Title: A Randomized, Open-Label, Cross-over Phase 1 Study to Evaluate the Food Effect of Single Oral Dose of TAK-536 Pediatric Formulation in Healthy Adult Male Subjects

NCT Number: NCT03434977

Statistical analysis plan Approve Date: 10-Jan-2018

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Azilsartan-1005

A Randomized, Open-Label, Cross-over Phase 1 Study to Evaluate the Food Effect of Single Oral Dose of TAK-536 Pediatric Formulation in Healthy Adult Male Subjects

A Phase 1 Food Effect Study of TAK-536 Pediatric Formulation

PHASE 1

Version: 1

Date: 10 January 2018

Prepared by:

PPD

Based on:

Protocol Version: Original (First Version)

Protocol Date: 8 December 2017

1.1 Approval Signatures

Study Title: A Randomized, Open-Label, Cross-over Phase 1 Study to Evaluate the Food Effect of Single Oral Dose of TAK-536 Pediatric Formulation in Healthy Adult Male Subjects

A Phase 1 Food Effect Study of TAK-536 Pediatric Formulation

Approvals:

PPD

PPD

PPD

PPD

PPD

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

Term	Definition
ACE	angiotensin converting enzyme
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BMI	body mass index
CKD	chronic kidney disease
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent AE

4.0 OBJECTIVES

4.1 Primary Objectives

To assess the food effect on the pharmacokinetics (PK) following single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects

4.2 Secondary Objectives

To assess the food effect on the safety of a single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects

4.3 Additional Objectives

Not applicable in this study.

4.4 Study Design

This is an open-label, 2×2 crossover study to assess the food effect on the PK and safety of a single oral dose of TAK-536 pediatric formulation in Japanese healthy adult male subjects under fasted or fed conditions in the morning.

The dosage, treatment condition, and number of subjects are shown in Table 4.a. Each subject will receive the study drug under one of the following treatment conditions in each period.

1. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fasted condition (fasted overnight for at least 10 hours prior to the study drug administration).
2. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fed condition (at 30 minutes after starting breakfast).

Table 4.a Dosage, Treatment Condition, and Number of Subjects

Sequence	Number of subjects	Dose of TAK-536	Regimen	
			Period 1	Period 2
A	6	TAK-536 10 mg Granules (TAK-536 10 mg)	Single oral dose under fasted condition	Single oral dose under fed condition
B	6	TAK-536 10 mg Granules (TAK-536 10 mg)	Single oral dose under fed condition	Single oral dose under fasted condition

Subjects will be screened for enrollment from 4 weeks (28 days) to 2 days (the day before admission) before the study drug administration (Day -28 to Day -2) in Period 1. Subjects will be admitted to the study site on the day before the study drug administration (Day -1) in both Periods 1 and 2, and will be hospitalized under medical supervision for 4 days (until 48 hours after the study drug administration). They will undergo daily examinations and observations from the day before the study drug administration (Day -1) during their

hospitalization according to the study schedule specified in the protocol section 3.0, and will be discharged from the study site on Day 3 after confirmation of safety by the investigator or sub-investigator. Subjects will return to the study site for follow-up examinations on Day 6. At least 6-day washout interval will be placed between the study drug administrations in Periods 1 and 2.

Subjects will visit the study site 5 times, including the visit for screening examinations, in this study. They will be hospitalized for a total of 8 days in Periods 1 and 2 (A schematic of the study design is shown in Figure 4.b).

The examinations scheduled on the day before the study drug administration (Day -1) in Period 2 can be replaced with the follow-up examinations (Day 6) in Period 1 if they are scheduled on the same day. If this is the case, the subject will visit the study site 4 times in this study.

Figure 4.b Schematic of Study Design

Element	Screening		Treatment (TAK-536 10 mg pediatric formulation) Period 1 and Period 2*				
Day	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3		Day 6
	Visit	Hospitalization					Visit
Content	Informed consent Screening	Admission	Study drug administration		Discharge	…	Follow-up examination

*: There will be at least 6-day washout interval between the study drug administrations in Periods 1 and 2. The examinations scheduled on the day before the study drug administration (Day -1) in Period 2 can be replaced with the follow-up examinations (Day 6) in Period 1, provided that they are scheduled on the same day.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

PK: Plasma concentrations and PK parameters of unchanged TAK-536 (C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2z}$, MRT, λ_z, CL/F, and V_z/F)

