Title: A Randomized, Open-Label, Single-Dose, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of TAK-438 OD (Orally Disintegrating) 20 mg Tablet When Administered without Water (Study 1) or with Water (Study 2) and TAK-438 20 mg Tablet When Administered with Water in Japanese Healthy Volunteer Male Subjects

NCT Number: NCT03808493

Statistical analysis plan Approve Date: 27-DEC-2018

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).

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438ODT-1001

A Randomized, Open-Label, Single-Dose, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of TAK-438 OD (Orally Disintegrating) 20 mg Tablet When Administered without Water (Study 1) or with Water (Study 2) and TAK-438 20 mg Tablet When Administered with Water in Japanese Healthy Volunteer Male Subjects

PHASE 1

Version: 1st

Date: 27 December 2018

Prepared by:

PPD

PPD

PPD

Based on:

Protocol Version: 1

Protocol Date: 12 December 2018

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 FIGURES

3.0 LIST OF ABBREVIATIONS

ALP	alkaline phosphatse
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	asparate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
ECG	electrocardiogram
GGT	gamma-glutamyl transferase
MedDRA	Medical Dictionary for Regulatory Activities
SOC	System Organ Class
TAK-438F	freebase of TAK-438
TEAE	treatment-emergent adverse event
PT	Preferred Term
PTE	pretreatment event

4.0 OBJECTIVES

4.1 Primary Objective

To evaluate the bioequivalence of a single oral administration of a TAK-438 OD 20 mg tablet without water in comparison with TAK-438 20 mg tablet (Study 1), and TAK-438 OD 20 mg tablet with water in comparison with TAK-438 20 mg tablet (Study 2) in Japanese healthy male volunteer subjects.

4.2 Secondary Objective

To assess the Pharmacokinetic (PK) parameters other than AUClast and Cmax of TAK-438F in Japanese healthy volunteer male subjects who take a single oral dose of TAK-438 20 mg.

4.3 Safety Objective

To assess the safety in Japanese healthy volunteer male subjects who take a single oral dose of TAK-438 20 mg.

4.4 Study Design

This study which consists of two studies, Study 1 and Study 2, is a PK study in healthy Japanese subjects to evaluate the bioequivalence of single oral dose of TAK-438 OD 20 mg tablet without water and TAK-438 20 mg tablet with water (Study 1), and TAK-438 OD 20 mg tablet with water and TAK-438 20 mg tablet with water (Study 2) in an open-label and crossover (2x2) design. The safety of TAK-438 OD 20 mg tablet, and TAK-438 20 mg tablet under fasted conditions without breakfast will also be evaluated.

Pilot and Pivotal BE studies are planned for Study 1 and Study 2 in accordance with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No.0229-10 dated 29 February 2012) as follows;

Pilot and Pivotal BE studies will be conducted in the same design (inclusion/exclusion criteria, dose, regimen and schedule). Pilot BE studies will be conducted first for the sample size estimation to demonstrate the bioequivalence in Pivotal BE study. Pivotal BE study with the estimated sample size will be conducted to demonstrate the bioequivalence. The data from Pilot BE studies can be merged with the data from Pivotal BE study as needed when the bioequivalence is evaluated. Pivotal BE studies will not be conducted in the case the bioequivalence is demonstrated in Pilot BE study, or the results from Pilot BE study indicate that it is not feasible to demonstrate the bioequivalence.

In the Pilot BE study, 24 subjects will be enrolled in each study (12 subjects in each treatment sequence). Subjects will be randomly assigned to either Treatment Sequences with 1:1 allocation in each study.

In the Pivotal BE study, 26 to 48 subjects will be enrolled in each study (13 to 24 subjects in each treatment sequence depending on outcome of the pilot BE study). Subjects will be randomly assigned to either Treatment Sequences with 1:1 allocation in each study.

In each treatment sequence of Pilot and Pivotal BE studies, subjects will receive a single dose of either of TAK-438 OD 20 mg tablet without water or TAK-438 20 mg tablet with water (Study 1), and either of TAK-438 OD 20 mg tablet with water or TAK-438 20 mg tablet with

water (Study 2) on Day 1 in Period 1 and 2. If a subject discontinues from the study, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The study site should contact the sponsor for the replacement of subject's treatment assignment and medication identification number.

The planned dose levels and dosing schedules of TAK-438 OD to be evaluated are outlined in Figure 4.a.

