STATISTICAL ANALYSIS PLAN

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: 01 May 2024 (Version 1.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug
Bempedoic Acid (ETC-1002)

Protocol No. 346-102-00003
English Translation

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Statistical Analysis Plan

Version: 1.0
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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
apo B	apolipoprotein B
AST	aspartate aminotransferase
BMI	body mass index
CRF	case report form
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
HbA1c	glycosylated hemoglobin
HDL-C	high-density lipoprotein-cholesterol
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
non-HDL-C	non-high-density lipoprotein-cholesterol
PT	preferred term
OC	observed cases
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) documents the detailed methods of the statistical analysis planned in Trial 346-102-00003. In this clinical trial, data will be summarized at the interim and final time points when observation for at least 24 weeks (or up to discontinuation) has been completed in all subjects. The interim data cutoff date will be 18 Mar 2024.

2 Trial Objectives

Primary:

- To assess the safety of ETC-1002 at 180 mg administered for 52 weeks in patients with hyper-low-density lipoprotein (LDL) cholesterolemia

Secondary:

- 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)

3 Trial Design

3.1 Type/Design of Trial

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 adverse events (AEs) over a longer period.

A schematic of the trial design is presented in Figure 3.1-1.

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.

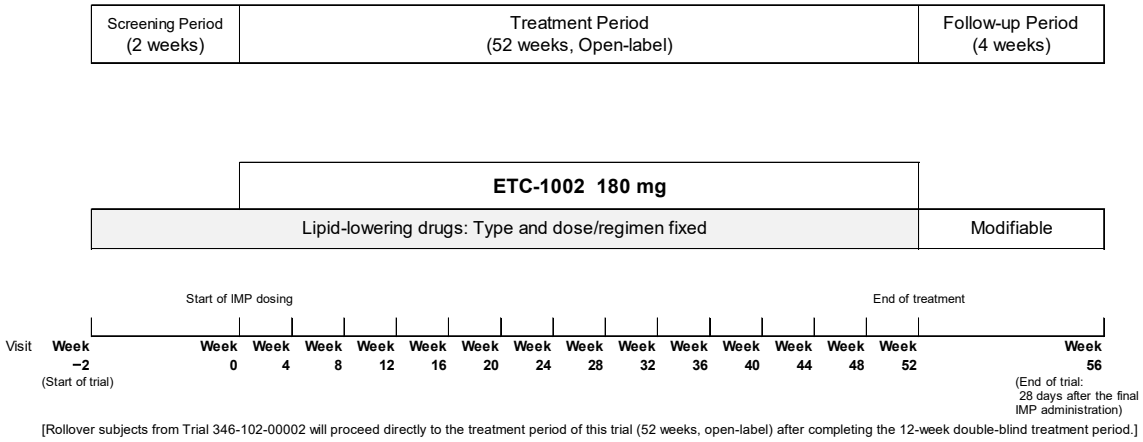

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

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.

3.3 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. 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.

3.4 Trial Visit Window

For the efficacy and safety endpoints (except for AEs), acceptable windows of analysis visits will be set, and the analysis will be based on the analysis visits, regardless of the time points recorded in the case report form (CRF). Analysis visits will be specified based solely on fasting data for non-HDL-C, TC, HDL-C, TG, and LDL-C (calculated using the Friedewald formula) among the fasting lipid parameters for the efficacy endpoints. The handling of fasting data is described in Section 5.3.

Acceptable windows of analysis visits are shown in Table 3.4-1. The start day of investigational medicinal product (IMP) administration is defined as Day 1. Baseline is defined as the last data before the start of IMP administration. If multiple data points are available for a certain acceptable window, the last data point will be used for the analysis. Data collected more than 2 days after the last IMP administration will be excluded. The last data obtained between the initial IMP administration and 2 days after the last IMP administration will be defined as the Last Visit.

