Title: A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose, Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-906 in Japanese Healthy Male Subjects

NCT Number: NCT03237156
Statistical analysis plan Approve Date: 10-Nov-2017

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-906-1004

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose, Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-906 in Japanese Healthy Male Subjects

Phase 1 TAK-906 Single and Multiple Ascending Dose Study in Japanese Healthy Male Subjects

PHASE 1

Version: Initial
Date: 10 November 2017

Prepared by:

Based on:
Protocol Version: Initial version
Protocol Date: 6 June 2017

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1.1 Approval Signatures

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the plasma concentration-time curve</td>
</tr>
<tr>
<td>BCRP</td>
<td>breast cancer resistance protein</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum observed plasma concentration</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CRO</td>
<td>contract research organization</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P-450</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EPS</td>
<td>extrapyramidal symptoms</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FIH</td>
<td>first-in-human</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GE</td>
<td>gastric emptying</td>
</tr>
<tr>
<td>GGT</td>
<td>gamma-glutamyl transferase</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GP</td>
<td>gastroparesis</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B virus surface antigen</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HDPE</td>
<td>high density polyeethylene</td>
</tr>
<tr>
<td>hERG</td>
<td>human ether-a-go-go related gene</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harminsation</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>IUD</td>
<td>intrauterine device</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function test</td>
</tr>
<tr>
<td>LLC</td>
<td>limited liability company</td>
</tr>
<tr>
<td>LOEL</td>
<td>lowest observed effect level</td>
</tr>
<tr>
<td>MAD</td>
<td>multiple-ascending dose</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>MCH</td>
<td>mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>mean corpuscular hemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>mean corpuscular volume</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MHW</td>
<td>Ministry of Health and Welfare</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
</tr>
<tr>
<td>OAT</td>
<td>organic anion transporter</td>
</tr>
<tr>
<td>OATP</td>
<td>organic anion transporting polypeptide</td>
</tr>
<tr>
<td>OCT</td>
<td>organic cation transporter</td>
</tr>
<tr>
<td>OTC</td>
<td>over-the-counter</td>
</tr>
<tr>
<td>PD</td>
<td>pharmacodynamics</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetics</td>
</tr>
<tr>
<td>P-gp</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>SAD</td>
<td>single-ascending dose</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SUSARs</td>
<td>suspected unexpected serious adverse reactions</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>tmax</td>
<td>maximum concentration time</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
</tbody>
</table>
4.0 OBJECTIVES

4.1 Primary Objectives
The primary objective of the study is to evaluate safety and tolerability of single and multiple oral doses of TAK-906 in Japanese healthy male subjects.

4.2 Secondary Objectives
The secondary objective of the study is to evaluate PK and PD of single and multiple oral doses of TAK-906 in Japanese healthy male subjects.

4.3 Additional Objectives

4.4 Study Design

4.4.1 Trial Design
This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple dose, parallel-group study in up to 3 cohorts of Japanese healthy male subjects, to assess the safety, tolerability, PK, and PD of TAK-906.

Each cohort will consist of 8 subjects where 6 subjects will be randomized to receive TAK-906 and 2 subjects will be randomized to receive matching placebo. The study population will be 24 Japanese healthy male subjects. The randomized subjects will receive a single dose of blinded study drug on Day 1 followed by multiple doses of blinded study drug BID for 5 days from Day 3 to Day 7, except that an evening dose of study drug will not be administered on Day 7. If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and Sponsor. The investigational site should contact the Sponsor for the replacement subject’s medication identification number.

In Cohorts 1 and 2, subjects will be randomized to receive TAK-906 maleate 50 mg, 100 mg, or matching placebo. In Cohort 3, subjects will be randomized to receive TAK-906 maleate 10 mg, or matching placebo. For each cohort, follow-up assessments will occur on Day 14 which is 7 days
after completion of the last treatment dose. Dose escalation to Cohort 2 will be based on a full blinded review of safety and tolerability data until follow-up assessments from Cohort 1. Cohort 3 will be conducted in parallel with Cohort 1 or 2. Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on safety and pharmacokinetic data in preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study; however, no higher dose than the proposed highest dose (100 mg BID) will be given without Sponsor and institutional review board (IRB) approval to revise the study protocol.