5.1.2 Secondary Endpoints

Safety: Adverse events (AEs), vital signs (sitting blood pressure, sitting pulse rate, and body temperature), weight, laboratory test results (hematology, serum chemistry, and urinalysis), and resting 12-lead ECGs

6.0 DETERMINATION OF SAMPLE SIZE

A total of 12 subjects (6 per sequence)

[Sample size justification]

A total of 12 subjects, with 6 subjects in each sequence, were considered sufficient sample size to evaluate the PK and safety of TAK-536. The sample size is not based on statistical considerations.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- Treatment-emergent adverse event (TEAE): Adverse events that occurred after the start of the study drug administration
    * Among the TEAEs, those that occurred from the start of the study drug administration in Period 1 to before the start of the study drug administration in Period 2 are deemed as "TEAEs that occurred in Period 1" and those that occurred after the start of the study drug administration in Period 2 as "TEAEs that occurred in Period 2."
- Pretreatment event(PTE):Adverse events that occurred after obtaining the consent but before the start of the study drug administration
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV)(%): Standard deviation / Mean x 100
- QTcF interval: QT interval corrected with Fridericia's correction
- Treatment conditions:
    - Single oral dose under fasted condition
    - Single oral dose under fed condition
- Treatment group:
    - A (Single oral dose under fasted condition → Single oral dose under fed condition)
    - B (Single oral dose under fed condition → Single oral dose under fasted condition)

7.1.2 Definition of Study Days

- Total Study Time in each time interval (hour): Time and date of test/observation/assessment - Time and date of start of study drug administration in each time interval (rounded to the fourth decimal place)

7.1.3 Definition of Study Visit Windows

For items of examinations, observations, and assessments described below, evaluable data (i.e., non-missing data) will be handled according to the following rules.

Evaluable data within the visit window will be used. If more than one evaluable data exist within the same visit window, the examinations, observations, and assessments with the closest Study Time to the scheduled Study Time will be used. If there are two evaluable equidistant to the scheduled Study Time, the later data will be used. The size of difference from the Study Time will be determined based on the total Study Time in each time interval (hour).

For items from examinations, observations, and assessments other than those described below, evaluable data will be handled as data at the corresponding visit based on the visits specified in the case report form. However, among the visits specified in the case report form, if the follow-up examination in Period 1 (Day 6) and the examination on the day before the study drug administration (Day -1) in Period 2 were conducted on the same day and only the evaluable data exists from either the follow-up examination (Day 6) for Period 1 or the day before the study drug administration (Day -1) for Period 2, that data will be handled though it were obtained at both visits.

Table 7.a Visit Window

Plasma drug concentration

Visit	Scheduled Study Time	Total Study Time in each time interval (hour)
Predose	Study Time (hour): 0	-5.000 - 0.000
0.5 Hour Postdose	Study Time (hour): 0.5	0.417 - 0.583
1 Hour Postdose	Study Time (hour): 1	0.917 - 1.083
1.5 Hours Postdose	Study Time (hour): 1.5	1.417 - 1.583
2 Hours Postdose	Study Time (hour): 2	1.917 - 2.083
2.5 Hours Postdose	Study Time (hour): 2.5	2.417 - 2.583
3 Hours Postdose	Study Time (hour): 3	2.917 - 3.083
3.5 Hours Postdose	Study Time (hour): 3.5	3.417 - 3.583
4 Hours Postdose	Study Time (hour): 4	3.917 - 4.083
5 Hours Postdose	Study Time (hour): 5	4.917 - 5.083
6 Hours Postdose	Study Time (hour): 6	5.917 - 6.083
8 Hours Postdose	Study Time (hour): 8	7.917 - 8.083
12 Hours Postdose	Study Time (hour): 12	11.917 - 12.083
16 Hours Postdose	Study Time (hour): 16	15.750 - 16.250
24 Hours Postdose	Study Time (hour): 24	23.750 - 24.250
48 Hours Postdose	Study Time (hour): 48	47.750 - 48.250

7.2 Analysis Sets

- Pharmacokinetic (PK) Analysis Set: All subjects who received the study drug, completed the minimum protocol-specified procedures without any major protocol deviations, and were evaluable for pharmacokinetics
  - Any subject who meets the following criteria will be excluded from this analysis set:
    1) Deviations of protocol entry criteria
       - Deviations of inclusion criteria

         Inclusion criteria 3, 4, and 5
       - Deviations of exclusion criteria

         Exclusion criteria 2, 4, 6, 7, 8, 9, 10, 11, and 17

2) Deviations related to treatment procedure or dose

- Deviations related to dose

Deviations of dosage

Subjects who received a dose of the study drug other than the doses specified in the protocol