Table 3.4-1 Acceptable Windows of Analysis Visits

Week	Trial Day Interval
Baseline	- 1
Week 4	2 - 43
Week 8	44 - 71
Week 12	72 - 99
Week 16	100 - 127
Week 20	128 - 155
Week 24	156 - 183
Week 28	184 - 211
Week 32	212 - 239
Week 36	240 - 267
Week 40	268 - 295
Week 44	296 - 323
Week 48	324 - 351
Week 52	352 - 375
Last Visit	Last data obtained between the initial IMP administration and 2 days after the last IMP administration in the treatment period
Week 56 (FU)	Time point recorded in the CRF

4 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.

5 Statistical Analysis Datasets

5.1 Efficacy Analysis Set

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 (direct method) measurements at baseline and at one or more time points after IMP administration during the treatment period.

5.2 Safety Analysis Set

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

5.3 Handling of Missing Data

Missing data will not be imputed.

Fasting lipid parameters will be handled as shown in the table below with regard to fasting conditions.

Fasting Lipid Parameters	Handling of Data
LDL-C (direct method)	Parameter to be used in the analysis, irrespective of fasting conditions
non-HDL-C, TC, HDL-C, TG, LDL-C (Friedewald formula)	Parameters to be used in the analysis only when obtained under fasting conditions

6 Primary and Secondary Outcome Variables

There are no primary or secondary outcome variables.

7 Disposition and Demographic Analysis

7.1 Subject Disposition

For consenting subjects, the number of subjects who provide informed consent and the number of screening failures will be summarized by rollover, newly enrolled, and overall subjects.

For subjects with IMP administration, the number and percentage (using the number of subjects with IMP administration as the denominator) of those who complete the trial and those who withdraw from the trial, as well as the reasons for withdrawal will be summarized by rollover, newly enrolled, and overall subjects.

For subjects with IMP administration, the number and percentage of subjects included in each analysis set will be summarized by rollover, newly enrolled, and overall subjects.

The same analysis will be performed for each statin response (inadequate response to statins/difficulties in treatment with statins; the same, hereinafter).

7.2 Demographic and Baseline Characteristics

For each analysis set, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum; the same, hereinafter) of age, height, body weight, body mass index (BMI), and estimated glomerular filtration rate (eGFR), and frequency distributions of age groups (<65 years, ≥65 years and <75 years, ≥75 years), categorized BMI (<25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2), categorized eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2), sex, race, ethnicity, country, presence/absence of past medical history, and presence/absence of complications will be summarized by rollover, newly enrolled, and overall subjects.

The same analysis will be performed for each statin response.

7.3 Baseline Disease Evaluation

For each analysis set, descriptive statistics of baseline LDL-C level and frequency distributions of LDL-C level category at baseline (<100 mg/dL, ≥100 mg/dL and <120 mg/dL, ≥120 mg/dL and <140 mg/dL, ≥140 mg/dL), presence/absence of hypercholesterolemia, presence/absence of familial hypercholesterolemia, risk assessment (history of coronary artery disease or familial hypercholesterolemia, high risk, or intermediate risk), presence/absence of diabetes mellitus, and statin response will be summarized by rollover, newly enrolled, and overall subjects.

The same analysis (excluding statin response) will be performed for each statin response.

For subjects with difficulties in treatment with statins in each analysis set, frequency distributions of the reasons treatment was judged to be difficult (muscle impairment, hepatic impairment, renal impairment, cognitive impairment, or other) and the presence/absence of statins with which treatment is judged to be difficult (atorvastatin calcium trihydrate, fluvastatin sodium, pitavastatin calcium, pravastatin sodium, rosuvastatin calcium, or simvastatin) will be summarized by rollover, newly enrolled, and overall subjects.

7.4 Treatment Compliance

For each analysis set, frequency distributions of the IMP compliance rate (<70%, ≥70% to <80%, ≥80% to <90%, or ≥90%) in the treatment period will be summarized by rollover, newly enrolled, and overall subjects. The IMP compliance rate will be calculated using the following formula.

$$\text{IMP compliance rate (\%)} = \frac{\text{Actual number of days taking the IMP}}{\text{Date of last IMP administration} - \text{Date of initial IMP administration} + 1} \times 100$$

The same analysis will be performed for each statin response.

