STATISTICAL ANALYSIS PLAN

A Single-center, Open-label, Randomized, Two-treatment, Two-period Crossover Trial to Investigate Bioequivalence Between Single Administration of ASC-01 (Aripiprazole/Sertraline Combination Drug) and Concomitant Single Administration of Aripiprazole and Sertraline and Food Effect on Pharmacokinetics of ASC-01 in Healthy Male Adults

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Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug
ASC-01

Protocol No.: 031-102-00214

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Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AUC_{168h}	Area under the concentration-time curve from 0 to 168 hours
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_∞	Area under the concentration-time curve from time zero to infinity
BE	Bioequivalence
BMI	Body mass index
C-SSRS	Columbia-suicide severity rating scale
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum (peak) plasma concentration of the drug
CV	Coefficient of Variation
FDA	Food and Drug Administration
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MRT_∞	Mean residence time from time 0 to infinity
NCA	Non Compartment Analysis
PT	Preferred Term
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
SOC	System Organ Class
$t_{1/2,z}$	Terminal-phase elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
λ_z	Terminal elimination rate constant
AUC_%Extrap	Ratio of area under the concentration-time curve from t_{last} to infinity to AUC_∞
CL/F/BW	Apparent clearance of drug from plasma after extravascular administration per unit body weight
Vz/F	Volume of distribution in the terminal phase after extravascular administration
Vz/F/BW	Volume of distribution in the terminal phase after extravascular administration per unit body weight
T_{last}	Last measurable time
λ_z(Rsq)	Coefficient of determination adjusted for degrees of freedom for λ_z

	estimation
λ_z(point)	Measurement points for λ_z estimation
λ_z(upper)	End time of the range of measurement points at the time of λ_z estimation
λ_z(lower)	Start time of the range of measurement points at the time of λ_z estimation

1 Introduction

This statistical analysis plan describes the detailed statistical analysis methods planned for Trial 031-102 00214.

2 Trial Objectives

2.1 Cohort 1

To investigate bioequivalence for aripiprazole between administration of one ASC-01 tablet and concomitant administration of one aripiprazole 3-mg tablet and two sertraline 50-mg tablets

2.2 Cohort 2

To investigate the effect of food on the plasma pharmacokinetics of aripiprazole and sertraline following single oral administration of ASC-01 under a fasting or fed condition

3 Trial Design

3.1 Type/Design of Trial

This is a single-center, open-label, randomized, two-treatment, two-period crossover trial in healthy male adults conducted using 2 cohorts to investigate bioequivalence for aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline and the effect of food on the pharmacokinetics of ASC-01.

The trial design is outlined in Figure 3.1-1.