- Deviations of regimen

Deviations of dosing interval (number of days for washout)

Subjects who received the study drug in Period 2 without undergoing a washout period of more than 6 days after the study drug administration in Period 1

Deviations of dosing conditions

Subjects who did not orally receive a single dose of any study drug under treatment conditions specified in that treatment period

3) Deviations concerning excluded medication or therapy

- Deviations concerning concomitant medications

Administration of excluded medication

Subjects who consumed drugs (prescribed or over-the-counter drugs) described in Table 7.a "Excluded Medications, Supplements, and Dietary Products" listed in the protocol section 7.3 within the given time

4) Deviations concerning pharmacokinetic measurements

- Plasma drug concentration

No conduct/missing of examinations and assessments concerning pharmacokinetic variables

Subjects whose plasma drug concentration data of TAK-536 was missing or not used at more than 1 visit

5) Others

- Matters of subject management

Matters concerning foods and beverages

Subjects who consumed meals other than the provided meals during hospitalization

Subjects who consumed meals within 10 hours before the study drug administration

Subjects who consumed meals within 4 hours after the study drug administration

Subjects who consumed beverages other than the drink provided as a part of breakfast (under fed condition) and water (200 mL)

taken with the study drug from 1 hour before to 4 hours after the study drug administration

Subjects who consumed foods described in Table 7.a "Excluded Medications, Supplements, and Dietary Products" listed in the protocol section 7.3 within the given time

Matters concerning smoking

Subjects who smoked during hospitalization

Matters concerning body position

Subjects who took a supine position for 4 hours after the study drug administration, unless it was required for examination.

- Safety Analysis Set: All subjects who received the study drug

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s):	Date First Subject Signed Informed Consent Form Date Last Subject Completed Study Drug Administration MedDRA Version SAS Version Used for Creating the Datasets
Analysis Method(s):	The following analysis will be performed for the above analysis variables. (1) Display of analysis variables

7.3.2 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s):	Randomization	[Eligible for Randomization, Not Eligible for Randomization]
	Primary Reason for Subject Not Being Eligible	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Sufficient Subject, Screening Failure, Study Termination by Sponsor, Voluntary Withdrawal, Other]
Analysis Method(s):	The following analysis will be performed for the above analysis variables. When calculating percentages for the primary reasons for subject not eligible for randomization, the total number of subjects who were not eligible for randomization will be used as the denominator. (1) Frequency distributions	

7.3.3 Disposition of Subjects

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Study Completion Status	[Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]
	Reason for Discontinuation of Study Visits	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Study Termination by Sponsor, Voluntary Withdrawal, Other]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups. When calculating percentages for the primary reasons for subject who did not complete all planned study visits, the total number of subjects who did not complete all planned study visits will be used as the denominator. (1) Frequency distributions	

7.3.4 Protocol Deviations and Analysis Sets

7.3.4.1 Protocol Deviations

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Protocol Deviations	[Deviations of Protocol Entry Criteria, Deviations Concerning Excluded Medication or Therapy, Noncompliance with Protocol, Deviations Related to Treatment Procedure or Dose, Deviations of Discontinuation Criteria, Major GCP Violations]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups. The number of subjects with protocol deviations will be calculated and the details of deviations will be shown after classifying the contents of deviations into the above categories. A subject who has several categories will be counted once in each appropriate category. (1) Frequency distributions	

7.3.4.2 Analysis Sets

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Handling of Subjects in Analysis Sets	[Categories are based on the specifications in the List of Subject Evaluability Assignments]
	Inclusion/Exclusion of Analysis Set	
	Safety Analysis Set	[Included]
	PK Analysis Set	[Included]
Analysis Method(s):	The following summaries will be provided by treatment group for (1), and by treatment group and by combining the treatment groups for (2). For (1), a subject who has several categories will be counted once in each appropriate category. (1) Frequency distributions for handling of cases in each analysis set (2) Frequency distributions for number of cases included in each analysis set	

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	Safety Analysis Set PK Analysis Set

Analysis Variable(s):	Age (years)	
	Height (cm)	
	Weight (kg) (prior to administration in Period 1)	
	BMI (kg/m^2) (prior to administration in Period 1)	
	Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
	Alcohol Classification	[Everyday, 2 to 3 Days a Week, 2 to 3 Days a Month, Never]
	Caffeine Classification	[Yes, No]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups.	
	(1) Frequency distributions for categorical variables and descriptive statistics for continuous variables	

7.5 Medical History and Concurrent Medical Conditions

Not applicable in this study.