For each analysis set, the number and percentage of subjects who do not change the type and dosage regimen of lipid-lowering drugs, which are mandatory concomitant medications in this trial, throughout the treatment period will be summarized by rollover, newly enrolled, and overall subjects.

The same analysis will be performed for each statin response.

7.5 Prior and Concomitant Medications

For the safety analysis set, frequency distributions of the medications used prior to or during the treatment period, including lipid-lowering drugs, by drug class and preferred term in the World Health Organization Drug Dictionary (WHODD) version Global B3 September 2022 will be summarized by rollover, newly enrolled, and overall subjects.

For each analysis set, frequency distributions of the presence/absence of statin use or ezetimibe use will be summarized by rollover, newly enrolled, and overall subjects. The preferred terms for statins and ezetimibe are shown in Appendix 4.

The same analysis will be performed for each statin response.

7.6 Protocol Deviations

For subjects with IMP administration, frequency distributions of the presence/absence of the following categorized deviations recorded in the CRF will be summarized by rollover, newly enrolled, and overall subjects.

- Dosing
- Inclusion/exclusion criteria
- Met withdrawal criteria but was not withdrawn
- Procedural deviations (affecting primary outcome variables)
- Prohibited concomitant medications

The same analysis will be performed for each statin response (inadequate response to statins/difficulties in treatment with statins).

8 Efficacy Analysis

Efficacy analyses will be performed using the efficacy analysis set, by rollover subjects, newly enrolled subjects, and overall (rollover and newly enrolled) subjects. The analysis visits will be Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, unless otherwise specified.

8.1 Efficacy Endpoints

Descriptive statistics of the actual value, change from baseline, and percent change from baseline will be calculated at each time point for LDL-C (direct method). In addition to the summarization at each time point, summarization at the Last Visit will also be performed.

Descriptive statistics of the actual value, change from baseline, and percent change from baseline will be calculated at each time point for non-HDL-C, TC, apo B, hsCRP, and HbA1c. The analysis visits for apo B, hsCRP, and HbA1c will be Weeks 12, 24, 36, and 52.

The number and percentage of subjects whose LDL-C values achieve the lipid management goal 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.

The time course of the mean ± standard deviation for the percent change from baseline in the efficacy endpoints will be plotted.

The same analysis will be performed for each statin response.

8.2 Other Efficacy Analyses

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

8.3 Subgroup Analyses

Subgroup analyses will be performed by the following items for the percent change in LDL-C (direct method) from baseline at Weeks 24 and 52. Statin intensity categories and types are shown in Appendix 6. In the data for each statin type, subjects who use multiple medications will be excluded from the summarization.

- Statin response (inadequate response to statins/difficulties in treatment with statins)
- Sex (Male, Female)
- Familial hypercholesterolemia (Yes, No)
- Diabetes mellitus (Yes, No)
- Age (<65 years, ≥65 years and <75 years, ≥75 years)
- Statin use (Yes, No)
- BMI (<25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2)
- eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2)
- LDL-C at baseline (<100 mg/dL, ≥100 mg/dL and <120 mg/dL, ≥120 mg/dL and <140 mg/dL, ≥140 mg/dL)
- Statin intensity (Low-intensity statins, High-intensity statins, No statins)
- Statin type (atorvastatin calcium trihydrate, fluvastatin sodium, pitavastatin calcium, pravastatin sodium, rosuvastatin calcium, simvastatin, no statins)

9 Safety Analyses

For the safety analysis set, the summarization will be performed by rollover, newly enrolled, and overall subjects. Baseline is defined as the last data before the start of IMP administration. The analysis visits will be Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, unless otherwise specified. The same analysis will be performed for each statin response (inadequate response to statins/difficulties in treatment with statins). Summarization at the Last Visit will also be performed in addition to summarization at each time point.

