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

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

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:

PPD

Based on:

Protocol Version: Initial version

Protocol Date: 6 June 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CYP	cytchrome P-450
DA	dopamine
CCI	[redacted]
eCRF	electronic case report form
ECG	electrocardiogram
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GE	gastric emptying
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GP	gastroparesis
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HDPE	high density poleythylene
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
ICH	International Conference on Harminsation
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LFT	liver function test
LLC	limited liability company
LOEL	lowest observed effect level
MAD	multiple-ascending dose

MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHW	Ministry of Health and Welfare
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OTC	over-the-counter
PD	pharmacodynamics
PK	pharmacokinetics
P-gp	P-glycoprotain
CCI	[redacted]
RBC	red blood cell
SAD	single-ascending dose
SAE	Serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
tmax	maximum concentration time
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
WBC	white blood cell

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

CCI

[redacted]

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) CCI [redacted] 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

Cohort (a)	TAK-906 malesate Dose (a, b, c)		Subjects
	Single Dose Period	Multiple Dose Period (d)	
1	50 mg single dose on Day 1	50 mg BID for 5 days from Days 3 to 7	6 TAK-906 2 Placebo
2	100 mg single dose on Day 1	100 mg BID for 5 days from Days 3 to 7	6 TAK-906 2 Placebo
3	10 mg single dose on Day 1	10 mg BID for 5 days from Days 3 to 7	6 TAK-906 2 Placebo

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.

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 #3or #4
- Subjects who met exclusion criteria #1, #4, #5, #6, #7, #9, #10, #12, #13, #15, #17, #18, #19, #23 or #25

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 #3or #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 and Subject Data Analysis Sets	[Entry Criteria]
	Safety Analysis Set	[Included, Excluded]
	PK Analysis Set	[Included, Excluded]

PD Analysis Set [Included, excluded]

Analytical Methods: **(1) Analysis Sets**

Frequency distributions will be provided by dose.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	PK Analysis Set	
	PD Analysis Set	
	Safety Analysis Set	
Analysis Variables:	Age (years)	[Min<= - <30, 30<= - <40, 40<= - <=Max]
	Height (cm)	[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
	Weight (kg) (Baseline)	[Min<= - <50.0, 50.0<= - <60.0, 60.0<= - <70.0, 70.0<= - <80.0, 80.0<= - <=Max]
	BMI (kg/m^2) (Baseline)	[Min<= - <18.5, 18.5<= - <=25.0, 25.0< - <=Max]
	Smoking Classification	[Never, Current, Former]
	Consumption of Alcohol	[Daily, A Few Times Per Week, A Few Times Per Month, No]
	Consumption of Caffeine	[Yes, No]

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 Variable: Plasma Concentrations of TAK-906 and M23

Visit: Day 1

C_{max}	t_{max}	AUC_{∞}
AUC_{last}	AUC_{24}	AUC_{τ}
$t_{1/2z}$	λ_z	CL/F (TAK-906 only)
V_z/F (TAK-906 only)	$MRT_{\infty,ev}$	

Visit: Day 7

$C_{max,ss}$	$t_{max,ss}$	$AUC_{\tau,ss}$
$t_{1/2z}$	λ_z	CL/F_{ss} (TAK-906 only)
V_z/F_{ss} (TAK-906 only)	$MRT_{\infty,ev}$	$C_{av,ss}$

$C_{min,ss}$	$t_{min,ss}$	PTF%
$R_{ac(AUC)}$	$R_{ac(Cmax)}$	

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_{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_{max} or AUCs.

(3) Dose-normalized exposure versus dose plots
Plots of dose-normalized Cmax and AUCs versus dose levels will be prepared with individual subjects data.

