reason. Serum uric acid increased may have been caused by inhibition of renal tubular organic anion transporter 2 by ETC-1002. Gout was reported in 1.4% of subjects receiving ETC-1002 and 0.4% of subjects receiving placebo. The slightly higher incidence of gout in the ETC-1002 group may be due to increased uric acid caused by ETC-1002.

Although gout did not occur in the Japanese phase 2 trial, blood uric acid increased was observed in 6 subjects (4.3%) and hyperuricaemia was observed in 5 subjects (3.5%) in the ETC-1002 groups. However, uric acid levels decreased rapidly after discontinuation in all subjects. Increased uric acid levels as an AE may cause gout, and is considered to be a significant potential risk.

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 addition, the incidence of muscle-related AEs or AEs associated with hepatic impairment, which are considered to be risk factors affecting drug adherence, was not significantly different from those in the placebo group. In the long-term trials conducted outside Japan, no new safety signals were identified for the long-term administration of ETC-1002 with the efficacy continuing to the end of the trial.

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 in Table 3-1.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary Objective: • To assess the safety of ETC-1002 at 180 mg administered for 52 weeks in patients with hyper-LDL cholesterolemia	Safety Assessments: • Adverse events, clinical laboratory tests, vital signs (blood pressure, pulse rate, and body temperature), body weight, physical examination, and 12-lead ECG
Secondary Objectives: • To assess the effects of ETC-1002 at 180 mg administered for 52 weeks on LDL-C in patients with hyper-LDL cholesterolemia • 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)	Efficacy Assessments: • Percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to Week 52 • Percent change in non-HDL-C, TC, apo B, hsCRP, and HbA1c from baseline to Week 52 • 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 52
Other Efficacy Assessments: • To assess the effects of ETC-1002 at 180 mg administered for 52 weeks on HDL-C and triglycerides (TG) in patients with hyper-LDL cholesterolemia	Other Efficacy Assessments: • Percent change in HDL-C and TG from baseline to Week 52

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a Japanese, multicenter, open-label, uncontrolled, phase 3 long-term trial to assess the safety and efficacy of ETC-1002 long-term administration 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 who are determined to have difficulty in treatment with statins and cannot achieve the lipid management goals. Patients with difficulty in treatment with statins are defined as those who cannot achieve the lipid management goals for the following reasons: patients who have experienced safety problems caused by statin administration which resolved after discontinuation or dose reduction, or patients who have a history of statin administration and are judged to have concerns of safety problems associated with the administration or dose increase of

statins. In addition, subjects who have completed the treatment period in the phase 3 confirmatory trial (Protocol No. 346-102-00002) can also be enrolled in this trial, as they are in the same population and their enrollment allows assessments of the occurrence of AEs over a longer period.

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

This trial consists of the screening period, the treatment period, and the follow-up period.

Subjects who are judged to be eligible at screening will proceed to the treatment period. Subjects proceeding to the treatment period who have been receiving treatment using lipid-lowering drugs since before informed consent should continue the treatment without changing the type or dose and regimen in addition to being orally administered ETC-1002 at 180 mg once daily for 52 weeks.

4.2 Scientific Rationale for Trial Design

This trial has been planned as an open-label trial with the primary objective of assessing the safety of ETC-1002 for 52 weeks in patients with hyper-LDL cholesterolemia based on "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (PAB/ELD Notification No. 592 dated 24 May 1995)." The trial population will include patients with hyper-LDL cholesterolemia with inadequate response to statins or difficulty in treatment with statins who cannot achieve the lipid management goals specified in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017,[1] and who are expected to similarly respond to ETC-1002 based on the results observed in the previous trials conducted outside Japan and the Japanese phase 2 trial.