Study 1: BE study when administered without water for TAK-438 OD tablet
Pilot BE Study

Sequence	Period 1	Period 2	Number of subjects
A	One TAK-438 OD 20 mg tablet without water	One TAK-438 20 mg tablet with 150 mL water	12
B	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet without water	12
Dosing Condition: Fasted (without breakfast) condition			

Pivotal BE Study

Sequence	Period 1	Period 2	Number of subjects
A	One TAK-438 OD 20 mg tablet without water	One TAK-438 20 mg tablet with 150 mL water	13- 24
B	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet without water	13-24
Dosing Condition: Fasted (without breakfast) condition			

Study 2: BE study when administered with water for TAK-438 OD tablet
Pilot BE Study

Sequence	Period 1	Period 2	Number of subjects
C	One TAK-438 OD 20 mg tablet with 150 mL water	One TAK-438 20 mg tablet with 150 mL water	12
D	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet with 150 mL water	12
Dosing Condition: Fasted (without breakfast) condition			

Pivotal BE Study

Sequence	Period 1	Period 2	Number of subjects
C	One TAK-438 OD 20 mg tablet with 150 mL water	One TAK-438 20 mg tablet with 150 mL water	13- 24
D	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet with 150 mL water	13-24
Dosing Condition: Fasted (without breakfast) condition			

Figure 4.a Schematic of Study Design

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- PK (plasma concentration): AUClast and Cmax of TAK-438F.

5.2 Secondary Endpoints

- PK (plasma concentration): AUCinf, tmax, MRTinf,ev and Lambda z of TAK-438F.

5.3 Safety Endpoints

- TEAEs, clinical laboratory tests, vital signs, weight, and ECG parameters.

6.0 DETERMINATION OF SAMPLE SIZE

In Studies 1 and 2, the planned number of subjects is 12 per sequence (total of 24 subjects) in the pilot study, and 24 per sequence (total of 48 subjects) in the pivotal study. Statistical basis for the sample size is presented below.

Assuming a root mean square error of 0.195 for PK parameters in the pilot study, the power of two one-sided t-tests to verify the bioequivalence [H_0: $\ln(\mu)\leq\ln(\theta_1)$, $\ln(\mu)\geq\ln(\theta_2)$; H_1: $\ln(\theta_1)<\ln(\mu)<\ln(\theta_2)$; where $\mu=\mu_t/\mu_s$, μ_t is the mean for TAK-438 OD tablet, μ_s is the mean for the concomitant administration of TAK-438 tablet, $\theta_1=0.80$, and $\theta_2=1.25$] at a one-sided significance level of 5% and $\mu=0.95$ to 1.05 would be ≥90% with a sample size of 12 subjects per sequence (total of 24 subjects).

In the case that the pivotal study will be implemented, the number of subjects will be recalculated based on the results from the pilot study. Assuming a maximal root mean square error of 0.195 for PK parameters in the pivotal study, two one-sided t-tests with a one-sided significance level of 5% and $\mu=0.90$ to 1.11 would need a maximum of 24 subjects per sequence (total of 48 subjects) to provide 90% power to verify the bioequivalence.

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.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after the start of study drug.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug.
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Coefficient of variation (CV) (%): Standard deviation / mean * 100.
- Formulation.
  - ✧ TAK-438 OD 20 mg tablet.
  - ✧ TAK-438 20 mg tablet.
- Sequence.
  - ✧ A: TAK-438 OD 20 mg tablet without water => TAK-438 20 mg tablet with water.
  - ✧ B: TAK-438 20 mg tablet with water => TAK-438 OD 20 mg tablet without water.
  - ✧ C: TAK-438 OD 20 mg tablet with water => TAK-438 20 mg tablet with water.
  - ✧ D: TAK-438 20 mg tablet with water => TAK-438 OD 20 mg tablet with water.

7.2 Analysis Sets

- Safety analysis set: All subjects who received at least one dose of study drug.
- Pharmacokinetic analysis set: All subjects who received at least one dose of study drug, and whose PK data are evaluable (e.g., withdrawal subjects who had no PK data in Period 2 will be excluded from this analysis set).

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 of Last Subject's Last Visit/Contact
MedDRA Version
SAS Version Used for Creating the Datasets

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

7.3.2 Screen Failures

Analysis Set: All Subjects Who Were Not Randomized
Analysis
Variable(s): Age (years)
Analytical
Method(s): (1) Screen Failures
Descriptive statistics will be provided.

