Title: An Open-Label, Single-center, Parallel, Phase 1 Study to Determine the Pharmacokinetics of Single- and Multiple- Oral Doses of TAK-438 10 mg and 20 mg in Healthy Adult Chinese

NCT Number: NCT03085836

SAP Approve Date: 30 August 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.
- 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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438_114

An Open-Label, Single-center, Parallel, Phase 1 Study to Determine the Pharmacokinetics of Single- and Multiple- Oral Doses of TAK-438 10 mg and 20 mg in Healthy Adult Chinese Subjects

PHASE 1

Version**:** Final 2

Date**:** 30 August 2017

Prepared by:

PPD

Based on:

Protocol Version: Amendment 02

Protocol Date: 21 December 2016

1.1 Approval Signatures

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

Study Title: An Open-Label, Single-center, Parallel, Phase 1 Study to Determine the Pharmacokinetics of Single- and Multiple- Oral Doses of TAK-438 10 mg and 20 mg in Healthy Adult Chinese

Approvals:

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
Ae_t	amount of drug excreted in urine from time 0 to time t
Ae_τ	amount of drug excreted in urine during a dosing interval
aPTT	activated partial thromboplastin time
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AUC_τ	area under the plasma concentration-time curve during a dosing interval
$AUC_{\tau,ss}$	area under the plasma concentration-time curve during a dosing interval, at steady state
BID	twice daily
BMI	body mass index
CFDA	China Food and Drug Administration
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration, at steady state
CRF	case report form
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
$f_{e,t}$	Fraction of administered dose of drug excreted in urine from time 0 to time t. Molecular weight adjustment needed for metabolites
$f_{e,\tau}$	Fraction of administered dose of drug excreted in urine during a dosing interval. Molecular weight adjustment needed for metabolites.
GGT	γ-glutamyl transferase
HDL	high density lipoprotein
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LLN	lower limit of normal
MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PK	pharmacokinetics
PT	Preferred Term
PT	prothrombin time
PT/INR	prothrombin time/international normalized ratio
PTE	pretreatment event
QD	once daily
QTcF	QT interval corrected by Fridericia's method
SAP	statistical analysis plan
SOC	System Organ Class
TAK-438F	freebase of TAK-438

TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of C_{max}
$t_{max,ss}$	time of first occurrence of C_{max}, at steady state
ULN	upper limit of normal
WHO Drug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is to determine the pharmacokinetics of TAK-438 in healthy adult Chinese subjects after both single and multiple dose administration.

4.2 Secondary Objectives

Not applicable.

4.3 Additional Objectives

CCI

[redacted]

4.4 Study Design

This is a phase 1, parallel, open-label, single- and multiple-dose study of oral TAK-438 involving 36 healthy Chinese subjects between the ages of 18 and 45, inclusive, and considered eligible based on the inclusion and exclusion entry criteria.

Screening for potential subjects will occur between 28 and 2 days prior to confinement at the phase 1 unit. Selected eligibility criteria will be reconfirmed on Day -1 (Check In) prior to assignment to the 10 mg or 20 mg once daily or 20 mg twice daily cohort, predose blood and urine sampling for pharmacokinetic (PK) measurements will also be taken. Having fasted for a minimum of 10-hours a single oral dose of TAK-438 will be administered on Day 1 followed by a pharmacokinetic sampling period of 48 hours. On Days 3 through 9, subjects will receive their assigned daily dose(s) of TAK-438 followed by another pharmacokinetic sampling period of 48 hours (for subjects on a once daily regimen), or 12 hours (for those assigned to the 20 mg twice daily regimen). The subject will be confined to the phase 1 unit from Day -1 (Check-In) through to Day 11 (Check-Out) and will be contacted by the study site for a follow-up phone call on Day 18.

Besides monitoring concomitant medications and adverse events (AE), physical examination, electrocardiogram (ECG), vital signs and clinical laboratory tests will be conducted to monitor safety. A schematic of the study design is presented in Figure 4.a.