The planned dose levels of TAK-906 to be evaluated are outlined in Table 1.

### Table 1 Summary of Dose Cohorts

<table>
<thead>
<tr>
<th>Cohort (a)</th>
<th>TAK-906 maleate Dose (a, b, c)</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Dose Period</td>
<td>Multiple Dose Period (d)</td>
</tr>
<tr>
<td>1</td>
<td>50 mg single dose on Day 1</td>
<td>50 mg BID for 5 days from Days 3 to 7</td>
</tr>
<tr>
<td>2</td>
<td>100 mg single dose on Day 1</td>
<td>100 mg BID for 5 days from Days 3 to 7</td>
</tr>
<tr>
<td>3</td>
<td>10 mg single dose on Day 1</td>
<td>10 mg BID for 5 days from Days 3 to 7</td>
</tr>
</tbody>
</table>

BID=twice daily
(a) Dose escalation to Cohort 2 will be based on a full blinded review of safety and tolerability data until follow-up assessments from Cohort 1. Cohort 3 will be conducted in parallel with Cohort 1 or 2.
(b) A single dose and all morning doses of trial medication in multiple dose periods will be administered after fast of at least 10 hours that continues for at least 4 hours after dosing with restricted water intake for at least 1 hour prior to and after dosing. The evening dose will be administered 12 hours after the morning dose and at least 2 hours after dinner.
(c) Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on safety and pharmacokinetic data in preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study
(d) An evening dose of study drug will not be administered on Day 7.

#### 4.4.2 Dose Escalation

The investigator will comprehensively examine the blinded safety results (AEs, physical examinations, vital signs, records of laboratory tests, and 12-lead ECG findings) obtained at all examinations by 14 days after the start of study drug administration in Cohort 1 and then determines the entry of Cohort 2 after discussion(s) with the Sponsor, and if appropriate, with medical experts.

Other criteria to consider discontinuation of the entry of Cohort 2 are as follows.

1. On an occasion that a SAE, of which relationship to the study drug cannot be denied, is observed.

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2. At the onset of an AE for which relationship to the study drug cannot be denied and for which it is considered difficult to give medications continuously. Furthermore, the maximum dose in this study was set at 100 mg BID for Cohort 2, based on the data from preceding studies, as described in Section 6.3.2 of protocol. Dose level in Cohort 2 may be changed within the range up to 100 mg, as appropriate, based on the safety and pharmacokinetic data of preceding cohorts, ie, 50 mg BID in Cohort 1 or 10 mg BID in Cohort 3 (if applicable) of this study.
5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint
The study’s primary endpoints of safety and tolerability will be assessed through TEAEs including QTc prolongation associated AE, neurologic AE, and hyperprolactinemia associated AE, physical examinations, vital signs, clinical laboratory tests, and 12-lead electrocardiogram (ECG).

5.2 Secondary Endpoints
Secondary endpoints include:
1. PK: Plasma and urine concentrations of TAK-906 and its metabolite, M23.
2. PD: Serum prolactin level.
6.0 DETERMINATION OF SAMPLE SIZE