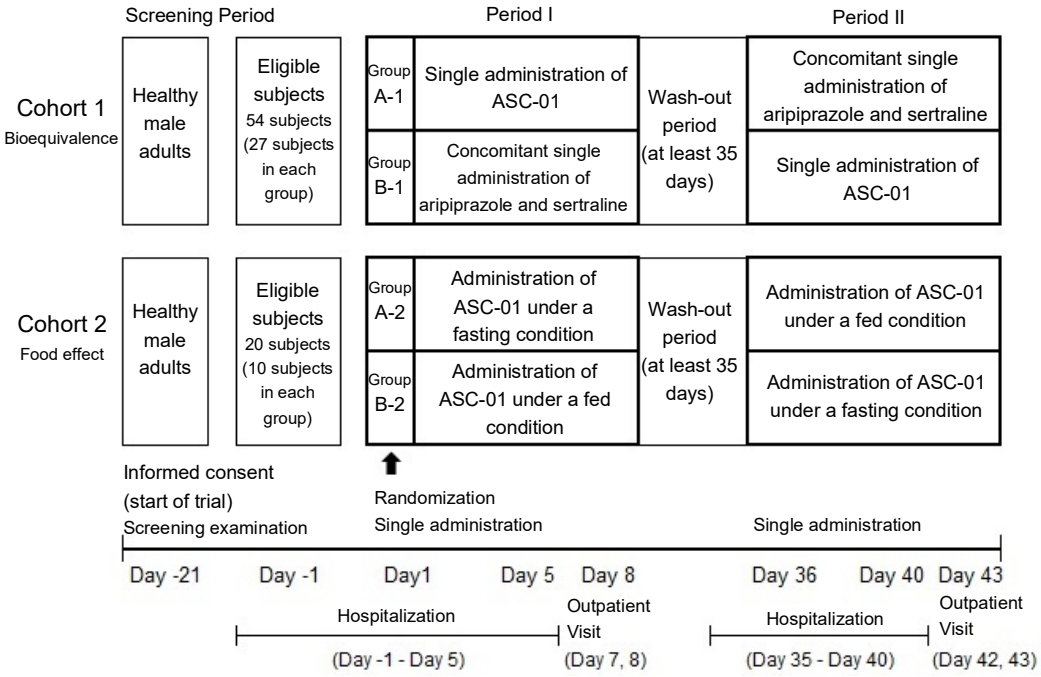

Figure 3.1-1 Trial Design Schematic

There will be a wash-out period of at least 35 days between investigational medicinal product administration in Periods I and II. The number of days with a wash-out period of 35 days is shown. Group A-1, group receiving administration of ASC-01 first; Group B-1, group receiving concomitant administration of aripiprazole and sertraline first; Group A-2, group receiving administration of ASC-01 under a fasting condition first; and Group B-2, group receiving administration of ASC-01 under a fed condition first

3.1.1 Cohort 1

A total of 54 healthy male adults will be randomized: 27 subjects into a group receiving administration of ASC-01 first (Group A-1) and 27 subjects into a group receiving concomitant administration of aripiprazole and sertraline first (Group B-1). On the respective administration days in Periods I and II, the investigational medicinal product (IMP) will be orally administered once after subjects have fasted for at least 10 hours. Subjects receiving ASC-01 in Period I will receive concomitant administration of aripiprazole and sertraline in Period II, and subjects receiving concomitant administration of aripiprazole and sertraline in Period I will receive ASC-01 in Period II. The plasma concentration of aripiprazole will be measured in each treatment period to examine pharmacokinetics.

The trial is designed in accordance with the BE Guideline.[1] Furthermore, the results in the trial will be handled in accordance with the BE Guideline.

Group	Period I	Wash-out	Period II

Group A-1 Group receiving administration of ASC-01 first	Single administration of ASC-01	period[a]	Concomitant single administration of aripiprazole and sertraline
Group B-1 Group receiving concomitant administration of aripiprazole and sertraline first	Concomitant single administration of aripiprazole and sertraline		Single administration of ASC-01

[a]: There will be a wash-out period of at least 35 days between investigational medicinal product administration in Periods I and II.

3.1.2 Cohort 2

A total of 20 healthy male adults will be randomized: 10 subjects into a group receiving administration of ASC-01 under a fasting condition first (Group A-2) and 10 subjects into a group receiving administration of ASC-01 under a fed condition first (Group B-2). On the respective administration days in Periods I and II, the IMP will be orally administered once after subjects have fasted for at least 10 hours (for administration under a fasting condition) or at 30 minutes after the start of breakfast (for administration under a fed condition). Subjects receiving administration under a fasting condition in Period I will receive administration under a fed condition in Period II, and subjects receiving administration under a fed condition in Period I will receive administration under a fasting condition in Period II. The plasma concentrations of aripiprazole and sertraline will be measured in each treatment period to examine pharmacokinetics.

Group	Period I		Period II
Group A-2 Group receiving ASC-01 under a fasting condition first	Administration under a fasting condition	Wash-out period[a]	Administration under a fed condition
Group B-2 Group receiving ASC-01 under a fed condition first	Administration under a fed condition		Administration under a fasting condition

[a]: There will be a wash-out period of at least 35 days between investigational medicinal product administration in Period I and Period II.