9.1 Extent of Exposure

Descriptive statistics will be calculated for the duration of IMP treatment in the treatment period (Date of final IMP administration − Date of initial IMP administration + 1) and for the total number of days of IMP administration (total number of days taking the IMP in the treatment period). For the duration of IMP treatment, frequency distributions of categorized durations (days) (1-84, 85-168, 169-252, 253-336, and ≥337) will be calculated by rollover, newly enrolled, and overall subjects, along with the descriptive statistics.

9.2 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. The incidence of the following events will be calculated by SOC, PT, and overall. If a subject experiences the same event more than once, the more severe event will be used.

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuations of the IMP

Treatment-emergent AEs that are potentially causally related to the IMP will be summarized in the same manner. Summary tables (only for events occurring in ≥5% of all subjects) will be prepared for TEAEs and for TEAEs that are potentially causally related to the IMP.

The number of subjects with TEAEs and the incidence by PT will be shown by initial onset time (days) (1-14, 15-28, 29-56, 57-84, 85-168, 169-252, 253-336, ≥337, after the end of treatment). Treatment-emergent AEs that are potentially causally related to the IMP will be summarized in the same manner.

The incidence of TEAEs that are not judged to be adverse reactions to the COVID-19 vaccine will be calculated by SOC, PT, and overall.

9.2.1 Adverse Events of Special Interest

The incidence of AEs of special interest will be calculated by SOC and PT.

Adverse events of special interest that are potentially causally related to the IMP will be summarized in the same manner. The classification of the AEs of special interest is shown in Appendix 5.

9.2.2 Subgroup Analyses of Adverse Events

The number of subjects with TEAEs and the incidence will be calculated by SOC and PT for each of the following subgroups. Treatment-emergent AEs that are potentially causally related to the IMP will be summarized in the same manner. Statin intensity categories and types are shown in Appendix 6. In the data for each statin type, subjects who use multiple medications will be excluded from the summarization.

- Sex (Male, Female)
- Familial hypercholesterolemia (Yes, No)
- Diabetes mellitus (Yes, No)
- Age (<65 years, ≥65 years and <75 years, ≥75 years)
- Statin use (Yes, No)
- BMI (<25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2)
- eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2)
- Statin intensity (Low-intensity statins, High-intensity statins, No statins)
- Statin type (atorvastatin calcium trihydrate, fluvastatin sodium, pitavastatin calcium, pravastatin sodium, rosuvastatin calcium, simvastatin, no statins)

For AEs of special interest, the number of subjects with the events and the incidence will be calculated by SOC and PT for each of the following subgroups. Adverse events of special interest that are potentially causally related to the IMP will be summarized in the same manner.

- eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2)

9.3 Clinical Laboratory Data

Among the urinalysis parameters in laboratory tests, those other than pH and specific gravity will be included in the qualitative urinalysis.

For parameters other than the 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 the criteria for identifying laboratory values of potential clinical relevance (Appendix 2: Criteria for Identifying Laboratory Values of Potential Clinical Relevance) and Hy’s law (Appendix 7: Criteria for Hy’s Law) after IMP administration will be calculated. All data obtained after IMP administration during the treatment period will be analyzed, including those obtained at unscheduled visits.

9.4 Vital Sign Data

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

The number and percentage of subjects meeting the criteria for identifying vital signs of potential clinical relevance (Appendix 1: Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance) after IMP administration will be calculated. All data obtained after IMP administration during the treatment period will be analyzed, including those obtained at unscheduled visits.

9.5 Physical Examination Data

Physical findings will be presented in a listing of subjects.

9.6 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 visit (Weeks 12, 24, 36, and 52).

The number and percentage of subjects with an actual value of QTcF of >450 ms, >480 ms, or >500 ms 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 ms or >60 ms at any postdose time point will be calculated. All data obtained after IMP administration will be analyzed, including those obtained at unscheduled visits. 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.