A sample size of 8 subjects per cohort (6 active: 2 placebo) will be used in this study, and is considered sufficient for the evaluation of TAK-906 safety, tolerability, PK and PD following oral single and multiple doses. The sample size is not based on statistical power considerations.
7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions
The following definitions and calculation formulas will be used.
- TEAE: An AE whose date of onset occurs on or after the start of study drug. A TEAE whose relationship to
  study drug is missing will be considered drug-related. A TEAE whose intensity is missing will be considered
  severe.
- PTE: An AE whose date of onset occurs before the start of study drug.
- Descriptive statistics: number of subjects with non-missing values, mean, standard deviation, maximum,
  minimum, and quartiles, including geo-mean, geo-CV as needed
- QTcF interval (msec): QT interval (msec) / (RR interval (msec)/1000)^0.33 (rounded to the nearest whole
  number)
- Baseline values: The last evaluable observation (ie, non-missing) before the first dose of study drug. If no
  evaluable observation is obtained before the first dose, the baseline value will be missing.
- TEAE occurred in single dose period: A TEAE occurred prior to start of multiple dosing.
- TEAE occurred in multiple dose period: A TEAE occurred from Day 3 postdose through Day 14 (follow-up
  visit).

7.1.2 Definition of Study Days
Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first
  dose will be defined as Study Day 1. Other study days are defined relative to Study Day 1, eg, the day 2 days prior
  to Study Day 1 is Day -2 and the day after Study Day 1 is Day 2.

7.1.3 Definition of Study Visit Windows
The baseline visit is defined as the period before the first dose of study drug, and post-baseline visits are defined in
  line with CRF-recorded visits. The last evaluable observation (ie. non-missing) in the baseline visit will be used as
  the baseline value, and all evaluable observation will be used for each post-baseline visit.

7.1.4 Method of Data Conversion and Handling of Missing Data
No imputation of missing data or of excluded data will be applied. Values below the lower limit of quantification
  will be handled as 0.

7.2 Analysis Sets
The Safety Analysis Set will be defined as all subjects who received at least one dose of the study drug.
The PK Analysis Set will consist of subjects who received at least one dose of the study drug, completed the
  minimum protocol specified procedures with no significant protocol deviations which are listed below, and were
  evaluable for the pharmacokinetics.
- Subjects who did not meet inclusion criteria #3 or #4
- Subjects who met exclusion criteria #1, #4, #5, #6, #7, #9, #10, #12, #13, #15, #17, #18, #19, #23 or #25

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The PD Analysis Set will consist of subjects who received at least one dose of the study drug, completed the minimum protocol specified procedures with no significant protocol deviations which are listed below, and were evaluable for the pharmacodynamics.

- Subjects who did not meet inclusion criteria #3 or #4
- Subjects who met exclusion criteria #1, #4, #5, #6, #7, #9, #10, #12, #13, #15, #17, #18, #19, #23 or #25

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: Date First Subject Signed Informed Consent Form
                     Date of Last Subject’s Last Visit/Contact
                     MedDRA Version
                     SAS Version Used for Creating the Datasets

Analytical Methods: (1) Study Information
                     Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set: All Subjects Who Did Not Enter the Treatment Period

Analysis Variables: Age (years) [Min<= - <30, 30<= - <40, 40<= - <=Max]

Analytical Methods: (1) Screen Failures
                     Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: Eligibility Status [Eligible for Randomization, Not Eligible for Randomization]
                     Primary Reason for Subject Not Being Eligible [Adverse Event, Death, Lost to Follow-Up, Protocol Deviation, Sample Size Sufficient, Screen Failure, Study Terminated by Sponsor, Withdrawal by subject, Other]

Analytical Methods: (1) Eligibility for Entrance into the Treatment Period
                     Frequency distributions will be provided. When calculating the percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.
7.3.4 Disposition of Subjects

Analysis Set: Randomized Set

Analysis Variables:
- Study Drug Administration Status [Randomized but Not Treated]
- Reason for Not Being Treated [Adverse Event, Death, Lost to Follow-Up, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by subject, Other]
- Study Drug Completion Status [Completed Study Drug, Prematurely Discontinued Study Drug]
- Reason for Discontinuation of Study Drug [Adverse Event, Death, Lost to Follow-Up, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by subject, Other]

Analytical Methods:

(1) Disposition of Subjects
Frequency distributions will be provided by dose and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of study drug, the total number of subjects who prematurely discontinued the study drug will be used as the denominator.