Warnings for hyperuricaemia and tendon rupture are provided in the non-Japanese package insert for ETC-1002. In the Japanese phase 2 trial, AEs related to hyperuricaemia (all events were moderate or lower in severity) also occurred in 7.8% (11/141 subjects) of the Japanese subjects treated with ETC-1002. Furthermore, the results of clinical trials conducted outside Japan have shown that the concomitant use of ETC-1002 with statins increases exposure to the statins. Based on the above, laboratory values such as uric acid and CK levels will be monitored regularly to minimize safety risks in the subjects during the trial. In addition, although tendon rupture did not occur in the Japanese phase 2 trial, it is considered necessary to continue to evaluate this AE in long-term administration as an AE of special interest in this trial.

Taken together, the trial design has been determined to be scientifically and ethically rational as the design can be feasibly implemented, while also ensuring the safety of the subjects.

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.

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 52 weeks of treatment with ETC-1002 and the Week 52 assessment will be defined as trial completers.

5 Trial Population

This trial will include Japanese patients with hyper-LDL cholesterolemia aged 18 years or older at the time of informed consent and with an inadequate response to statins or difficulty in treatment with statins, 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 treatment period. The subjects who have completed the treatment period in the phase 3 confirmatory trial (Protocol No. 346-102-00002) can also be enrolled in this trial, as they are in the same population. Such subjects who are determined to be eligible based on the results of the scheduled tests at Week 8, after obtaining written informed consent for participation in this trial following Week 8, will proceed to the treatment period of this trial and start receiving the IMP, ETC-1002 at 180 mg for this trial, after completion of the Week 12 assessments. The number of subjects starting the treatment is set at 120 to ensure that at least 100 patients will complete the treatment at Week 52. The number of patients who have difficulty in treatment with statins is planned to be at least 20% among the entire number in this trial.

5.1 Subject Selection and Numbering

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:

- Newly Enrolled Subjects
  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 who have difficulty in treatment with statins as defined below

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

  - Inadequate response to statins: Patients with hyper-LDL cholesterolemia who are currently taking or have previously taken statins, and cannot achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)), meeting any of the following a), b), or c)
    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 for fibrates and selective peroxisome proliferator-activated receptor [PPAR]α modulators, and at least 3 months for proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors)
    c) Patients who have previously experienced failure to achieve the lipid management goals of LDL-C based on the risk assessment (see inclusion criterion 4)) even after taking statins within the approved dose range for at least 4 weeks and currently, based on medical judgment, who are taking only nonstatins at the same dose and regimen from at least 4 weeks before informed consent (at least 6 weeks for selective PPARα modulators, and at least 3 months for PCSK9 inhibitors)

       An outline is shown below.

Category	LDL-C during the screening period	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 • PCSK9 inhibitors: From at least 3 months 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
c)		Only nonstatins	• Fibrates, selective PPARα modulators: From at least 6 weeks before • PCSK9 inhibitors: From at least 3 months before • Drugs other than the above: From at least 4 weeks before	Same dose and regimen

- Difficulty in treatment with statins:

  Of 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, or of those patients who have a history of statin administration and who are judged to have concerns of safety problems associated with the administration or dose increase of statins, those 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), b), or 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 for fibrates and selective PPARα modulators, and at least 3 months for PCSK9 inhibitors)

  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 for fibrates and selective PPARα modulators, and at least 3 months for PCSK9 inhibitors)

Category	LDL-C during the screening period	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 • PCSK9 inhibitors: From at least 3 months 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 • PCSK9 inhibitors: From at least 3 months 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 during the screening period
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 −2, 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 Week −2

- Rollover subjects from the phase 3 confirmatory trial
  1) Patients who provide written informed consent prior to the start of the trial
  2) Subjects who have completed the 12-week treatment period in the phase 3 confirmatory trial (Protocol No. 346-102-00002) and do not meet the discontinuation criteria for the IMP at Week 12

[Rationale for the inclusion criteria]

- Newly Enrolled Subjects
  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 safety and efficacy of ETC-1002.
  5) This criterion is set in consideration of the safety of the subjects. It is also considered that it will be difficult to appropriately evaluate LDL-C values using the Friedewald formula.

