STATISTICAL ANALYSIS PLAN

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

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

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Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug

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English Translation

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Statistical Analysis Plan
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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
apo B	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
CRF	Case report form
FAS	Full analysis set
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
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
non-HDL-C	Non-high-density lipoprotein cholesterol
PPAR	Peroxisome proliferator-activated receptor
PT	Preferred term
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAS	Statistical Analysis System
SOC	System organ class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
WHODD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) documents the detailed methods for the statistical analysis planned in Trial 346-102-00001.

2 Trial Objectives

Primary:

- To assess the low-density lipoprotein cholesterol (LDL-C)-lowering efficacy of ETC-1002 at 60 mg, 120 mg, and 180 mg versus placebo when administered for 12 weeks in combination with ongoing stable statin therapy and/or other lipid-modifying therapy in patients with hypercholesterolemia who have inadequate control of LDL-C
- To characterize the dose-response of ETC-1002 and investigate the appropriate dosage for a phase 3 trial

Secondary:

- To assess the effect of ETC-1002 on high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), triglyceride (TG), apolipoprotein B (apo B), high-sensitivity C-reactive protein (hsCRP), and glycosylated hemoglobin (HbA1c)
- To assess the proportion of subjects achieving the lipid management goal of LDL-C by treatment with ETC-1002
- To assess the pharmacokinetic plasma trough and near-peak concentrations of ETC-1002 and its active metabolite (ESP15228)
- To characterize the safety and tolerability of ETC-1002 in patients with hypercholesterolemia when administered in combination with ongoing stable statin therapy and/or other lipid-modifying therapy

3 Trial Design

3.1 Type/Design of Trial

This is a placebo-controlled, randomized, multicenter, double-blind, parallel-group trial to assess the efficacy and safety of ETC-1002 in patients with hypercholesterolemia who are being treated with hypercholesterolemia drugs but have inadequate control and cannot achieve the lipid management goal. The trial population will include patients with statin tolerance who do not sufficiently respond to statins and cannot achieve the lipid management goal despite being treated with statins, and patients with statin intolerance who have experienced safety problems at the time of starting or increasing the dose of statins, that were successfully resolved after stopping or reducing the dose of statins, and

cannot achieve the lipid management goal in spite of taking statins at (or below) the lowest approved daily dose and/or hypercholesterolemia drugs other than statins.

A schematic of the trial design is presented in Figure 3.1-1. This trial consists of the screening period, [redacted] the treatment period, and the follow-up period.

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

3.2 Trial Treatments

In the treatment period, subjects will receive either of ETC-1002 60 mg/day, 120 mg/day, 180 mg/day, or placebo for 12 weeks in addition to continued hypercholesterolemia drugs that have been taken from before informed consent. The medications to be taken in the [redacted] treatment period are detailed below.

[redacted]

3.2.2 Treatment period

1) Medications

- Mandatory concomitant medications:
  Hypercholesterolemia drugs (statins and/or drugs other than statins) that have been taken from before informed consent
- IMP:
  - ETC-1002 60-mg tablets
  - Placebo tablets

2) Dose and regimen

- Mandatory concomitant medications:
  Hypercholesterolemia drugs [redacted] will be continued without changing the type and the dose and regimen during the treatment period.
- IMP:

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

3) Treatment duration
   12 weeks

3.3 Trial Population

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

3.4 Trial Visit Window

Data observed at CRF Visit will be used at each analysis visit (but data at discontinuation will not be used in analysis). Data from unscheduled visits will not be used. Efficacy analysis will be performed using the data obtained up until 2 days after final IMP administration. In assessment of efficacy endpoints, baseline for fasting lipid parameters is defined as the mean of the values for Day 1 (Visit T1) and Week −1 (Visit S3). If only one value is obtained, that value will be used as baseline. For efficacy endpoints other than fasting lipid parameters, baseline is defined as the value for Day 1 (Visit T1). For safety endpoints, baseline is defined as the last data obtained prior to initial IMP administration in the treatment period.

4 Sample Size

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

5 Statistical Analysis Datasets

5.1 Full Analysis Set (FAS)

The full analysis set (FAS) will include all subjects who receive at least one dose of IMP during the treatment period and for whom LDL-C values at baseline (baseline for efficacy endpoints) and at least one postdose visit (up until 2 days after final IMP administration) are observed.