The number and percentage of subjects meeting the criteria for identifying ECG measurements of potential clinical relevance (Appendix 3: Criteria for Identifying ECG Measurements of Potential Clinical Relevance) after IMP administration will be calculated. All data obtained after IMP administration will be analyzed, including those obtained at unscheduled visits.

9.7 Other Safety Data

9.7.1 Body Weight

For body weight, descriptive statistics of the actual value and change from baseline will be calculated at each visit (Weeks 4, 12, 20, 24, 28, 36, 44, and 52).

The number and percentage of subjects meeting the criteria for identifying body weight of potential clinical relevance (Appendix 1: Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance) after IMP administration will be calculated. All data obtained after IMP administration will be analyzed, including those obtained at unscheduled visits.

10 Pharmacokinetic Analyses

No pharmacokinetic analysis is planned.

11 Pharmacodynamic Analyses

No pharmacodynamic analysis is planned.

12 Pharmacogenomic Analyses

No pharmacogenomic analysis is planned.

13 Interim Analysis

No interim analysis is planned.

14 Changes in the Planned Analyses

Not applicable.

15 References

Not applicable.

Appendix 1 Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Pulse rate	>120 bpm	≥15 bpm increase
Pulse rate	<50 bpm	≥15 bpm decrease
Systolic blood pressure	>160 mmHg	≥20 mmHg increase
Systolic blood pressure	<90 mmHg	≥20 mmHg decrease
Diastolic blood pressure	>100 mmHg	≥15 mmHg increase
Diastolic blood pressure	<50 mmHg	≥15 mmHg decrease
Weight	N/A	≥7% increase
Weight	N/A	≥7% decrease

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST	≥3 × upper limit of normal (ULN)
ALT	≥3 × ULN
Bilirubin, Total	≥2 ×ULN
ALP	≥3 × ULN
Urea nitrogen	≥30 mg/dL
Creatinine	≥2.0 mg/dL
Creatine kinase (CK)	≥4 × ULN
Uric acid	≥9 mg/dL
Hematology	
Hematocrit	Males: ≤37% and ≥3 percentage points decrease from baseline Females: ≤32% and ≥3 percentage points decrease from baseline
Hemoglobin	Males: ≤11.5 g/dL Females: ≤9.5 g/dL
Leukocyte count	≤2,800 10^6/L
Leukocyte count	≥16,000 10^6/L
Platelet count	≤7.5 10^{10}/L
Platelet count	≥70 10^{10}/L
Urinalysis	
Protein	Increase of ≥2 units
Glucose	Increase of ≥2 units
Additional criteria	
Chloride	≤90 mEq/L
Chloride	≥118 mEq/L
Potassium	≤2.5 mEq/L
Potassium	≥6.5 mEq/L
Sodium	≤126 mEq/L
Sodium	≥156 mEq/L
Calcium	≤8.2 mg/dL
Calcium	≥12 mg/dL
Glucose	Fasting: ≥126 mg/dL Non-Fasting: ≥200 mg/dL
Glucose	≤50 mg/dL
Total cholesterol	≥240 mg/dL
LDL cholesterol	≥160 mg/dL
HDL cholesterol	<40 mg/dL
Triglycerides, Fasting	≥150 mg/dL

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate	≥120 bpm	increase of ≥15 bpm
Heart rate	≤50 bpm	decrease of ≥15 bpm
PR	≥200 ms	increase of ≥50 ms
QRS	≥120 ms	increase of ≥20 ms

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

Appendix 4 Preferred Terms for Statins and Ezetimibe

Drug	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 digits
Statins	Pravastatin sodium	PRAVASTATIN SODIUM	00880402001	008804
	Simvastatin	SIMVASTATIN	00848101001	008481
	Rosuvastatin calcium	ROSUVASTATIN CALCIUM	01588602001	015886
	Pitavastatin calcium	PITAVASTATIN CALCIUM	06470002001	064700
	Atorvastatin calcium trihydrate	ATORVASTATIN CALCIUM TRIHYDRATE	01326106001	013261
	Fluvastatin sodium	FLUVASTATIN SODIUM	01224502001	012245
	Caduet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Caduet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Caduet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Caduet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Amaluet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Amaluet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Amaluet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Amaluet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
Ezetimibe	Ezetimibe	EZETIMIBE	01587001001	015870
	Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834