- Rollover subjects from the phase 3 confirmatory trial
  1) This criterion is set based on ethical considerations.
  2) These criteria are set to appropriately evaluate the safety and efficacy of ETC-1002.

5.2.2 Exclusion Criteria

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

- Newly Enrolled Subjects
  1) Females who are pregnant or breast-feeding, or who have a positive pregnancy test (urine) result at screening (Week −2) 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 any of the following cardiovascular diseases, or those who had developed any of the following AEs during the screening 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 −2)
6) Patients with uncontrolled and serious hematologic or coagulation disorders or with hemoglobin of <10.0 g/dL at screening (Week −2)
7) Patients with uncontrolled diabetes with HbA1c of ≥9% at screening (Week −2)
8) Patients with uncontrolled hypothyroidism with thyroid-stimulating hormone (TSH) of >1.5 × the upper limit of normal (ULN) at screening (Week −2)
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 −2)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of ≥3 × ULN or total bilirubin of ≥2 × ULN at screening (Week −2)

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 −2)
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 −2)
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 −2)
15) Patients with a history of drug, alcohol, or cocaine abuse within the past 2 years prior to screening (Week −2)
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 −2)

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 −2)

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 52

	Drugs (including food) or therapies	**Prohibited period**
1.	Systemic corticosteroids	From 3 months prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, if the drug has been used with the same dose and regimen since 3 months prior to Week −2, it may be used concomitantly with no change in dose until the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
2.	Lomitapide	From 3 months prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Probenecid	From Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Red yeast rice and food containing red yeast rice	From 2 weeks prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
5.	LDL apheresis	From 3 months prior to Week −2 to the end of the tests at Week 52 (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 52

	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 52 (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 52 (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 52 (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 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

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

- Rollover subjects from the phase 3 confirmatory trial
  1) Females who are pregnant or breast-feeding, or who have a positive pregnancy test (urine) result 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 any of the following AEs during the phase 3 confirmatory trial (Protocol No. 346-102-00002)
  - Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, symptomatic carotid artery stenosis, symptomatic peripheral arterial disease, or decompensated heart failure
  - Abdominal aortic aneurysm
  - Unexplained syncope or torsade de pointes-type ventricular tachycardia
  4) 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 on Day 1
  5) Patients with uncontrolled and serious hematologic or coagulation disorders, or with hemoglobin of <10.0 g/dL at Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)
  6) Patients with a liver disease or dysfunction, including:
  - Patients with positive serology for HBsAg or a positive HCV antibody test by Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)
  - Patients with AST or ALT of ≥3 × ULN or total bilirubin of ≥2 × ULN by Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)
  7) Patients with a history or current renal dysfunction, nephritic syndrome, or nephritis, and with eGFR of ≤30 mL/min/1.73 m^2 at Week 8 in the phase 3 confirmatory trial (Protocol No. 346-102-00002)
  8) 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 52

	Drugs (including food) or therapies	Prohibited period
1.	Systemic corticosteroids	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, if the drug is being used with the same dose and regimen as before participation during the phase 3 confirmatory trial, it may be used concomitantly with no change in dose until the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
2.	Lomitapide	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Probenecid	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Red yeast rice and food containing red yeast rice	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
5.	LDL apheresis	From Day 1 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

9) 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 52

	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 52 (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 52 (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 52 (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 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

10) 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]

- Newly Enrolled Subjects

  1) to 2) These criteria are set in consideration of safety, because the safety of administration of ETC-1002 during pregnancy and breast-feeding has not been established.

  3) to 9), 12), 15), 21) These criteria are set in consideration of the safety of the subjects.

  10) to 11), 14), 18) 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 the subjects.

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

- Rollover subjects from the phase 3 confirmatory trial

  1) to 2) These criteria are set in consideration of safety, because the safety of administration of ETC-1002 during pregnancy and breast-feeding has not been established.