3.2 Method of Administration

3.2.1 Cohort 1

3.2.1.1 ASC-01 Tablets

One tablet of ASC-01 (3-mg aripiprazole/100-mg sertraline combination drug) will be administered once with approximately 150 mL of water after subjects have fasted for at least 10 hours.

3.2.1.2 Aripiprazole Tablets and Sertraline Tablets

One aripiprazole 3-mg tablet and two sertraline 50-mg tablets will be administered once with approximately 150 mL of water after subjects have fasted for at least 10 hours.

3.2.2 Cohort 2

3.2.2.1 Administration under a fasting condition

One tablet of ASC-01 will be administered once with approximately 150 mL of water after subjects have fasted for at least 10 hours.

3.2.2.2 Administration under a fed condition

One tablet of ASC-01 will be administered once with approximately 150 mL of water at 30 minutes after the start of breakfast.

3.3 Trial Population

Fifty-four healthy male adults aged 20 to 40 years, inclusive, will be enrolled in Cohort 1 and 20 in Cohort 2.

A few reserve subjects may be allowed to stand by until completion of IMP administration in Period I. If a subject to be treated withdraws consent or the investigator or subinvestigator determines that the subject should not be administered the IMP, the subject will be replaced with a reserve subject. Subjects who are withdrawn from the trial after randomization will not be replaced.

3.4 Handling of Time Points

Data measured at the time points specified in the protocol will be used. Data from examinations at discontinuation and unscheduled examinations will be presented in listings but not used for tabulation.

4 Sample Size

For Cohort 1, the sample size was determined by the method of Diletti[2] as the number of subjects required for the 90% confidence intervals for the differences in the log-converted mean C_{max} and AUC_{168h} of aripiprazole between single administration of ASC-01 and concomitant single administration of aripiprazole and sertraline to be within the acceptable range for bioequivalence of ln(0.8) to ln(1.25) based on the BE Guideline.[1]

In the results of a pharmacokinetic trial conducted to examine the bioavailability of ASC-01 (031-11-004), the ratios of the geometric mean C_{max} and AUC_{168h} of aripiprazole were respectively 1.12 and 1.05 and the within-subject variances were 0.029 and 0.006. The proportion of subjects excluded from the pharmacokinetic analysis due to vomiting or withdrawal was approximately 40%.

Assuming the ratio of the geometric mean C_{max} of aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline and the within-subject variance to be, respectively, 1.1 and 0.029, the number of subjects required to ensure a statistical power of 90% or higher is 16 per group (32 subjects in total). Assuming a 40% rate of exclusion from analysis due to withdrawal or vomiting, the sample size for Cohort 1 is set at 27 subjects per group (54 subjects in total).

For Cohort 2, referring to the FDA guidance,[3] the sample size required for the analysis of food effect on the pharmacokinetics of ASC-01 is 6 subjects per group (12 subjects in total). In consideration of the possibility of exclusion from analysis due to withdrawal or vomiting, the sample size for Cohort 2 is set at 10 subjects per group (20 subjects in total).

4.1 Decision to Conduct Add-on Subject Study

For Cohort 1, if bioequivalence cannot be demonstrated in this trial due to an insufficient number of subjects, an add-on subject study may be performed once in the same manner as the trial. However, the add-on subject study should be conducted using at least half the number of subjects included in the trial. The add-on subject study will not be conducted in the following cases:

- The difference in the mean log-converted C_{max} and AUC_{168h} between administration of ASC-01 and concomitant administration of aripiprazole and sertraline does not fall within the range of ln(0.8) to ln(1.25) as a result of this trial.
- The number of subjects required for the add-on subject study calculated from the results of the trial is considered unfeasible from an ethical or scientific point of view.

When data from the add-on subject study are pooled and analyzed with the data from this trial, study as a variable factor will also be incorporated into the analysis.