5.2 Safety Analysis Set

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

5.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include subjects who receive ETC-1002 and for whom time of blood collection for plasma drug concentration measurement is recorded.

5.4 Handling of Missing Data

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

In analysis of the percent change from baseline to Week 12 for secondary endpoints and of the proportion of subjects achieving the lipid management goals of LDL-C, missing values will be handled in the same manner as above. Missing values will not be imputed for sensitivity analysis and pharmacokinetic analysis.

Fasting lipid parameters will be handled as shown in the table below.

Condition	Fasting Lipid Parameters
Parameter to be used in analysis, irrespective of fasting condition	LDL-C (direct measurement)
Parameters to be used in analysis only when obtained under a fasting condition	LDL-C (Friedewald formula), HDL-C, non-HDL-C, TC, TG

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variables

Percent change in LDL-C from baseline to Week 12

6.2 Secondary Outcome Variables

- Percent change in HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c from baseline to Week 12
- Proportion of subjects whose LDL-C value achieves the lipid management goals based on risk assessment (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk], or <140 mg/dL [intermediate risk]) and the proportion of subjects whose LDL-C value achieves <70 mg/dL at Week 12

7 Disposition and Demographic Analysis

7.1 Subject Disposition

The number of subjects who provide informed consent, the number of screening failures, and the number and percentage (using the number of subjects who provide informed consent as the denominator) of IMP-treated subjects and discontinued subjects and the reasons for discontinuation [redacted] will be summarized.

The number of randomized subjects and the number and percentage (using the number of randomized subjects as the denominator) of subjects who receive IMP, who complete the trial, and who withdraw from the trial and the reasons for withdrawal in the treatment period will be summarized by treatment group (by dose and overall for ETC-1002).

For subjects who are randomized, the number and percentage of subjects included in each analysis set will be summarized by treatment group (by dose and overall for ETC-1002).

The same analysis will also be performed by the randomization stratification factor (statin response).

7.2 Demographic and Baseline Characteristics

For each analysis set, descriptive statistics (mean, standard deviation, median, minimum, and maximum, the same hereinafter) of age, height, body weight, and BMI and frequency distributions of categorized age (<65 years, ≥65 years), sex, race, ethnicity, country, presence/absence of medical history, and presence/absence of complications will be summarized by treatment group (by dose and overall for ETC-1002). For body weight, values at screening will be used.

The same analysis will also be performed by the randomization stratification factor (statin response).

7.3 Baseline Disease Evaluation

For the FAS and safety analysis set, frequency distributions of 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 (statin tolerance/statin intolerance) will be summarized by treatment group (by dose and overall for ETC-1002).

The same analysis except for statin response will also be performed by the randomization stratification factor (statin response).

For subjects with statin intolerance in the FAS and safety analysis set, frequency distributions of presence/absence of statin intolerance-associated symptoms (muscle impairment, hepatic impairment, renal impairment, cognitive impairment, or other) and presence/absence of causal medication for statin intolerance (atorvastatin calcium trihydrate, fluvastatin sodium, pitavastatin calcium, pravastatin sodium, rosuvastatin calcium, or simvastatin) will be summarized by treatment group (by dose and overall for ETC-1002).

7.4 Treatment Compliance

For the FAS and safety analysis set, frequency distributions of IMP compliance rate (<70%, ≥70% to <80%, ≥80% to <90%, or ≥90%) in the treatment period will be summarized by treatment group (by dose and overall for ETC-1002). The IMP compliance rate will be calculated using the following formula.

$$\text{IMP compliance rate (\%)} = \frac{\text{Actual number of days of taking 3 tablets of the IMP}}{\text{Date of final IMP administration} - \text{Date of initial IMP administration} + 1} \times 100$$

The same analysis will also be performed by the randomization stratification factor (statin response).

For the FAS, the number and percentage of subjects who do not change the type and the dose and regimen of hypercholesterolemia drugs, which are mandatory concomitant medication in this trial, throughout the treatment period will be summarized by treatment group (by dose and overall for ETC-1002).

The same analysis will also be performed by the randomization stratification factor (statin response).

7.5 Prior and Concomitant Medications

For the FAS, frequency distributions of medications used prior to or during the treatment period by drug class and by preferred term in World Health Organization Drug Dictionary (WHODD) version B3 September 2020 will be summarized by treatment group (by dose and overall for ETC-1002).