7.3.5 Protocol Deviations

Analysis Set: Randomized Set

Analysis Variables:
- Protocol Deviation [Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Methods:

(1) Protocol Deviations
Frequency distribution will be provided by dose and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.6 Analysis Sets

Analysis Set: Randomized Set

Analysis Variables:
- Handling of Subjects [Entry Criteria]
- Safety Analysis Set [Included, Excluded]
- PK Analysis Set [Included, Excluded]
7.4 **Demographic and Other Baseline Characteristics**

Analysis Set: PK Analysis Set  
PD Analysis Set  
Safety Analysis Set

Analysis Variables:  
- Age (years)  
- Height (cm)  
- Weight (kg) (Baseline)  
- BMI (kg/m²) (Baseline)  
- Smoking Classification  
- Consumption of Alcohol  
- Consumption of Caffeine

Analytical Methods:  
(1) **Summary of Demographics and Other Baseline Characteristics**  
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by dose and overall.

7.5 **Medical History and Concurrent Medical Conditions**

There will be no analysis of medical history and concurrent medical conditions.

7.6 **Medication History and Concomitant Medications**

There will be no analysis of medication history and concomitant medications.

7.7 **Study Drug Exposure and Compliance**

Not applicable

7.8 **Efficacy Analysis**

Not applicable
7.9  Pharmacokinetic/Pharmacodynamic Analysis

7.9.1  Pharmacokinetic Analysis

7.9.1.1  Plasma Concentrations of TAK-906 and M23

Analysis Set:             PK Analysis Set except subjects with placebo
Analysis Variable:       Plasma Concentrations of TAK-906 and M23
Time Point:              Visit: Days 1 and 7
                        Pre–morning dose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 hours post–morning dose
                        (relative to start time of morning dose at Day 1 or 7)
                        Visit: Days 3-6
                        Pre–morning dose (0 hours)

Analytical Methods:      The following summaries will be provided for each analyte by dose.
                        (1) Summary of Plasma Concentrations by Time Point
                            Descriptive statistics for observed values will be provided for each time point. In
                            addition, geometric mean, geometric standard deviations, and %CV will be provided
                        (2) Concentration-time Profiles for Individual Subjects
                            Observed values will be plotted using individual case plot.
                        (3) Mean Concentration-time Profiles with Standard Deviations
                            Mean of plasma concentration will be plotted by time point using linear scale for Days
                            1-7, Day 1 and Day 7 respectively.
                        (4) Geometric Mean Concentration-time Profiles with Geometric Standard Deviations
                            Geometric Mean of plasma concentration will be plotted by time point using
                            natural log scale for Days 1-7, Day 1 and Day 7 respectively.

7.9.1.2  Plasma PK Parameters of TAK-906 and M23

Analysis Set:             PK Analysis Set except subject with placebo
Analysis Visit and       Plasma Concentrations of TAK-906 and M23
Variable:                Visit: Day 1
                        $C_{\text{max}}$  $t_{\text{max}}$  $AUC_{\infty}$
                        $AUC_{\text{last}}$  $AUC_{24}$  $AUC_t$
                        $t_{1/2}$  $\lambda_z$  CL/F (TAK-906 only)
                        $V/F$ (TAK-906 only)  MRT_{\text{incl,eq}}$
                        Visit: Day 7
                        $C_{\text{max,ss}}$  $t_{\text{max,ss}}$  $AUC_{t,ss}$
                        $t_{1/2}$  $\lambda_z$  CL/F_{ss} (TAK-906 only)
                        $V/F_{ss}$ (TAK-906 only)  MRT_{\text{incl,eq}}
                        $C_{av,ss}$
Analytical Methods: The following summaries will be provided for each analyte by dose.

1. **Summary of Plasma PK Parameters**
   Descriptive statistics for PK parameters will be provided. In addition, geometric mean and %CV will be computed for $C_{\text{max}}$ and AUCs.

2. **Exposure versus dose plots**
   Scatter plot will be created with the X axis as dose levels and Y axis as $C_{\text{max}}$ or AUCs.