7.3.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis
Variable(s): 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
Method(s): (1) Eligibility for Randomization
Frequency distributions will be provided. When calculating 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
Variable(s): Study Completion Status [Completed Study, Prematurely Discontinued Study]
Reason for Discontinuation of Study Visits [Adverse Event, Death, Lost to Follow-up, Protocol Deviation,

Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s): (1) Disposition of Subjects
Frequency distributions will be provided for each sequence and overall by study. When calculating percentages for the reasons for discontinuation, the total number of subjects who did not complete all planned study visits will be used as the denominator.

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Analysis Set: Randomized Set

Analysis Variable(s): Significant Protocol Deviation [Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s): (1) Protocol Deviations
Frequency distribution will be provided for each sequence and overall by study. 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.

7.3.5.2 Analysis Sets

Analysis Set: Randomized Set

Analysis Variable(s): Handling of Subjects [Categories are based on the specifications in List of Subject Evaluability Assignments]

Analysis Sets
- Safety Analysis Set [Included]
- Pharmacokinetic Analysis Set [Included]

Analytical Method(s): (1) Subjects Excluded from Analysis Sets
Frequency distributions will be provided for each sequence by study.

A subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

(2) Analysis Sets

Frequency distributions will be provided for each sequence and overall by study.

7.4 Demographic and Other Baseline Characteristics

Analysis Set: Safety Analysis Set
Pharmacokinetic Analysis Set

Analysis Variable(s):

Age (years)	
Height (cm)	
Weight (kg) (Predose of Period 1)	
BMI (kg/m^2) (Predose of Period 1)	
Caffeine Classification	[Yes, No]
Alcohol Classification	[Daily, A Few Times Per Week, A Few Times Per Month, No]
Smoking Classification	[Never, Current, Former]

Analytical Method(s): (1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided for each sequence and overall by study.

7.5 Medical History and Concurrent Medical Conditions

Not applicable.

7.6 Medication History and Concomitant Medications

Not applicable.

7.7 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set

Analysis Variable(s): Number of Times the Study Drug was Taken [1, 2]

Analytical Method(s): (1) Study Drug Exposure

Frequency distributions will be provided for each sequence by study.

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

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

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

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

In each of Study 1 and Study 2, the study drugs will be assessed for bioequivalence according to the Guideline for Bioequivalence Studies of Generic Products. If any of the following criteria is satisfied, TAK-438 OD tablet and TAK-438 tablet will be concluded to be bioequivalent.

- For AUClast and Cmax of TAK-438F, the two-sided 90% CI of the difference in the means of log-transformed (natural log) parameter between the formulations is between 0.8 and 1.25, inclusive.

- For AUClast and Cmax of TAK-438F, the difference in the means of log-transformed (natural log) parameter between the formulations is between 0.90 and 1.11, inclusive. Furthermore, the results of the elution test satisfy the requirements specified in the Guideline for Bioequivalence Studies of Generic Products.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Plasma Concentrations of TAK-438F

Visit: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 Hours Postdose

Analytical Method(s): The following summaries will be provided by study.

(1) Summary of Plasma Concentrations by Visit
Descriptive statistics will be provided for each formulation by visit.

(2) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each formulation. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(3) Mean Plot of Plasma Concentrations
Mean will be plotted for each formulation. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

7.9.1.2 Pharmacokinetic Parameters

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic parameters of TAK-438F

AUClast	Cmax	AUCinf
AUC48	tmax	CL/F
Vz/F	t1/2z	Lambda z
MRTinf,ev	MRTlast,ev	R(AUClast)
R(Cmax)		

Analytical Method(s): The following summaries will be provided by by study.

(1) Summary of Pharmacokinetic Parameters
For AUClast, Cmax, AUCinf and AUC48, descriptive statistics, geometric mean, and CV will be provided for each formulation.
For tmax, descriptive statistics will be provided for each formulation.
For R(AUClast) and R(Cmax), descriptive statistics will be provided.
For all other variables, descriptive statistics and CV will be provided for each formulation.

7.9.1.3 Assessment of Bioequivalence

Primary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic parameters of TAK-438F

AUClast	Cmax

Analytical Method(s): The following analyses will be performed by study.

(1) The difference in the least square means between the formulations (TAK-438 OD 20 mg tablet - TAK-438 20 mg tablet) and the two-sided 90% confidence interval will be provided using an ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variable as dependent variable, and formulation, sequence, and period as independent variables.

(2) For reference, the same analyses will be performed for untransformed analysis variables.

Secondary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic parameters of TAK-438F

AUCinf tmax MRTinf,ev

Lambda z

Analytical Method(s): The following analyses will be performed by study.

(1) The difference in the least square means between the formulations (TAK-438 OD 20 mg tablet - TAK-438 20 mg tablet) and the two-sided 90% confidence interval will be provided using an ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variable as dependent variable, and formulation, sequence, and period as independent variables.