For the FAS, frequency distributions of presence/absence of statin use or ezetimibe use will be summarized by treatment group (by dose and overall for ETC-1002). The preferred terms for statins and ezetimibe are shown in Appendix 4.

The same analysis will also be performed by the randomization stratification factor (statin response).

7.6 Protocol Deviations

For subjects who are randomized, frequency distributions of presence/absence of the following deviations recorded in the CRF will be summarized by treatment group (by dose and overall for ETC-1002).

- Dosing
- Inclusion/exclusion criteria
- Met withdrawal criteria but was not withdrawn
- Procedural deviations (Affecting primary outcome variables)

- Prohibited concomitant medications

The same analysis will also be performed by the randomization stratification factor (statin response).

8 Efficacy Analysis

Efficacy analysis will be performed for the FAS using values measured by the central laboratory. For LDL-C, values obtained by direct measurement will be used unless otherwise stated. Efficacy analysis for the treatment period is described below.

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in LDL-C from baseline to Week 12.

8.1.1 Primary Efficacy Analysis

For the primary analysis of the primary endpoint, analysis of covariance will be performed using treatment group and statin response (statin tolerance/statin intolerance), the randomization stratification factor, as factors and baseline value of LDL-C as a covariate. The overall Type I error rate will be controlled by performing comparison versus the placebo group starting from the highest ETC-1002 dose group by a closed testing procedure at a two-sided significance level of 0.05. Baseline is defined as the mean of the LDL-C values for Day 1 (Visit T1) and Week −1 (Visit S3). If only one value is observed, that value will be used as baseline. In the analysis of covariance described above, the least squares mean for each treatment group and the differences in the mean of the least squares between each ETC-1002 group and the placebo group, together with the two-sided 95% confidence intervals, will be calculated. The same analysis will also be performed for the percent change in LDL-C from baseline at each visit (Week 2, Week 4, Week 6, Week 8, and Week 12) using measured values (Observed case, OC).

The percent change in LDL-C from baseline to Week 12 will be tested using a contrast for low-dose saturation (L-end), medium-dose saturation (M-end), and linear (L-end: 3-1-1-1, M-end: 5 1-3-3, Linear: 3 1-1-3) to investigate the dose-response relationship between placebo and ETC-1002 low dose, medium dose, and high dose. Multiplicity will not be considered in the analyses for dose-response relationship.

8.1.2 Sensitivity Analyses

A mixed-effects model repeated measures (MMRM) analysis assuming missing at random will be performed using OC data to calculate the least squares mean for each treatment group and the differences in the mean of the least squares between each ETC-

1002 group and the placebo group, together with the two-sided 95% confidence intervals, for the percent change in LDL-C from baseline at each visit (Week 2, Week 4, Week 6, Week 8, and Week 12). The MMRM model will include treatment group, the randomization stratification factor, visit, and treatment group-by-visit interaction as factors and baseline and baseline-by-visit interaction as covariates using an unstructured error covariance matrix. The Kenward-Roger method will be used to calculate the degree of freedom. If the MMRM procedure fails to converge in variance component estimation, the following error covariance structures will be used in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry, and the first structure to yield convergence will be used. If a structure other than unstructured is selected, a sandwich estimator of standard error will be used.

8.1.3 Technical Computational Details for Primary Efficacy Analysis

Analysis of covariance, which is the primary analysis, will be performed using the following SAS code.

```
proc mixed;
  class treatment strata;
  model pchange = treatment strata baseline / solution;
  lsmeans treatment / pdiff=control('placebo') cl;
run;
```

Analysis using a contrast to investigate the dose-response relationship will be performed using the following SAS code.

```
proc mixed;
  class treatment strata;
  model pchange = treatment strata baseline / solution;
  lsmeans treatment / pdiff=control('placebo') cl;
  contrast 'L-end' treatment 3 -1 -1 -1;
  contrast 'M-end' treatment 5 1 -3 -3;
  contrast 'Linear' treatment 3 1 -1 -3;
run;
```