3. **Dose-normalized exposure versus dose plots**
   Plots of dose-normalized $C_{\text{max}}$ and AUCs versus dose levels will be prepared with individual subjects data.

4. **Dose proportionality**
   Dose proportionality of $C_{\text{max}}$ and AUCs across dose levels will be assessed using linear and power model.

### 7.9.1.3 Urine PK Parameters of TAK-906 and M23

**Analysis Set:** PK Analysis Set except subject with placebo

**Analysis Visit and Variable:** Urine PK Parameters of TAK-906 and M23, and the Total of TAK-906 and M23

Visit:
- Day 1
  - $A_{e,24}$
  - $f_{e,24}$
  - $CL_R$

Visit: Day 7
- $A_{e,7}$
- $f_{e,7}$
- $CL_R$

Analytical Methods: The following summaries will be provided for each analyte by dose.

1. **Summary of Urine PK Parameters**
   Descriptive statistics for PK parameters will be provided. Here, only $f_e$ will be summarized for the total of TAK-906 and M23.

### 7.9.2 Pharmacodynamic Analysis

#### 7.9.2.1 Serum Concentrations of prolactin level

**Analysis Set:** PD Analysis Set

**Analysis Variables:** Serum concentration of prolactin

Visit:
- Day 1: Predose, 1, 2, 4, 6, and 24 hours post single dose.
- Days 3-6: Just before morning dose.
- Day 7: Predose, 1, 2, 4, 6, and 24 hours post morning dose.
- Day 14

Analytical Methods: The following summaries will be provided by dose.

1. **Summary of Serum Concentrations by Time Point**
Descriptive statistics for observed values and change from Day 1 predose will be provided for each time point. In addition, geometric mean, geometric standard deviations, and %CV will be provided.

(2) Concentration-time Profiles for Individual Subjects
Observed values will be plotted using individual case plot.

(3) Mean Concentration-time Profiles with Standard Deviations
Mean of serum concentration will be plotted by time point using linear scale for Days 1-7, Day 1 and Day 7 respectively.

(4) Geometric Mean Concentration-time Profiles with Geometric Standard Deviations
Geometric Mean of serum concentration will be plotted by time point using natural log scale for Days 1-7, Day 1 and Day 7 respectively.

7.9.2.2 PD Parameters of Serum prolactin level
Analysis Set: PD Analysis Set
Analysis Visit and Variable: Serum concentration of prolactin
Visit: Day 1
\[ C_{\text{max}} \quad t_{\text{max}} \quad AUC_{\infty} \]
\[ \text{AUC}_{\text{last}} \quad \text{AUC}_{24} \quad AUC_{\tau} \]
\[ t_{1/2z} \quad \lambda_z \]
Visit: Day 7
\[ C_{\text{max,ss}} \quad t_{\text{max,ss}} \quad AUC_{\tau,ss} \]
\[ t_{1/2z} \quad \lambda_z \]
Analytical Methods: The following summaries will be provided by dose.

(1) Summary of PD Parameters
Descriptive statistics for PD Parameters will be provided. In addition, geometric mean and %CV will be computed for \( C_{\text{max}} \) and AUCs.

(2) PD Parameters versus dose plots
Plots of Cmax and AUCs versus dose levels will be prepared with individual subjects data.

7.10 Other Outcomes
Not applicable

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events
Analysis Set: Safety Analysis Set
Analysis Variables: TEAE
Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]

Analytical Methods: The following summaries will be provided by dose.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects
- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3) and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events
For each summary, the total number of events will be calculated.

7.11.1.2 Overview of Treatment-Emergent Adverse Events Occurred in Single Dose Period

Analysis Set: Safety Analysis Set
Analysis Variables: TEAE occurred in single dose period
Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]

Analytical Methods: The following summaries will be provided by dose.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of
subjects)
2) Relationship of Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
3)Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

4) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
5) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
6) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
7) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects
- Summaries for 2) and 5)
  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3) and 5)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events
For each summary, the total number of events will be calculated.