  3) to 7), 10) These criteria are set in consideration of the safety of the subjects.

  8) to 9) These criteria are set to appropriately evaluate the efficacy and safety 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 −2 to the end of tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable) in principle. 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 −2 to the end of the tests at Week 52 (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 consumption or the number of cigarettes smoked during the trial period. Subjects will be monitored at each visit for any significant changes from Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable), and the results will be recorded 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 during the trial period to the extent possible. In addition, the investigator or subinvestigator will instruct subjects at each visit to refrain from strenuous exercise from approximately 1 week before the scheduled visits 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 does not receive the IMP in the treatment period regardless of a newly enrolled subject or a rollover subject from the phase 3 confirmatory trial (Protocol No. 346-102-00002). 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/difficulties in treatment with statins) • For patients with difficulties in treatment with statins: Reasons for judging that treatment with statins is difficult and the name/daily dose of the statin

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

*If a rollover subject from Trial 346-102-00002 is a screen failure, no AE collection will be necessary on the eCRF in this trial.

Screen failures 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 intervention used in this trial is a test product. No trial interventions are used in this trial other than the IMP.

6.1 Trial Treatments Administered

Subjects who are judged to be eligible at screening will proceed to the treatment period. Subjects proceeding to the treatment period who have been receiving treatment using lipid-lowering drugs since before informed consent should continue the treatment without changing the type or dose and regimen, in addition to orally receiving ETC-1002 at 180 mg once daily. 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.

No change in the dose of lipid-lowering drugs is allowed in principle during the trial. However, if the lipid management target in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (2017) are not achieved on and after Week 12, and if the investigator or subinvestigator considers that further treatment is necessary and there are no safety problems, starting a dose increase or concomitant treatment with other lipid-lowering drugs will be permitted.

For information regarding the dose regimen and treatment period (including the post-treatment follow-up period), see Section 4.1.

6.1.1 Medical Devices

Not applicable.

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 (test product) 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

This is an open-label trial.

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 52 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.
- 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 concomitant medications (including prescription medications, over the-counter medications, herbal remedies) and therapies in the eCRF.

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

Concomitant medications or therapies	Collection period
Lipid-lowering drugs	From 6 weeks prior to the date of informed consent to Week 52 or discontinuation However, for PCSK9 inhibitors, the information should be collected from 3 months before informed consent.
Diabetes medications	From 10 weeks prior to the date of informed consent to Week 52 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 52 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

The use or intake of medications, food, and preference products listed in Table 6.5.1-1 is prohibited during the applicable period.

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 −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable) However, if the drug has been used with the same dose and regimen since 3 months prior to Week −2, it may be used concomitantly with no change in dose until the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable).
2.	Lomitapide	From 3 months prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
3.	Probenecid	From Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
4.	Red yeast rice and food containing red yeast rice	From 2 weeks prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

6.5.2 Prohibited Therapies

LDL apheresis is prohibited from 3 months prior to Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable). If performed, the subject will discontinue the trial.

6.5.3 Permitted Medications or Therapies

Treatment with lipid-lowering drugs from before informed consent should continue without changing the type or dose and regimen until the end of the tests at Week 52 of the treatment period (or to the completion of the assessments at Discontinuation Visit, if applicable). If any medication or therapy shown in Table 6.5.3-1 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 in principle.

Table 6.5.3-1 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 52 (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 52 (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 52 (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 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
5.	Diet therapy	From Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)
6.	Exercise therapy	From Week −2 to the end of the tests at Week 52 (or to the completion of the assessments at Discontinuation Visit, if applicable)

No change in the dose of lipid-lowering drugs is allowed in principle during the trial. However, if the lipid management goals in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (2017) are not achieved on and after Week 12, and if the investigator or subinvestigator considers that further treatment

is necessary and there are no safety problems, starting a dose increase or concomitant treatment with other lipid-lowering drugs will be permitted.