5 Statistical Analysis Datasets

5.1 Pharmacokinetic Analysis Set

Subjects who received the IMP and whose plasma concentration was measured

5.2 Bioequivalence Analysis Set

Subjects from whom C_{max} and AUC_{168h} were obtained in both Periods I and II in Cohort 1

5.3 Food Effect Analysis Set

Subjects from whom C_{max}, AUC_t, AUC_∞, and AUC_{168h} were obtained in both Periods I and II in Cohort 2

5.4 Safety Analysis Set (SAS)

Subjects who received at least one dose of IMP

5.5 Handling of Missing Data

Missing data will not be imputed.

6 Primary and Secondary Outcome Variables

6.1 Cohort 1

6.1.1 Primary Outcome Variables

- C_{max} and AUC_{168h} of aripiprazole

6.1.2 Secondary Outcome Variables

1) Plasma concentration of aripiprazole
2) Pharmacokinetic parameters of aripiprazole
3) Ratios of the C_{max}, AUC_t, AUC_∞, AUC_{168h}, MRT_∞, and λ_z of aripiprazole following administration of ASC-01 to those following concomitant administration of aripiprazole and sertraline and the difference in the t_{max} of aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline (t_{max} for ASC-01 administration minus t_{max} for concomitant administration)

6.2 Cohort 2

6.2.1 Primary Outcome Variables

- C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole and sertraline

6.2.2 Secondary Outcome Variables

1) Plasma concentrations of aripiprazole and sertraline
2) Pharmacokinetic parameters of aripiprazole and sertraline
3) Ratios of the C_{max}, AUC_t, AUC_∞, AUC_{168h}, $t_{1/2,z}$, and CL/F of aripiprazole and sertraline for administration under a fed condition to those for administration under a fasting condition and the difference in the t_{max} of aripiprazole and sertraline between administration under a fed condition and administration under a fasting condition (t_{max} for a fed condition minus t_{max} for a fasting condition)

7 Disposition and Demographic Analysis

7.1 Subject Disposition

The number of subjects screened will be ascertained, and the number randomized, the number who complete the trial, the number who discontinue the trial, and the number for each reason for discontinuation will be calculated overall and by group for each cohort. In addition, of the randomized subjects, the number who complete the trial, the number who discontinue the trial, and the percentage by reason for discontinuation will be calculated.

The number and proportion of subjects included in each analysis set will be calculated in randomized subjects overall and by group for each cohort.

7.2 Demographic and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) will be calculated for age, height, body weight (screening period), and BMI for each randomized group and for the entire population in the bioequivalence analysis set in Cohort 1 and in the food effect analysis set in Cohort 2. In addition, frequency distributions of the presence/absence of previous illness and present illness (number of subjects and percentage) will be generated for each randomized group and for the entire population. Similar summarizations will be performed for the pharmacokinetic analysis set and the safety analysis set by cohort as necessary.

7.3 Treatment Compliance

No tabulation will be performed in this study.

7.4 Prior and Concomitant Medications

No tabulation will be performed in this study.

7.5 Protocol Deviations

No tabulation will be performed in this study.

8 Efficacy Analysis

Not applicable.

9 Safety Analyses

For the safety analysis set, data will be tabulated by cohort and treatment. Baseline will be the value immediately before IMP administration (before administration on the day of IMP administration) in each period.

9.1 Extent of Exposure

The number and percentage of subjects treated in each period will be summarized overall and by group.

9.2 Adverse Events

All adverse events (AEs) will be coded by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1). The number and percentage of subjects (using the number of subjects who received each treatment as the denominator) with the following events will be calculated overall and by SOC and PT:

- Treatment-emergent AEs (TEAEs),
- TEAEs by severity.

TEAEs in each period are defined as AEs occurring after the start of administration of the IMP until 8 days after administration of the IMP. If a subject experiences the same event multiple more than once during the same period, the highest severity will be used.

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

In addition, the number and percentage of subjects (using the number of subjects who received each treatment as the denominator) with the following events will be calculated:

- TEAEs with an outcome of death,
- Serious TEAEs.