7.11.1.3 Overview of Treatment-Emergent Adverse Events Occurred in Multiple Dose Period

Analysis Set: Safety Analysis Set
Analysis Variables: TEAE occurred in multiple dose period
Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]
Analytical Methods: The following summaries will be provided by dose.

(1) Overview of Treatment-Emergent Adverse Events
1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number

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of events, number and percentage of subjects)

5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

6) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)

7) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)

8) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

**Number of subjects**
- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3) and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

**Number of events**
For each summary, the total number of events will be calculated.

### 7.11.1.4 Displays of Treatment-Emergent Adverse Events

**Analysis Set:** Safety Analysis Set

**Analysis Variables:** TEAE

**Categories:** Intensity [Mild, Moderate, Severe]

**Analytical Methods:** The following summaries will be provided using frequency distribution by dose. TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

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(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(9) QTc prolongation associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(10) Neurologic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(11) Hyperprolactinemia associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(12) Drug-Related QTc prolongation associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(13) Drug-Related Neurologic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(14) Drug-Related Hyperprolactinemia associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

**Number of subjects**
- Summary tables other than (5), and (6)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.
- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

### 7.11.1.5 Displays of Treatment-Emergent Adverse Events Occurred in Single Dose Period

**Analysis Set:** Safety Analysis Set

**Analysis Variables:** TEAE occurred in single dose period

**Categories:**
- Intensity: [Mild, Moderate, Severe]

**Analytical Methods:** The following summaries will be provided using frequency distribution by dose. TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(2) Treatment-Emergent Adverse Events by System Organ Class
(3) Treatment-Emergent Adverse Events by Preferred Term
(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term
(7) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(8) QTc prolongation associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(9) Neurologic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(10) Hyperprolactinemia associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(11) Drug-Related QTc prolongation associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(12) Drug-Related Neurologic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(13) Drug-Related Hyperprolactinemia associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), and (6)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.
- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

7.11.1.6 Displays of Treatment-Emergent Adverse Events Occurred in Multiple Dose Period

Analysis Set: Safety Analysis Set
Analysis Variables: TEAE occurred in multiple dose period
Categories: Intensity [Mild, Moderate, Severe]
Analytical Methods: The following summaries will be provided using frequency distribution by dose.
  TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.
(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) QTc prolongation associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(10) Neurologic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(11) Hyperprolactinemia associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(12) Drug-Related QTc prolongation associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(13) Drug-Related Neurologic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(14) Drug-Related Hyperprolactinemia associated Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), and (6)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

7.11.1.7 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: PTE

Analytical Methods: The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will
be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term
(2) Serious Pretreatment Events by System Organ Class and Preferred Term
The frequency distribution will be provided according to the rules below.

Number of subjects
A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variables:

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Serum Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs (×10^12/L)</td>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>WBCs (×10^9/L)</td>
<td>Alkaline Phosphatase (U/L)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>AST (U/L)</td>
</tr>
<tr>
<td>Platelets (×10^10/L)</td>
<td>GGT (I/U/L)</td>
</tr>
<tr>
<td>White blood cell differential (Neutrophils (×10^9/L), Eosinophils (×10^9/L), Basophils (×10^9/L), Monocytes (×10^9/L), Lymphocytes (×10^9/L))</td>
<td>Bilirubin (Total) (mg/dL)</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>C-reactive Protein (mg/dL)</td>
</tr>
<tr>
<td>MCHC (%)</td>
<td>Albumin (g/dL)</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>Creatinine (mg/dL)</td>
</tr>
<tr>
<td>Protein (Total) (g/dL)</td>
<td>Blood Urea Nitrogen(mg/dL)</td>
</tr>
<tr>
<td>Uric Acid (mg/dL)</td>
<td>Total Cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>Phosphorus (mg/dL)</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>Glucose (mg/dL)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>Potassium (mEq/L)</td>
</tr>
</tbody>
</table>

Visit: Baseline, Days 2, 5, 8 and 14

Analytical Methods: The following summaries will be provided by dose.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided for each visit.