MMRM analysis as sensitivity analysis will be performed using the following SAS code.

```
proc mixed;
```

```
    class treatment strata visit subjid;
    model pchange = treatment visit baseline treatment*visit baseline*visit strata /
ddfm=kr;
    repeated visit / type=un subject=subjid;
    lsmeans treatment*visit / diff cl;
  run;
```

8.2 Secondary Efficacy Analyses

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

For the percent change from baseline to Week 12 in each assessment parameter (HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c), analysis of covariance will be performed using treatment group and the randomization stratification factor (statin tolerance/statin intolerance) as factors and the baseline value for each assessment parameter as a covariate. The least squares mean for each treatment group and the differences in the mean of the least squares between each ETC-1002 group and the placebo group, together with the two-sided 95% confidence intervals, will be calculated. The same analysis will also be performed for the percent change in each assessment parameter from baseline at each visit (Week 2, Week 4, Week 6, Week 8, and Week 12) using measured OC data. In addition to for the primary endpoint LDL-C, the timecourse of the least squares mean ± standard error for the percent change from baseline in each assessment parameter (HDL-C, non-HDL-C, TC, TG, apoB, hsCRP, HbA1c, and LDL-C [calculated by Friedewald formula]) at each visit from baseline to Week 12 in the treatment period will be plotted for each treatment group. The same timecourses will also be plotted by the randomization stratification factor (statin response).

The proportion of subjects whose LDL-C value achieves the lipid management goal (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk], or <140 mg/dL [intermediate risk]) at Week 12, and the proportion of subjects whose LDL-C value achieves <70 mg/dL at Week 12 will be analyzed by Cochran-Mantel-Haenszel test stratified by statin response (statin tolerance/statin intolerance) to calculate the differences between each ETC-1002 group and the placebo group and the two-sided 95% confidence intervals (based on

Cochran-Mantel-Haenszel). The proportion in each treatment group and the two-sided 95% interval (based on Clopper-Pearson method) will also be calculated. The same analysis will also be performed for the proportion of subjects whose LDL-C value achieves the lipid management goal and the proportion of subjects whose LDL-C value achieves <70 mg/dL at each visit (Week 2, Week 4, Week 6, Week 8, and Week 12) using measured OC data. For the proportion of subjects whose LDL-C value achieves the lipid management goal at Week 12 and the proportion of subjects whose LDL-C value achieves <70 mg/dL at Week 12, the proportion in each treatment group and the two-sided 95% interval (based on Clopper-Pearson method), together with the differences of proportion between each ETC-1002 group and the placebo group and the two-sided 95% confidence intervals (based on score statistic) will be calculated by the randomization stratification factor (statin response). The same analysis will also be performed at each visit (Week 2, Week 4, Week 6, Week 8, and Week 12) using measured OC data.

For other efficacy endpoints including the measured value and change and percent change from baseline at each visit for each assessment parameter (LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, and HbA1c), descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) by treatment group will be calculated at each visit (Week 2, Week 4, Week 6, Week 8, Week 12, and Week 16 [FU]). The same descriptive statistics will also be calculated for LDL-C calculated by the Friedewald formula (TC − HDL-C − TG/5). The timecourse of the mean ± standard deviation for the percent change from baseline in each assessment parameter (LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, hsCRP, HbA1c, and LDL-C [calculated by Friedewald formula]) at each visit from baseline to Week 12 in the treatment period will be plotted for each treatment group. The same timecourses will also be plotted by the randomization stratification factor (statin response).

8.3 Subgroup Analyses

Subgroup analyses will be performed by the following items for the percent change in LDL-C from baseline to Week 12, the primary endpoint. Using the same analysis of covariance as for the primary analysis, the least squares mean for each treatment group and the differences in the mean of the least squares between each ETC-1002 group and the placebo group, together with the two-sided 95% confidence intervals, will be calculated for each subgroup. In the analysis for the statin response subgroup, the randomization stratification factor (statin response) will not be included in the model.

- Statin response (statin tolerance, statin intolerance)
- Sex (male, female)

- Familial hypercholesterolemia (yes, no)
- Diabetes mellitus (yes, no)
- Age (<65 years, ≥65 years)
- Statin use (yes, no)

9 Safety Analyses

Tabulation by treatment group (by dose and overall for ETC-1002) will be performed in the safety analysis set. Baseline is defined as the last data before the start of IMP administration in the treatment period. The same tabulation will be performed by the randomization stratification factor (statin response). In addition to analysis for the specified visit, an additional analysis will be conducted at Week 12 with missing data being imputed based on the LOCF principle (Week 12 [LOCF]). The procedure for imputation will be the same as that for efficacy endpoints.