7.6 Medication History and Concomitant Medications

Not applicable in this study.

7.7 Study Drug Exposure and Compliance

Not applicable in this study.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint

Not applicable in this study.

7.8.2 Secondary Efficacy Endpoint

Not applicable in this study.

7.8.3 Additional Efficacy Endpoint

Not applicable in this study.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applied in this study.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results or data determined to be non-evaluable according to this Statistical Analysis Plan will not be used for hypothesis testing and estimations.

Values below the lower limit of quantification in drug concentrations and laboratory test values will be treated as zero, and values above the upper limit of quantification in laboratory test values will be treated as the upper limit of quantification.

7.8.4.3 Multicenter Studies

Not applied in this study.

7.8.4.4 Multiple Comparison/Multiplicity

Not applied in this study.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applied in this study.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applied in this study.

7.8.4.7 Examination of Subgroups

Not applied in this study.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Analysis Set: PK Analysis Set
Analysis Variable(s): Plasma Concentrations of TAK-536
Visit: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 Hours Postdose
Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) Descriptive statistics will be provided for each treatment condition by visit.
(2) Mean and standard deviation will be plotted simultaneously for both treatment conditions (vertical axis: normal scale).
(3) Mean will be plotted simultaneously for both treatment conditions (vertical axis: common logarithmic scale).

7.9.1.2 Pharmacokinetic Parameters

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536

Cmax	tmax	AUClast
AUCinf	t1/2z	MRTlast,ev
MRTinf,ev	Lambda z	CL/F
Vz/F		

Analysis Method(s): The following analysis will be performed for the above analysis variables by treatment condition.

(1) Summary of Pharmacokinetic Parameters
For Cmax, AUClast, and AUCinf, descriptive statistics, geometric mean, and CV will be provided.
For Tmax, descriptive statistics will be provided.
For all other variables, descriptive statistics and CV will be provided.

7.9.1.3 Assessment of Food Effect

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536

Cmax	tmax	AUClast
AUCinf	t1/2z	MRTlast,ev
MRTinf,ev	Lambda z	CL/F
Vz/F		

Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) The difference in the least square means between treatment conditions (single oral dose under fed condition – single oral dose under fasted condition) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variables other than tmax as the dependent variable, and treatment condition, treatment group, and period as independent variables.

(2) The difference in the least square means between treatment conditions (single oral dose under fed condition – single oral dose under fasted condition) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include non-natural log-transformed tmax as the dependent variable, and treatment condition, treatment group, and period as independent variables.

7.9.1.4 Individual Plasma Concentrations

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s): Plasma Concentrations of TAK-536

Visit: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 Hours Postdose

Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) Individual plasma concentrations will be plotted simultaneously for both treatment conditions (vertical axis: normal scale).

7.9.1.5 Subject Data Listings for Pharmacokinetic Parameters

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s): Pharmacokinetic Parameters of TAK-536

Cmax	tmax	AUClast
AUCinf	t1/2z	MRTlast,ev
MRTinf,ev	Lambda z	

Measuring points of estimating Lambda z (start point, end point, and number of points) and adjusted R-squared contribution rate

CL/F	Vz/F

Analysis Method(s): Subject data listings including the following variables will be displayed.

(1) Subject ID, subject number, treatment group, treatment condition, and timing

7.9.2 Pharmacodynamic Analysis

Not applicable in this study.

7.10 Other Outcomes

Not applicable in this study.

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 Variable(s): TEAE
Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]
Analysis Method(s): The following analysis will be performed for the above analysis variables by treatment condition.

(1) Overview of TEAE
   1) All TEAEs (number of events, number and percentage of subjects)
   2) Relationship of TEAEs to study drug (number of events, number and percentage of subjects)
   3) Intensity of TEAEs (number of events, number and percentage of subjects)
   4) TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
   5) Serious TEAEs (number of events, number and percentage of subjects)
   6) Relationship of serious TEAEs to study drug (number of events, number and percentage of subjects)
   7) Serious TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
   8) TEAEs resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below. When calculating percentages for TEAE, the number of subjects who were treated by the study drug under that treatment condition in the safety analysis set will be used as the denominator.