(2) Case Plots
Spaghetti plots will be prepared for each ECG parameters by dose levels.

(3) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided. For each laboratory test, the laboratory values will be classified as "Low", "Normal", or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

(4) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Test results
Overall frequency distributions of MAV after first dose will be provided. If a laboratory test result has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

Urinalysis

Analysis Set:  Safety Analysis Set
Analysis Variables:
- pH: [Min<=, 5.0<=, 8.5<, Max]
- Specific gravity: [Min<=, 1.005<, 1.030<, Max]
- Protein: [-+, 1+, 2+, 3+, 4+]
- Glucose: [-+, 1+, 2+, 3+, 4+]
- Nitrites: [-, 1+, 2+]
- Ketones: [-, 1+, 2+, 3+]
- Urobilinogen: [-, -+, 1+, 2+, 3+, 4+]
- Blood: [-, 1+, 2+, 3+]
- Urine microscopy:
  - RBC/high-power field: [1-5/WF, 6-10/WF, 0-1/LF, 1-5/HF, 6-10/HF, 11-20/HF, 21-50/HF, 51-99/HF, 100≤/HF]
  - WBC/high-power field: [1-5/WF, 6-10/WF, 0-1/LF, 1-5/HF, 6-10/HF, 11-20/HF, 21-50/HF, 51-99/HF, 100≤/HF]
  - Squamous epithelial cells: [1-5/WF, 6-10/WF, 0-1/LF, 1-5/HF, 6-10/HF, 11-20/HF, 21-50/HF, 51-99/HF, 100≤/HF]

Visit: Baseline, Days 2, 5, 8, and 14.
Analytical Methods: The following summaries will be provided by dose. For only specific gravity, summary (2) will be provided.

(1) Summary of Shifts of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(2) Case Plots
Plots over time for each subject will be presented.
7.11.3 Vital Signs

Analysis Set: Safety Analysis Set
Analysis Variables: Body Temperature (°C)
Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
Respiratory Rate (bpm)
Pulse (bpm)

Visit:
Day 1: Predose, 1, 2, 4, 6, and 24 hours post single dose.
Days 3-6: Before morning dose.
Day 7: Predose, 1, 2, 4, 6, and 24 hours post morning dose.
Day 14

Analytical Methods: For each variable, following summary will be provided by dose.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-Day 1: Predose) will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters
Overall frequency distributions of MAV after first dose will be provided. If a vital sign parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

7.11.4 12-Lead ECGs

Analysis Set: Safety Analysis Set
Analysis Variables: Heart Rate (bpm)
RR Interval (msec)
PR Interval (msec)
QT Interval (msec)
QTcF Interval (msec)
QRS Interval (msec)
12-Lead ECG Interpretation ["Within Normal Limits", "Abnormal, Not Clinically Significant", "Abnormal, Clinically Significant"]

Visit:
Day 1: Predose, 1, 2, 4, 6, and 24 hours post single dose.
Day 5: Predose, 1, and 2 hours post morning dose.
Day 7: Predose, 1, 2, 4, 6, and 24 hours post morning dose.

Analytical Methods: For each variable other than 12-lead ECG interpretations, summary (1), (2), and (3) will be provided by dose.
For 12-lead ECG interpretations, summary (4) will be provided by dose.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-Day 1: Predose) will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
Overall frequency distributions of MAV after first dose will be provided. If an ECG parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(4) Summary of Shifts of ECG Parameters
Shift tables showing the number of subjects in each category at Day 1 Predose and each post-Day 1 Predose visit will be provided.