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 in the treatment period – Date of initial IMP administration in the treatment period + 1) and for the total number of days of IMP administration in the treatment period (The total number of days of taking 3 tablets of the IMP in the treatment period).

9.2 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. The incidence of the following events will be calculated by SOC, by PT, and overall. If a subject experiences the same event more than once, the more severe event will be used.

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

TEAEs potentially causally related to the IMP will be summarized in the same manner. Summary tables only for events occurring in 2 or more subjects in any group will be prepared for TEAEs and for TEAEs potentially causally related to the IMP.

9.2.1 AEs of special interest

The incidence of AEs of special interest will be calculated by SOC and by PT. AEs of special interest potentially causally related to the IMP will be summarized in the same manner. The classification of AEs of special interest is shown in [redacted].

9.3 Clinical Laboratory Data

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

For parameters other than qualitative urinalysis, descriptive statistics of the actual value and change from baseline will be calculated at each visit. For qualitative urinalysis parameters, shift tables at each visit 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 visit 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) will be calculated.

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 visit.

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) will be calculated.

9.5 Physical Examination Data

Physical findings recorded in the CRF 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.

The number and percentage of subjects with a QTcF of >450 msec, >480 msec, or >500 msec at any postdose visit will be calculated. In addition, the number and percentage of subjects who have a change in QTcF from baseline of >30 msec or

>60 msec at any postdose visit will be calculated. The number and percentage of subjects meeting these criteria at each postdose visit will also be calculated.

For assessment of normality/abnormality, shift tables at each visit from baseline 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) will be calculated.

9.7 Other Safety Data

9.7.1 Body weight

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

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) will be calculated.

10 Pharmacokinetic Analyses

For the PK analysis set, descriptive statistics (number of subjects, number of subjects actually analyzed, mean, standard deviation, coefficient of variation, minimum, median, and maximum) will be calculated for the plasma concentrations of ETC-1002 and its active metabolite ESP15228 at each dose, visit, and postdose time point (before or at 2 to 4 hours after administration at each visit). In the calculation of descriptive statistics, plasma drug concentrations below the lower limit of quantitation will be regarded as “0” (zero).

Timecourse plots of the plasma drug concentrations of ETC-1002 and its active metabolite ESP15228 before administration at each visit will be prepared (horizontal axis: visit, longitudinal axis: plasma drug concentration). The mean ± standard deviation of plasma drug concentrations before administration at each visit calculated by dose and by visit will be plotted. Similarly, the individual timecourses for all subjects will be plotted by dose.

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

Regarding the definition of the pharmacokinetic analysis set in Section 5.3, since measurement results of plasma drug concentration will not be available at the time of unblinding, an equivalent analysis set is defined based on available records on the time of blood sampling.

Regarding the following calculations for QTcF in ECG in Section 9.6, calculations at baseline that were planned in the protocol will not be performed.

- The number and percentage of subjects with a QTcF of >450 msec, >480 msec, or >500 msec at any postdose time point will be calculated.
- The number and percentage of subjects who have a change in QTcF from baseline of >30 msec or >60 msec at any postdose time point will be calculated.

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 <50 bpm	≥15 bpm increase ≥15 bpm decrease
Systolic Blood Pressure	>160 mmHg <90 mmHg	≥20 mmHg increase ≥20 mmHg decrease
Diastolic Blood Pressure	>100 mmHg <50 mmHg	≥15 mmHg increase ≥15 mmHg decrease
Weight	N/A	≥7% increase ≥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 x upper limit of normal (ULN)
ALT	≥3 x ULN
Bilirubin, Total	≥2 x ULN
ALP	≥3 x ULN
Urea Nitrogen	≥30 mg/dL
Creatinine	≥2.0 mg/dL
Creatine Kinase (CK)	≥4 x 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/mm^3 or ≥16,000/mm^3
Platelet Count	≤75,000/mm^3 or ≥700,000/mm^3
Urinalysis	
Protein	Increase of ≥2 units
Glucose	Increase of ≥2 units
Additional Criteria	
Chloride	≤90 mEq/L or ≥118 mEq/L
Potassium	≤2.5 mEq/L or ≥6.5 mEq/L
Sodium	≤126 mEq/L or ≥156 mEq/L
Calcium	≤8.2 mg/dL or ≥12 mg/dL
Glucose	
Fasting	≥126 mg/dL
Non-fasting	≥200 mg/dL
Total Cholesterol, Fasting	≥240 mg/dL
LDL Cholesterol, Fasting	≥160 mg/dL
HDL Cholesterol, Fasting	<40 mg/dL
Triglycerides, Fasting	≥150 mg/dL