Figure 4.a Schematic of Study Design

Screening Period		Treatment Period						Follow-Up
Screening	Check-In	Single Dose/ PK	48-hour PK	Multiple Dosing (a)	Dosing and PK	48-hour PK / Observation	Check-Out	Follow-up Telephone Visit
Days -28 to -2	Day -1	Day 1	Day 2	Days 3-8	Day 9	Day 10	Day 11	Day 18 ± 3 days
		TAK-438 single dose 10 mg or 20 mg		TAK-438 once daily 10 mg or 20 mg or twice daily 20 mg				
	← Confinement →							

PK=pharmacokinetic.

A summary of the dose cohorts is presented in Table 4.a.

Table 4.a Summary of Dose Cohorts

Cohort	TAK-438 Dose (shown as free base amount)	Subjects
1	TAK-438 10 mg once daily	12
2	TAK-438 20 mg once daily	12
3	TAK-438 20 mg twice daily	12

A schematic of the dosing schedule and sampling, by cohort, is provided in Table 4.b.

Table 4.b Schematic of Dosing and PK Sampling, by Cohort

Regimen	Event	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11
Cohort 1 (10 mg QD)	Dosing	↑		↑	↑	↑	↑	↑	↑	↑		
	PK sampling	←→			•	•	•	•	•	←→		
Cohort 2 (20 mg QD)	Dosing	↑		↑	↑	↑	↑	↑	↑	↑		
	PK sampling	←→			•	•	•	•	•	←→		
Cohort 3 (20 mg BID)	Dosing	↑		↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓		
	PK sampling	←→			•	•	•	•	•	↔		

↑: Morning dose,; ↓: Evening dose; ↔: Serial PK; • Trough PK

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The Primary endpoints for this study are the pharmacokinetic parameters derived from the plasma and urine concentrations of TAK-438F and its metabolites M-I, M-II, M-III and M-IV-Sul assessed after the first dose on Day 1 and after the final repeat dose on Day 9 as required.

The following pharmacokinetic parameters will be calculated from plasma concentrations of TAK-438F, M-I, M-II, M-III and M-IV-Sul:

Day 1

- Maximum observed plasma concentration (C_{max}).
- Time to reach C_{max} (t_{max}).
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
- Area under the plasma concentration-time curve during a dosing interval (AUC_{τ}).
- Terminal disposition half-life ($t_{1/2z}$).

Day 9

- Maximum observed plasma concentration, at steady state ($C_{max,ss}$).
- Time to reach C_{max} at steady state ($t_{max,ss}$).
- Area under the plasma concentration-time curve during a dosing interval, at steady state ($AUC_{\tau,ss}$).

The following pharmacokinetic parameters will be calculated from urine concentrations of TAK-438F, M-I, M-II, M-III and M-IV-Sul:

Day 1

- Amount of drug excreted in urine from time 0 to time t (Ae_t).
- Fraction of administered dose of drug excreted in urine from time 0 to time t ($f_{e,t}$).
- Renal clearance (CL_R).

Day 9

- Amount of drug excreted in urine during a dosing interval (Ae_{τ}).
- Fraction of administered dose of drug excreted in urine during a dosing interval ($f_{e,\tau}$).
- Renal clearance (CL_R).

5.2 Additional Endpoints

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The sample size of 12 subjects per cohort is sufficient to evaluate the PK profile after single- and multiple-dose administration of TAK-438 10 mg and 20 mg. The sample size chosen for this study is based on precedent set by other pharmacokinetic studies of similar nature and guidelines issued by the China Food and Drug Administration (CFDA); it was not based on statistical considerations of power and sample size of TAK-438. The sample size is considered though to be sufficient for investigating the objectives of the study.

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.
- Significant TEAE: Any AEs (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment or significant additional concomitant therapy.
- Descriptive statistics: number of subjects with non-missing values, mean, standard deviation, maximum, minimum, and quartiles
- Duration of exposure to study medication (days): date of last dose of study medication - date of first dose of study medication + 1
- 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 medication. If no evaluable observation is obtained before the first dose, the baseline value will be missing.

7.1.2 Definition of Study Days

Study Day: The day before the first dose of the study medication 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

7.1.3.1 Plasma Concentrations of TAK-438F and Its Metabolites M-I, M-II, M-III and M-IV-Sul

For each time, all evaluable observation (ie, non-missing) obtained in the corresponding time interval will be used. If more than one observation lies within the same time window, the observation with the closest sampling time to the scheduled time will be used. If there are two observations equidistant to the scheduled time, the later observation will be used.