9.3 Clinical Laboratory Data

For each clinical laboratory parameter other than urine qualitative test parameters, descriptive statistics of the measured values at each time point and change from baseline will be determined. For qualitative urinalysis parameters in clinical laboratory tests, shift tables from baseline to each time point will be generated. Clinical laboratory parameters other than qualitative urinalysis parameters will be classified as “within reference range,” “below reference range,” or “above reference range” using institutional reference values, and shift tables from baseline to each time point will be generated.

9.4 Vital Sign Data

For each vital sign parameter, descriptive statistics of the measured values at each time point and change from baseline will be determined.

9.5 Physical Examination Data

For physical examination, physical findings of individual subjects will be listed.

9.6 Electrocardiogram Data

For each parameter of 12-lead electrocardiography, descriptive statistics of the measured values at each time point and change from baseline will be determined. For normal/abnormal assessment of 12-lead electrocardiography, a shift table from baseline to each time point will be prepared. The number and percentage of subjects who meet the following criteria for the measured values of corrected QT interval (Fridericia correction method [QTcF] and Bazzett correction method [QTcB]) and their changes from baseline after IMP administration will be calculated.

- Measured value is “>450 msec,” “>480 msec,” or “>500 msec.”
- Change from baseline is “>30 msec” or “>60 msec.”

9.7 Body Weight

For body weight, descriptive statistics of the measured values at each time point and change from baseline will be determined.

9.8 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS of individual subjects will be presented in a listing.

10 Pharmacokinetic Analyses

10.1 Statistical Analysis of Primary Endpoint

The following analyses will be performed on the bioequivalence analysis set for Cohort 1 and the food effect analysis set for Cohort 2.

In Cohort 1, analysis of variance will be performed on log-converted (natural logarithm) values for the C_{max} and AUC_{168h} of aripiprazole-using group (group receiving administration of ASC-01 first or group receiving concomitant administration of aripiprazole and sertraline first), treatment (ASC-01 or concomitant administration of aripiprazole and sertraline), subjects within group, and treatment period as factors. The 90% confidence intervals for the differences in the mean C_{max} and AUC_{168h} of aripiprazole between ASC-01 administration and concomitant administration of aripiprazole and sertraline will be calculated. If the 90% confidence intervals are within the range of ln(0.8) to ln(1.25), single administration of ASC-01 and single concomitant administration of aripiprazole and sertraline will be judged to be bioequivalent for aripiprazole.

If an add-on subject study is conducted, bioequivalence will be assessed based on the combined results of the trial and the add-on subject study using the same criteria. When data from the add-on subject study are pooled and analyzed with the data from the trial, study will also be included as a variable factor (fixed effect) in the mixed effects model for analysis of variance and sensitivity analysis of the primary analysis.

In Cohort 2, analysis of variance will be performed on log-converted (natural logarithm) values for the C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole- and sertraline-using group (group receiving ASC-01 under a fasting condition first or group receiving ASC-01 under a fed condition first), treatment (administration under a fasting condition or under a fed condition), subjects within group, and treatment period as factors. The 90% confidence intervals for the differences in the mean C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole and sertraline between administration under a fasting condition and administration under a fed condition will be calculated.

If there are any subjects in each cohort from whom evaluable parameters cannot be obtained in both Periods I and II, sensitivity analysis including those subjects will be performed. For the pharmacokinetic parameters of the primary endpoint, the 90% confidence interval of the mean difference between the treatments will be determine for each cohort using the mixed effects model by use of log-converted (natural logarithm) values with group, treatment, and treatment period as fixed effects and subjects within

group as a random effect. The Kenward-Roger method will be used to calculate the degrees of freedom.

10.2 Pharmacokinetic Analysis Methods

For each cohort, blood collection will be performed before and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 144, and 168 hours after administration on Day 1 in each period. PK parameters and their descriptive statistics will be calculated in the pharmacokinetic analysis set as follows.