For any of the medications or therapies shown in Table 6.5.3-1, no change in the dose and regimen or the details of the concomitant therapy is allowed in principle during the trial. However, only in cases where the investigator or subinvestigator considers the change to be necessary due to safety reasons on and after Week 12, changing the dose and regimen or frequency will be permitted. However, only a dose reduction will be permitted for obesity medications.

6.5.4 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

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 proceeding to the treatment period, 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 treatment period, the assessments at Discontinuation Visit (Week 52) specified in Table 1.3-1 will be performed to the extent possible, and the subject will proceed to the follow-up period.

7.3.3 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for the reasons listed below: Only one reason for treatment discontinuation (primary reason) will be recorded in the source document and eCRF with the date of discontinuation and 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
- In the event of a significant deviation from the protocol
  - Revealed to have not met the inclusion criteria or fall under the exclusion criteria
  - Use of prohibited therapies

- Lost to follow-up
- Pregnancy (see Section 10.3)
- Site terminated by the sponsor
- Trial terminated by the sponsor
- Withdrawal of IMP administration at 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 Future Biospecimen Research (FBR) substudy associated with this trial are provided in the ICF for the FBR.

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 Week 52 in the treatment period, 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. Investigations and assessments will be performed according to Table 1.3-1, and the results will be recorded in the source document and eCRF.

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.

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 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 test results will not be reported to the trial sites and the sponsor for the blind items at Week −4 and Day 1 in the rollover subjects from the phase 3 confirmatory trial (Protocol No. 346-102-00002). The test results will be stored strictly by the central laboratory, disclosed to the trial site after unblinding in the phase 3 confirmatory trial (Protocol No. 346-102-00002), and provided to the sponsor in electronic files.

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

[redacted]

[redacted]

[redacted]

[redacted]

8.7 Safety Assessments

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 electronic informed consent form (eICF)/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. 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.

Since serum uric acid increased was observed with administration of ETC-1002 in the clinical trials conducted outside Japan, the US package insert includes a cautionary statement that the presence or absence of signs and symptoms of hyperuricemia at administration of ETC-1002 should be monitored and treatment with antihyperuricemics should be initiated as necessary. The investigator or subinvestigator will check the results of uric acid measurements in subjects on and after Day 1 and take appropriate measures as necessary. Since ETC-1002 exposure in blood was increased by administration of probenecid in the clinical trials conducted outside Japan, antihyperuricemics other than probenecid should be administered if drug therapy for uric acid increased is required for the subject.

In addition, since statin exposure was increased by co-administration of ETC-1002, the time course of laboratory values such as CK, AST, ALT, or total bilirubin should be carefully monitored to confirm the presence or absence of muscle-related AE or AEs associated with hepatic impairment due to administration of statins, and if any abnormal

value is observed, appropriate measures including discontinuation of administration should be taken.

In the clinical trials conducted outside Japan, ETC-1002 was associated with AST and ALT increased, hemoglobin decreased, as well as creatinine and urea nitrogen increased, although these were not clinically significant. Therefore, changes in these laboratory test values should be carefully monitored, and appropriate measures should be taken if any abnormal value is observed.

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 screening 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 are observed compared with Day 1 in the treatment and follow-up periods, the 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

Body temperature, systolic and diastolic blood pressure, and pulse rate will be measured in a sitting position after resting for at least 5 minutes. Vital signs will be collected at the time points described in the Schedule of Assessments (Table 1.3-1) and before blood sampling to the extent possible. Subjects should be monitored for potentially clinically significant vital signs values. 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.

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 subjects should be monitored for potentially clinically significant ECG findings. 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 according to the procedures specified at each trial site 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). The same scale should be used for the same subject as much as possible.

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

[*] 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.

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. In addition, if an AE that developed in a rollover subject during the phase 3 confirmatory trial (Protocol No. 346-102-00002) continues without recovery/resolution but does not worsen, the event will not be included as an AE in this trial. 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.