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

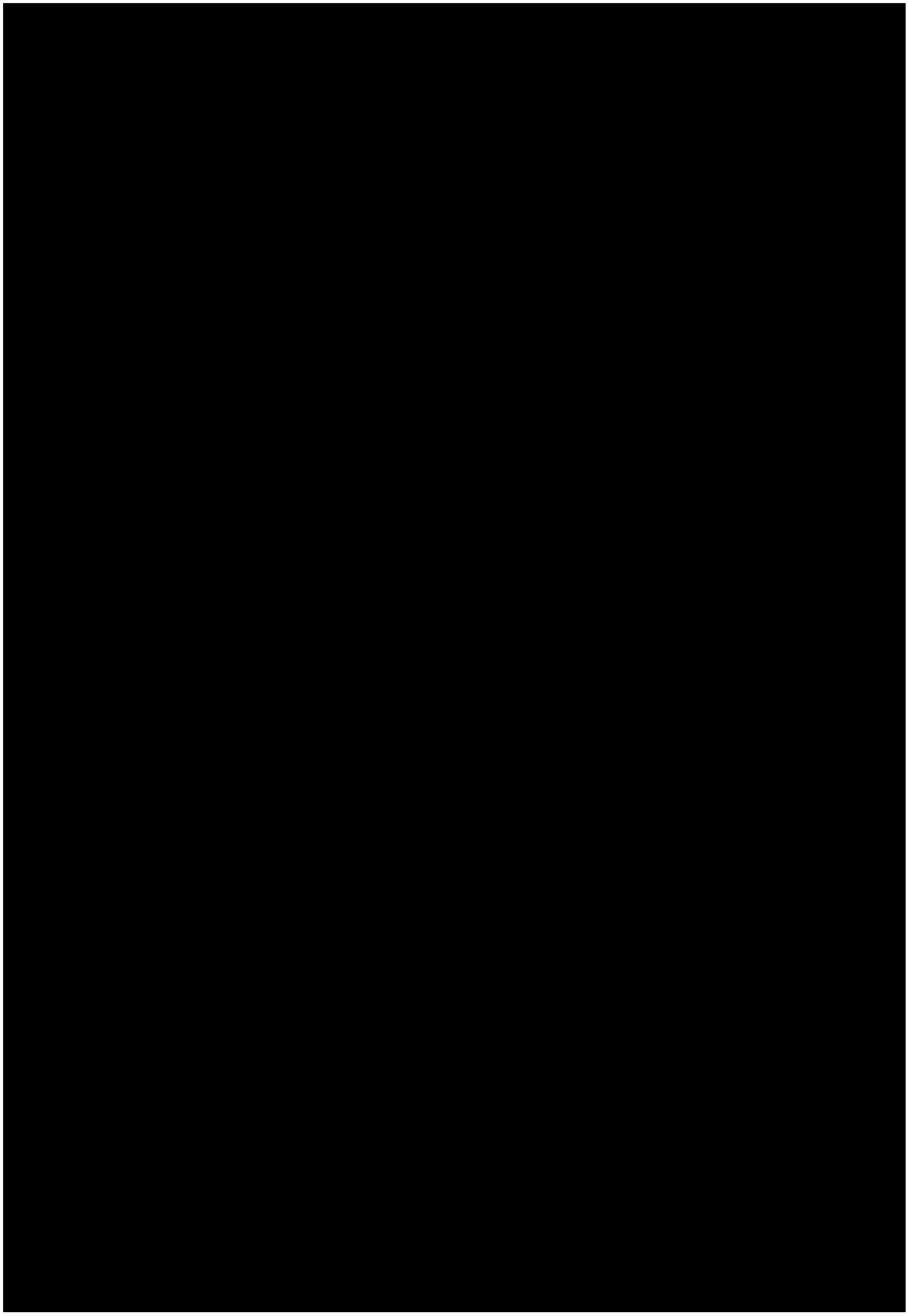
Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate	≥120 bpm	Increase of ≥15 bpm
Heart Rate	≤50 bpm	Decrease of ≥15 bpm
PR	≥200 msec	Increase of ≥50 msec
QRS	≥120 msec	Increase of ≥20 msec