(2) For reference, the same analyses will be performed for untransformed analysis variables.

7.9.1.4 Individual Plasma Concentrations

Analysis Set: Randomized Set

Analysis Variable(s): Plasma Concentrations of TAK-438F

Visit: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 Hours Postdose

Analytical Method(s): The following case plots will be provided by study.

(1) Individual Plasma Concentrations of TAK-438F (vertical axis: normal scale)

7.9.2 Pharmacodynamic Analysis

Not applicable.

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 Variable(s): TEAE

Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]

Analytical Method(s): The following summaries will be provided for each formulation by study.

(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. Percentages for each formulation will be based on the number of subjects who were treated by that formulation in the safety analysis set.

<u>Number of subjects</u>

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., 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 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
Analytical Method(s):	The following summaries will be provided using frequency distribution for each formulation by study. 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 System Organ Class 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) Special Interest Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	

The frequency distribution will be provided according to the rules below. Percentages for each formulation will be based on the number of subjects who were treated by that formulation in the safety analysis set.

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.
- 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.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variable(s): PTE

Analytical Method(s): 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

7.11.2.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s): Hematology

RBC WBC

WBC Differentials (Neutrophils, Eosinophils, Basophils, Monocytes,

Lymphocytes)		
Hemoglobin	Hematocrit	Platelets
Serum Chemistry		
ALT	Albumin	ALP
AST	Total Bilirubin	Total Protein
Creatinine	BUN	Creatine Kinase
GGT	Potassium	Sodium
Glucose	Chloride	

Visit: Predose, 48 Hours Postdose

Analytical Method(s): The following summaries will be provided for each formulation by study.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (48 Hours Postdose - Predose) will be provided by visit.

(2) Case Plots of Laboratory Test Results
Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose visit and 48 Hours Postdose 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. The shift tables will be based on these classifications.

7.11.2.2 Urinalysis

Analysis Set: Safety Analysis Set

Analysis Variable(s): pH
Specific Gravity
Protein
Glucose

Visit: Predose, 48 Hours Postdose

Analytical Method(s): For specific gravity, summaries (1) to (3) will be provided for each formulation by study.
For each variable other than specific gravity, summaries (3) will be provided for each formulation by study.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (48 Hours Postdose - Predose) will be provided by visit.
(2) Case Plots of Urine Laboratory Test Results
Plots over time for each subject will be presented.
(3) Number of Subjects in Categories of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose visit and 48 Hours Postdose visit will be provided.

7.11.3 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis Variable(s): Temperature
Respiration Rate
Systolic Blood Pressure
Diastolic Blood Pressure
Pulse
Weight

Visit: Predose, 48 Hours Postdose

Analytical Method(s): The following summaries will be provided for each formulation by study.
(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (48 Hours Postdose - Predose) will be provided by visit.
(2) Case Plots of Vital Signs Parameters and Weight
Plots over time for each subject will be presented.

7.11.4 12-Lead ECGs

Analysis Set: Safety Analysis Set

Analysis Variable(s): Heart Rate
RR Interval
PR Interval
QT Interval
QRS Interval

QTcF Interval
Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit: Predose, 48 Hours Postdose

Analytical Method(s): For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided for each formulation by study.
For 12-lead ECG interpretation, summary (3) will be provided for each formulation by study.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (48 Hours Postdose - Predose) will be provided by visit.

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

(3) Summary of Shift of 12-lead ECG Interpretation
Shift table showing the number of subjects in each category at Predose visit and 48 Hours Postdose visit will be provided.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

In this study, an analysis will be performed after the completion of the pilot study to determine whether the results may warrant further analysis in the pivotal study for both Studies 1 and 2. On the basis of bioequivalence assessment in the pilot study, the Sponsor will decide, after discussion(s) with the medical experts, on whether to proceed to the pivotal study and promptly notify the investigator of the decision (in regard to Criteria of bioequivalence, refer to Section 7.8.4.6).

In the case that the results from the analysis satisfy the criteria of bioequivalence:

The study (Study 1 or 2) will be completed with the pilot study and without implementing the pivotal study.

In the case that the results from the analysis do not meet the criteria of bioequivalence:

The pivotal study will be implemented after the number of subjects required to conclude the bioequivalence in the study (Study 1 or 2) is calculated based on the results from the pilot study. Any evidence from the pilot study suggesting difficulties in bioequivalence testing in the pivotal study may lead to the pivotal study not being implemented.

7.13 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

No reference.