Appendix 5 Classification of Adverse Events of Special Interest

AE of Special Interest	PT Code	PT Term
Hepatic dysfunction-related	10001547	Alanine aminotransferase abnormal
Hepatic dysfunction-related	10001551	Alanine aminotransferase increased
Hepatic dysfunction-related	10003477	Aspartate aminotransferase abnormal
Hepatic dysfunction-related	10003481	Aspartate aminotransferase increased
Hepatic dysfunction-related	10058477	Blood bilirubin abnormal
Hepatic dysfunction-related	10005364	Blood bilirubin increased
Hepatic dysfunction-related	10062685	Hepatic enzyme abnormal
Hepatic dysfunction-related	10060795	Hepatic enzyme increased
Hepatic dysfunction-related	10068237	Hypertransaminasaemia
Hepatic dysfunction-related	10024690	Liver function test abnormal
Hepatic dysfunction-related	10077692	Liver function test increased
Hepatic dysfunction-related	10062688	Transaminases abnormal
Hepatic dysfunction-related	10054889	Transaminases increased
Hepatic dysfunction-related	10019670	Hepatic function abnormal
Myopathy-related	10028372	Muscular weakness
Myopathy-related	10028320	Muscle necrosis
Myopathy-related	10028334	Muscle spasms
Myopathy-related	10028411	Myalgia
Myopathy-related	10028653	Myositis
Myopathy-related	10028625	Myoglobin blood increased
Myopathy-related	10059888	Myoglobin blood present
Myopathy-related	10028631	Myoglobin urine present
Myopathy-related	10058735	Myoglobinaemia
Myopathy-related	10028629	Myoglobinuria
Myopathy-related	10028641	Myopathy
Myopathy-related	10028648	Myopathy toxic
Myopathy-related	10074769	Necrotising myositis
Myopathy-related	10033425	Pain in extremity
Myopathy-related	10039020	Rhabdomyolysis
Myopathy-related	10005468	Blood creatine phosphokinase abnormal
Myopathy-related	10005470	Blood creatine phosphokinase increased
Myopathy-related	10005477	Blood creatine phosphokinase MM increased
Tendon rupture/disorder-related	10043248	Tendon rupture
Tendon rupture/disorder-related	10028331	Muscle rupture
Tendon rupture/disorder-related	10039227	Rotator cuff syndrome
Tendon rupture/disorder-related	10074599	Tendon discomfort
Tendon rupture/disorder-related	10043239	Tendon disorder
Tendon rupture/disorder-related	10043242	Tendon injury
Tendon rupture/disorder-related	10069650	Tendon necrosis
Tendon rupture/disorder-related	10066371	Tendon pain
Tendon rupture/disorder-related	10043255	Tendonitis
Diabetes-related	10005554	Blood glucose abnormal
Diabetes-related	10005557	Blood glucose increased
Diabetes-related	10012601	Diabetes mellitus
Diabetes-related	10012607	Diabetes mellitus inadequate control
Diabetes-related	10012671	Diabetic ketoacidosis
Diabetes-related	10018429	Glucose tolerance impaired
Diabetes-related	10018478	Glucose urine present
Diabetes-related	10018473	Glycosuria