(4) Dose proportionality
Dose proportionality of C_{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

Ae_{24}	$f_{e,24}$	CL_R

Visit: Day 7

Ae_{τ}	$f_{e,\tau}$	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 fe 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 1predose 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_{max}	t_{max}	AUC_{∞}
AUC_{last}	AUC_{24}	AUC_{τ}
$t_{1/2z}$	λ_z	

Visit: Day 7

$C_{max,ss}$	$t_{max,ss}$	$AUC_{\tau,ss}$
$t_{1/2z}$	λ_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_{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

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

(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 : Hematology

RBCs ($\times 10^{10}$/L)	WBCs ($\times 10^{8}$/L)	Hemoglobin (g/dL)
Hematocrit (%)	Platelets ($\times 10^{10}$/L)	
White blood cell differential (Neutrophils ($\times 10^{8}$/L), Eosinophils ($\times 10^{8}$/L), Basophils ($\times 10^{8}$/L), Monocytes ($\times 10^{8}$/L), Lymphocytes ($\times 10^{8}$/L))		
MCH (pg)	MCHC (%)	MCV (fL)

Serum Chemistry

ALT (U/L)	Alkaline Phosphatase (U/L)	AST (U/L)
GGT (IU/L)	Bilirubin (Total) (mg/dL)	
Lactose Dehydrogenase (U/L)	C-reactive Protein (mg/dL)	Albumin (g/dL)
Protein (Total) (g/dL)	Creatinine (mg/dL)	Blood Urea Nitrogen(mg/dL)
Uric Acid (mg/dL)	Total Cholesterol (mg/dL)	Phosphorus (mg/dL)
Triglycerides (mg/dL)	Glucose (mg/dL)	Potassium (mEq/L)
Sodium (mEq/L)	Magnesium (mg/dL)	Calcium (mg/dL)
Chloride (mmol/L)		

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, 5.0<= - <=8.5, 8.5< - <=Max]
	Specific gravity	[Min<= - <1.005, 1.005<= - <=1.030, 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, summarie (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

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
RBCs ($\times 10^6/\mu L$)	-	-	<0.8×LLN	>1.2×ULN
Platelets ($\times 10^3/\mu L$)	-	-	<75	>600
WBCs ($\times 10^3/\mu L$)	-	-	<0.5×LLN	>1.5×ULN

Serum Chemistry

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Protein (total) (g/dL)	-	-	<0.8×LLN	>1.2×ULN
Albumin (g/dL)	-	-	<2.5	-
Blood urea nitrogen (mg/dL)	-	-	-	>30
Uric acid (mg/dL)	-	-	-	>13.0
Creatinine (mg/dL)	-	-	-	>2.0

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Total cholesterol (mg/dL)	-	-	-	>300
Triglycerides (mg/dL)	-	-	-	>2.5×ULN
Bilirubin (total) (mg/dL)	-	-	-	>2.0
Sodium (mEq/L)	-	-	<130	>150
Potassium (mEq/L)	-	-	<3.0	>6.0
Chloride (mEq/L)	-	-	<75	>126
Calcium (mg/dL)	-	-	<7.0	>11.5
Phosphorus (mg/dL)	-	-	<1.6	>6.2
Alkaline phosphatase (IU/L)	-	-	-	>3×ULN
AST (IU/L)	-	-	-	>3×ULN
ALT (IU/L)	-	-	-	>3×ULN
GGT (IU/L)	-	-	-	>3×ULN
Glucose (mg/dL)	-	-	<50	>350
Magnesium (mg/dL)	-	-	<1.2	>3.0

Vital Signs

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Systolic blood pressure (mmHg)	-	-	<85	>180
Diastolic blood pressure (mmHg)	-	-	<50	>110
Pulse (bpm)	-	-	<50	>120
Body temperature (°C)	-	-	<35.6	>37.7

12-lead ECG

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Heart rate (bpm)	-	-	<50	>120
QTinterval (msec)	-	-	<=50	>=460
QTcF interval (msec)	-	-	<=50	-

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.

Parameter	Gender	Age	MAV Criteria
			Upper Criteria
QTcF Interval (msec)	-	-	If either of the following conditions is met: • observed value >=500 • change from Day 1 Predose >= 30 and observed value >=450