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.

Adverse Events of Special Interest (AESIs): A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as immediately reportable events (IREs). No AESIs have been identified for the IMP to be administered during this trial.

Immediately Reportable Event:

- 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.

Occupational exposure refers to the exposure of a medical personnel member to a medicinal product during the preparation and/or administration of the product. Any AE related to occupational exposure should be reported to the sponsor using forms including an IRE form, as soon as possible.

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. 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 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

This trial does not use blinding procedures.

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 56, 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 the 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 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.

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 Day 1 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 −2 in newly enrolled subjects 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. Since the eligibility of the rollover subjects has been confirmed in the phase 3 confirmatory trial (Protocol No. 346-102-00002), it is not necessary to conduct the test in this trial.

9 Statistical Considerations

9.1 Sample Size

Assuming a withdrawal of approximately 20 subjects during the treatment period, the target number of subjects is set at 120 to ensure that 100 subjects will complete the 1-year treatment to assess the safety of ETC-1002 at 180 mg in long-term administration.

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 efficacy 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

Missing data will not be imputed.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Efficacy analyses will be performed using the efficacy analysis set by rollover subjects, newly enrolled subjects, and overall (rollover and newly enrolled) subjects. Baseline is defined as the last data before the start of IMP administration in the treatment period.

9.4.1.1 Efficacy Endpoint Analysis

Descriptive statistics of the actual value and the percent change from baseline will be calculated at each time point for LDL-C.

Descriptive statistics of the actual value and the percent change from baseline will be calculated at each time point for non-HDL-C, TC, apo B, hsCRP, and HbA1c.

The number and percentage 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]) will be calculated at each time point.

9.4.1.2 Other Efficacy Endpoint Analysis

Descriptive statistics of the actual value and the percent change from baseline will be calculated at each time point for HDL-C and TG.

9.4.2 Safety Analysis

Safety analyses will be performed using the safety analysis set by rollover subjects, newly enrolled subjects, and overall (rollover and newly enrolled) subjects. Baseline is defined as the last data before the start of IMP administration in the treatment period.

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized:

- 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
- TEAEs of special interest (including muscle-related TEAE and TEAE associated with hepatic impairment)

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

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

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.

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

9.4.2.4 Electrocardiogram Data

For ECG parameters (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF), descriptive statistics of the actual value and change from baseline will be calculated at each time point. The number and percentage of subjects with an actual value of QTcF of >450 msec, >480 msec, or >500 msec at any postdose time point will be calculated. In addition, the number and percentage of subjects with a change from baseline in QTcF of >30 msec or >60 msec at any postdose time point will be calculated. Similarly, the number and percentage of subjects meeting these criteria at each postdose time point will also be calculated.

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

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.

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

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. The summarization will be performed by rollover subjects, newly enrolled subjects, and overall (rollover and newly enrolled) subjects.

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.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

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

10.1.1 Ethics and Responsibility

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

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

10.1.2 Informed Consent

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

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

In support of the site's standard process for administering informed consent, this trial will also allow for eICF as a tool within applicable regions and trial sites. The eICF utilizes the IRB approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

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.

Prospective trial subjects will be provided with controlled access to the eICF application by trial site staff. When the trial site staff and the subject agree that the subject has enough information to make an informed decision to participate, the subject will electronically sign in the eICF application of the trial site and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. Any other parties required by the IRB (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the eICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied. After the completion of the trial, the investigator or subinvestigator will store the electronic original (PDF) output from the eICF application.

For the paper ICF, 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, 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*

*Testing will be performed in the fasting state.

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.

10.4.1 Protocol Amendment(s)/Administrative Change(s)

Not applicable.

11 References

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13 Ministry of Health, Labour and Welfare. Guideline on Genomic Sampling and Management of Genomic Data, PSEHB/PED Notification No. 0118-1. 2018.

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
	DD Mon YYYY
Signature	Date

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