7.11.5 Other Observations Related to Safety
Not applicable

7.12 Interim Analysis
Not applicable

7.13 Changes in the Statistical Analysis Plan
From the SAP version 1.0, the following parts were updated. In 7.11.2, the units for white blood cell differential modified. In Appendix 1, since there is no abnormal criteria for white blood cell differential in the site, the MAV criteria for white blood cell differential was deleted.
8.0 REFERENCES
Not applicable
Appendix 1. Criteria for Markedly Abnormal Values

Hematology, Serum Chemistry, Urinalysis, Vital Signs, and 12-lead ECG (except Upper MAV Criteria of QTcF Interval)

For each parameter, all evaluable data obtained up to Day 14 (or Day 8 for 12-lead ECG) will be classified as a MAV or not. The criteria in the table below will be used. The lower limit of the normal range and the upper limit of the normal range are abbreviated as LLN and ULN.

For each parameter and subject, classifications will be made according to the conditions i) to iii) provided below. The lower and the upper criteria will be considered separately.

i) A subject with at least one evaluable data after baseline or "Day 1: Predose" that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline or "Day 1: Predose" that doesn't meet the MAV criteria will be considered as a subject without MAV.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV for that parameter.

### Hematology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>Age</th>
<th>MAV Criteria</th>
<th>Lower Criteria</th>
<th>Upper Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs ($\times 10^6/\mu L$)</td>
<td>-</td>
<td>-</td>
<td>&lt;0.8×LLN</td>
<td>$&gt;1.2\times ULN$</td>
<td></td>
</tr>
<tr>
<td>Platelets ($\times 10^3/\mu L$)</td>
<td>-</td>
<td>-</td>
<td>&lt;75</td>
<td>$&gt;600$</td>
<td></td>
</tr>
<tr>
<td>WBCs ($\times 10^3/\mu L$)</td>
<td>-</td>
<td>-</td>
<td>&lt;0.5×LLN</td>
<td>$&gt;1.5\times ULN$</td>
<td></td>
</tr>
</tbody>
</table>

### Serum Chemistry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>Age</th>
<th>MAV Criteria</th>
<th>Lower Criteria</th>
<th>Upper Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (total) (g/dL)</td>
<td>-</td>
<td>-</td>
<td>&lt;0.8×LLN</td>
<td>$&gt;1.2\times ULN$</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>-</td>
<td>-</td>
<td>&lt;2.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>$&gt;30$</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>$&gt;13.0$</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>$&gt;2.0$</td>
<td></td>
</tr>
</tbody>
</table>
### Parameter

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Criteria</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bilirubin (total) (mg/dL)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Vital Signs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>Age</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower Criteria</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>-</td>
<td>-</td>
<td>&lt;85</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>-</td>
<td>-</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>-</td>
<td>-</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>-</td>
<td>-</td>
<td>&lt;35.6</td>
</tr>
</tbody>
</table>

### 12-lead ECG

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>Age</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower Criteria</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>-</td>
<td>-</td>
<td>&lt;50</td>
</tr>
<tr>
<td>QT interval (msec)</td>
<td>-</td>
<td>-</td>
<td>&lt;=50</td>
</tr>
<tr>
<td>QTcF interval (msec)</td>
<td>-</td>
<td>-</td>
<td>&lt;=50</td>
</tr>
</tbody>
</table>
12-lead ECG (Upper MAV Criteria of QTcF Interval)

All evaluable data (ie, non-missing data) obtained up to Day 8 will be classified as a MAV or not. The criteria in the table below will be used. Note that the observed value and the change from Day 1 Predose used for classification should be measurements taken on the same day.

For each subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject with at least one evaluable data after Day 1 Predose that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after Day 1 Predose that meets any of the following will be considered as a subject without MAV.
   - Observed value is less than 450 msec and not missing.
   - Change from Day 1 Predose is less than 30 msec and not missing, and observed value is less than 500 msec and not missing.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>Age</th>
<th>MAV Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF Interval (msec)</td>
<td>-</td>
<td>-</td>
<td>If either of the following conditions is met:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>・ observed value &gt;=500</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>・ change from Day 1 Predose &gt;= 30 and observed value &gt;=450</td>
</tr>
</tbody>
</table>