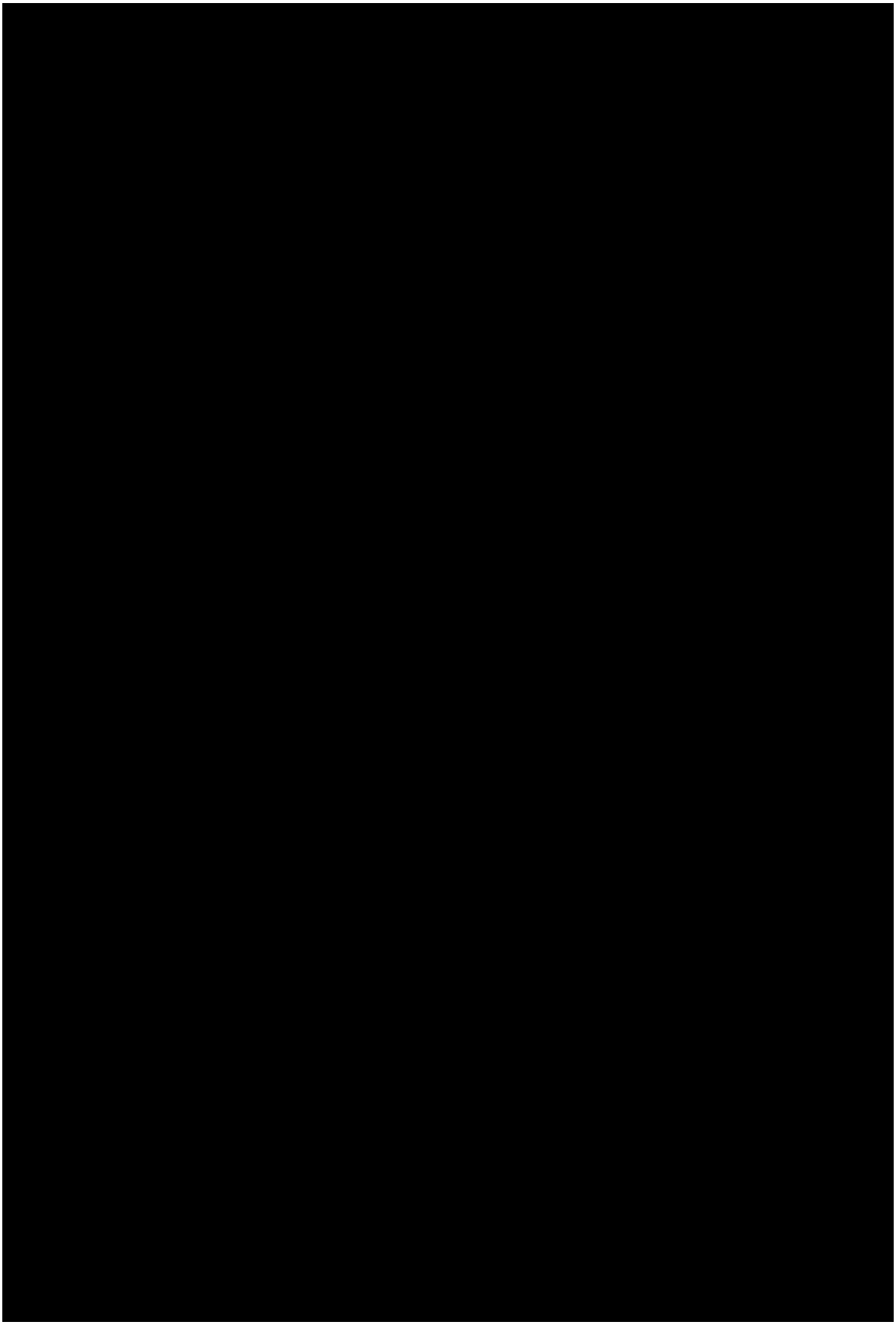
[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