[Number of subjects with TEAEs]

- In case of "frequency distributions by relationship to study drug"
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- In case of "frequency distributions by intensity"
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- In case of distributions other than the above
  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 Displays of Treatment-Emergent Adverse events

Analysis Set: Safety Analysis Set
Analysis Variable(s): TEAE
Categories: Intensity [Mild, Moderate, Severe]
Analysis Method(s): The following analysis will be performed for the above analysis variables by treatment condition.
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) All TEAEs by SOC and PT
(2) All TEAEs by SOC
(3) All TEAEs by PT
(4) Drug-Related TEAEs by SOC and PT
(5) Intensity of All TEAEs by SOC and PT
(6) Intensity of Drug-Related TEAEs by SOC and PT
(7) TEAEs Leading to Study Drug Discontinuation by SOC and PT
(8) Serious TEAEs by SOC and PT

The method of counting events when conducting each frequency distribution will be as follows:
[Number of subjects with TEAEs]

- In case of "frequency distributions by SOC and PT, by SOC only, or PT only"
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT. Also, when calculating percentages for TEAE, the number of subjects who were treated by the study drug under that treatment condition in the safety analysis set will be used as the denominator.
- In case of "frequency distributions by SOC and PT"
  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. Also, when calculating percentages for TEAE, the number of subjects who were treated by the study drug under that treatment condition in the safety analysis set will be used as the denominator.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis Variable(s): PTE
Analysis Method(s): The following analysis will be performed for the above analysis variables.

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

(1) All PTEs by SOC and PT
(2) Serious PTEs by SOC and PT

The method of counting events when conducting each frequency distribution will be as follows:

[Number of subjects with PTEs]

- A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s): Hematology

RBC	WBC	Hemoglobin
Hematocrit	Platelets	

WBC Differentials (Neutrophil, Basophil, Eosinophil, Lymphocyte, and Monocyte)

Serum Chemistry

ALT	AST	
Alkaline Phosphatase		
GGT	Total Bilirubin	Total Protein
Albumin	Creatinine	Urea Nitrogen
Potassium	Sodium	Chloride
Calcium	Iinorganic Phosphorus	Total Cholesterol
Fasting Triglycerides	Urine Acid	LDH
Creatine Kinase		Fasting Glucose

Categories: Results of determination based on reference values [Below lower limit of reference value, Within the range of reference value, Over upper limit of reference value]

Visit: Predose, 24 and 48 Hours Postdose, Follow-up Examination (Day 6)

Analysis Method(s): The following analysis will be performed for the above analysis variables by treatment condition.

(1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided.
(2) Case Plots
(3) A shift table for each visit before and after administration will

be provided for the results of determination based on the reference values.

7.11.2.2 Urinalysis

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	Specific Gravity pH Glucose Protein Blood Ketone Body Bilirubin Urobilinogen
Categories:	Results of determination based on reference values [Below lower limit of reference value, Within the range of reference value, Over upper limit of reference value]
Visit:	Predose, 24 and 48 Hours Postdose, Follow-up Examination (Day 6)
Analysis Method(s):	For specific gravity, summaries (1) to (3) will be provided by treatment condition. For each variable other than specific gravity, summary (3) will be provided by treatment condition. (1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided. (2) Case Plots (3) A shift table for each visit before and after administration will be provided for the results of determination based on the reference values.

7.11.3 Vital Signs and Weight

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	Body Temperature (axillary) Sitting Systolic Blood Pressure Sitting Diastolic Blood Pressure Sitting Pulse Rate Weight
Visit:	Body Temperature (axillary), Sitting Systolic Blood Pressure, Sitting Diastolic Blood Pressure, Sitting Pulse Rate: Predose, 4, 24, and 48 Hours Postdose, Follow-up Examination (Day 6) Weight: Predose, 48 Hours Postdose, Follow-up Examination (Day 6)
Analysis Method(s):	The following analysis will be performed for the above analysis

variables by treatment condition.

(1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided.
(2) Case Plots

7.11.4 12-Lead ECGs

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	Heart Rate	
	RR Interval	
	PR Interval	
	QRS Interval	
	QT Interval	
	QTcF Interval	
	12-Lead ECG Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit:	Predose, 48 Hours Postdose, Follow-up Examination (Day 6)	
Analysis Method(s):	For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by treatment condition.	
	For 12-lead ECG, summary (3) will be provided by treatment condition.	
	(1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided.	
	(2) Case Plots	
	(3) A shift table for each visit before and after administration will be provided.	

7.11.5 Other Observations Related to Safety

Not applicable in this study.

7.12 Interim Analysis

Not applicable in this study.

7.13 Changes in the Statistical Analysis Plan

The analysis plan described in this Statistical Analysis Plan is the same as the analysis plan described in the protocol.

8.0 REFERENCES

Not applicable in this study.