In Cohort 1, pharmacokinetic parameters (C_{max}, AUC_t, AUC_∞, AUC_{168h}, t_{max}, $t_{1/2,z}$, λ_z, t_{last}, CL/F, CL/F/BW, V_z/F, V_z/F/BW, AUC_%Extrap, and MRT_∞) of aripiprazole will be calculated by non-compartmental analysis (NCA). Descriptive statistics of plasma concentrations and pharmacokinetic parameters of aripiprazole will be presented by treatment (ASC-01 or concomitant administration of aripiprazole and sertraline).

In Cohort 2, pharmacokinetic parameters (C_{max}, AUC_t, AUC_∞, AUC_{168h}, t_{max}, $t_{1/2,z}$, λ_z, t_{last}, CL/F, CL/F/BW, V_z/F, V_z/F/BW, AUC_%Extrap, and MRT_∞) of aripiprazole and sertraline will be calculated by NCA. Descriptive statistics of plasma concentrations and pharmacokinetic parameters of aripiprazole and sertraline will be presented by treatment (administration under a fasting condition or under a fed condition).

10.3 Details of Pharmacokinetic Statistical Analysis Methods

10.3.1 Exclusion from Pharmacokinetic Analysis

10.3.1.1 When Blood Collection Time Is Outside Acceptable Time Window

If the blood collection time is outside the acceptable time window and the data are determined to be inappropriate for calculation of descriptive statistics of plasma concentrations, the data will be included in NCA but excluded from calculation of descriptive statistics.

10.3.1.2 When a Subject Vomits

If vomiting occurs within less than twice the median t_{max}, the subject will be excluded from pharmacokinetic analysis. The median t_{max} value for the group to which the subject belongs calculated by excluding the subject who vomited will be used as the criterion for assessment.

10.3.1.3 When Prohibited Concomitant Medication Is Used

If a subject uses a prohibited medication that could affect the pharmacokinetics of the IMP, the subject will be excluded from pharmacokinetic analysis.

10.3.2 Reporting of Concentrations and Parameters

1) Drug concentration values below the lower limit of quantitation will be considered as 0.
2) CL/F/BW and V_z/F/BW will be calculated by dividing CL/F and V_z/F respectively by body weight (kg) measured prior to IMP administration.
3) Descriptive statistics to be calculated will be the number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum for plasma drug concentrations, and the number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum for parameters other than t_{max} and t_{last}. For t_{max} and t_{last}, the number of subjects, minimum, median, and maximum will be calculated. Descriptive statistics will not be calculated for λ_z (Rsq), λ_z (point), λ_z (upper), and λ_z (lower). If the number of subjects included is 0, descriptive statistics will not be calculated. If the number of subjects included is 1 or 2, only the number of subjects, arithmetic mean, geometric mean (parameters other than t_{max} and t_{last}), maximum, and minimum will be calculated.
4) Arithmetic mean and standard deviation will be used to plot the plasma concentration versus time profile.
5) Individual values and descriptive statistics of pharmacokinetic parameters will be displayed in the number of digits in Table 10.3.2-1. The coefficient of variation (CV%) of the descriptive statistics will be rounded to the first decimal place.

Table 10.3.2-1 List of Handling of Numerical Values

AUC_t, AUC_∞, AUC_{168h}	Three significant digits
AUC%Extrap	First decimal place
C_{max}	Three significant digits
CL/F, CL/F/BW	Three significant digits
MRT_∞	First decimal place
t_{max}	First decimal place
t_{last}	First decimal place
$t_{1/2,z}$	First decimal place
λ_z	Three significant digits
λ_z (point)	Integer
λ_z (lower), λ_z (upper)	Second decimal place
λ_z (Rsq)	Fourth decimal place
V_z/F, V_z/F/BW	Three significant digits
Geometric mean ratio (GMR)	Fourth decimal place
Confidence interval of GMR	Fourth decimal place

11 Pharmacodynamic Analyses

There will be no pharmacodynamic analyses in this trial.

12 Pharmacogenomic Analyses

There will be no pharmacogenomic analyses in this trial.

13 Interim Analysis

None

14 Changes in the Planned Analyses

For categorical analysis of corrected QT interval, the number and percentage of subjects who met the criteria after IMP administration, not at each time point, will be calculated.