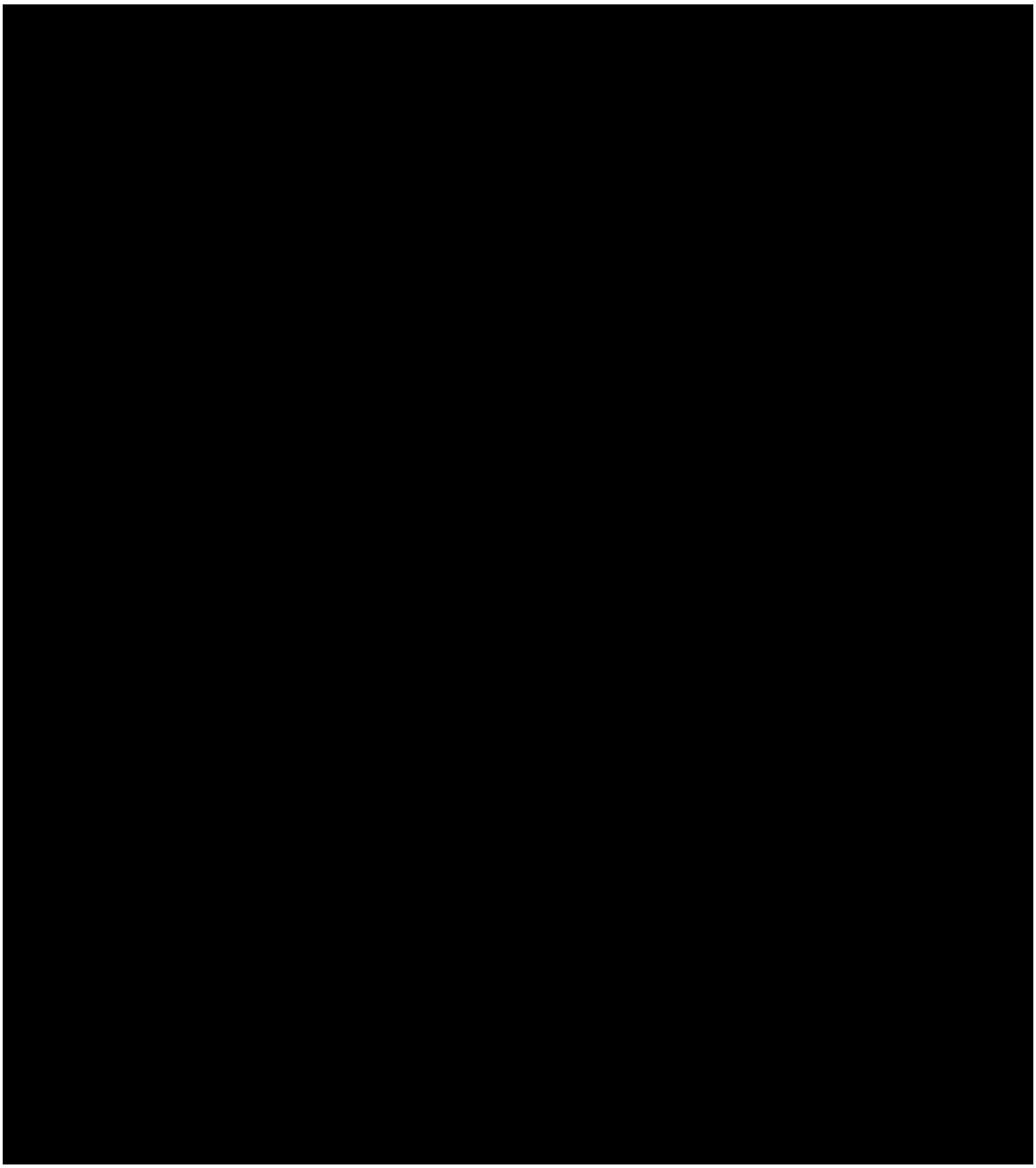
Appendix 4 Preferred Terms for Statins and Ezetimibe

Drug	EDC 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	ATORVASTATIN CALCIUM	01326102001	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
Ezetimibe	Ezetimibe	EZETIMIBE	01587001001	015870
	Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720

Drug	EDC Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 Digits
	Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410







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