AE of Special Interest	PT Code	PT Term
Diabetes-related	10018484	Glycosylated haemoglobin increased
Diabetes-related	10020635	Hyperglycaemia
Diabetes-related	10056997	Impaired fasting glucose
Diabetes-related	10023379	Ketoacidosis
Diabetes-related	10023388	Ketonuria
Diabetes-related	10023391	Ketosis
Diabetes-related	10067585	Type 2 diabetes mellitus
Diabetes-related	10057597	Urine ketone body present
Renal dysfunction-related	10069339	Acute kidney injury
Renal dysfunction-related	10005481	Blood creatinine abnormal
Renal dysfunction-related	10005483	Blood creatinine increased
Renal dysfunction-related	10005846	Blood urea abnormal
Renal dysfunction-related	10005851	Blood urea increased
Renal dysfunction-related	10050760	Blood urea nitrogen/creatinine ratio increased
Renal dysfunction-related	10068447	Creatinine renal clearance abnormal
Renal dysfunction-related	10011372	Creatinine renal clearance decreased
Renal dysfunction-related	10018356	Glomerular filtration rate abnormal
Renal dysfunction-related	10018358	Glomerular filtration rate decreased
Renal dysfunction-related	10030302	Oliguria
Renal dysfunction-related	10072370	Prerenal failure
Renal dysfunction-related	10038435	Renal failure
Renal dysfunction-related	10061480	Renal function test abnormal
Renal dysfunction-related	10062237	Renal impairment
Metabolic acidosis	10027417	Metabolic acidosis
Hypoglycemia-related	10005554	Blood glucose abnormal
Hypoglycemia-related	10005555	Blood glucose decreased
Hypoglycemia-related	10020993	Hypoglycaemia
Hypoglycemia-related	10021000	Hypoglycaemic coma
Hypoglycemia-related	10021002	Hypoglycaemic encephalopathy
Hypoglycemia-related	10048803	Hypoglycaemic seizure
Hypoglycemia-related	10040576	Shock hypoglycaemic
Cognitive dysfunction-related	10057668	Cognitive disorder
Cognitive dysfunction-related	10010305	Confusional state
Cognitive dysfunction-related	10013395	Disorientation
Cognitive dysfunction-related	10027175	Memory impairment
Cognitive dysfunction-related	10048294	Mental status changes
Cognitive dysfunction-related	10001949	Amnesia
Elevated uric acid-related	10005861	Blood uric acid increased
Elevated uric acid-related	10020903	Hyperuricaemia
Elevated uric acid-related	10018627	Gout
Decreased hemoglobin-related	10018884	Haemoglobin decreased
Decreased hemoglobin-related	10018838	Haematocrit decreased
Decreased hemoglobin-related	10002034	Anaemia

Appendix 6 Statin Intensity and Type

Item	Category	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 digits
Statin Intensity	Low-intensity	Pravastatin sodium	PRAVASTATIN SODIUM	00880402001	008804
		Simvastatin	SIMVASTATIN	00848101001	008481
		Fluvastatin sodium	FLUVASTATIN SODIUM	01224502001	012245
	High-intensity	Rosuvastatin calcium	ROSUVASTATIN CALCIUM	01588602001	015886
		Pitavastatin calcium	PITAVASTATIN CALCIUM	06470002001	064700
		Atorvastatin calcium trihydrate	ATORVASTATIN CALCIUM TRIHYDRATE	01326106001	013261
		Caduet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Amaluet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723

Item	Category	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 digits
		Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
		Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
		Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
		Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
		Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
		Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
Statin Medication	Atorvastatin calcium trihydrate	Atorvastatin calcium trihydrate	ATORVASTATIN CALCIUM TRIHYDRATE	01326106001	013261
		Caduet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Amaluet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723

Item	Category	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 digits
		Amaluet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
		Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Fluvastatin sodium	Fluvastatin sodium	FLUVASTATIN SODIUM	01224502001	012245
	Pitavastatin calcium	Pitavastatin calcium	PITAVASTATIN CALCIUM	06470002001	064700
		Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
		Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
	Pravastatin sodium	Pravastatin sodium	PRAVASTATIN SODIUM	00880402001	008804
	Rosuvastatin calcium	Rosuvastatin calcium	ROSUVASTATIN CALCIUM	01588602001	015886
		Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
		Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Simvastatin	Simvastatin	SIMVASTATIN	00848101001	008481

Appendix 7 Criteria for Hy's Law

ALT or AST $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN

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