Visit: Days 1 and 9

Visit	Time	Scheduled Time (min)	Time Interval (min) Sampling Time
Days 1 and 9	Pre–morning dose	0	-30 – 0
	0.25 hours post–morning dose	15	10 – 20
	0.5 hours post–morning dose	30	25 – 35
	0.75 hours post–morning dose	45	40 – 50
	1 hour post–morning dose	60	55 – 65
	1.5 hours post–morning dose	90	85 – 95
	2 hours post–morning dose	120	115 – 125
	3 hours post–morning dose	180	175 – 185
	4 hours post–morning dose	240	235 – 245
	6 hours post–morning dose	360	355 – 365
	8 hours post–morning dose	480	470 – 490
	10 hours post–morning dose	600	590 – 610
	12 hours post–morning dose	720	710 – 730
	16 hours post–morning dose*	960	950 – 970
	24 hours post–morning dose*	1440	1430 – 1450
	36 hours post–morning dose*	2160	2150 – 2170
	48 hours post–morning dose*	2880	2870 – 2890

* Blood samples collection at these time points on Day 9 is not scheduled for Cohort 3, ie, subjects assigned to the 20 mg BID regimen.

Visit: Days 4-8

Visit	Time	Scheduled Time (min)	Time Interval (min) Sampling Time
Days 4 - 8	Pre–morning dose	0	-30 – 0

7.1.3.2 Other Endpoints

The baseline visit is defined as the period before the first dose of study medication, 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 used for primary analysis will consist of subjects who received at least 1 dose of the study drug.

The PK analysis set will consist of subjects who received the study drug, who have sufficient plasma/urine concentration data to calculate at least 1 pharmacokinetic parameter, and completed the minimum protocol specified procedures with no significant protocol deviations, which are listed below:

- Subjects who did not meet inclusion criteria #3, #4 or #5.
- Subjects who met exclusion criteria #1, #4, #6, #7, #8, #10, #11, #12, #13, #14, or #18.
- Subjects who have violated the rules specified in section 7.3 (excluded medications and dietary products) of the protocol up to 48 hours after the last dose on Day 9.
- Subjects who did not receive the study drug at some scheduled time of administration.

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
	WHO Drug 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]
	Gender	[Male, Female]
	Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]
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	[Yes, No]
	Primary Reason for Subject Not Being Eligible	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Did Not Meet Entrance Criteria, 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:	All Subjects Who Entered the Treatment Period	
Analysis Variables:	Study Drug Administration Status	[No]
	Reason for Not Being Treated	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Other]
	Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Other]

Analytical Methods: **(1) Disposition of Subjects**

Frequency distributions will be provided for each cohort 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.

(2) Flow Chart of Subject Distribution

Flow chart will be provided.

7.3.5 Protocol Deviations and Analysis Sets

Protocol Deviations

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variables:	Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]
Analytical Methods:	**(1) Protocol Deviations**	
	Frequency distribution will be provided by cohort 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.	

Analysis Sets

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variables:	Analysis Sets	
	PK Analysis Set	[Included]
	Safety Analysis Set	[Included]
Analytical Methods:	**(1) Analysis Sets**	
	Frequency distributions will be provided by cohort and overall.	

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	PK Analysis Set	
	Safety Analysis Set	
Analysis Variables:	Age (years)	[Min<= - <30, 30<= - <40, 40<= - <=Max]
	Gender	[Male, Female]
	Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]
	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<= - <19.0, 19.0<= - <=24.0, 24.0< - <=Max]
	Smoking Classification	[The Subject Has Never Smoked, The Subject Is a Current Smoker, The Subject Is an Ex-smoker]
	Consumption of Alcohol	[Drink Every day, Drink a Couple of Days Per Week, Drink a Couple of Days Per Month, Never Drink]
	Consumption of Caffeine	[Yes, No]
	CYP2C19 Genotype	[*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3]
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 cohort and overall.	

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that stopped at or prior to the time of informed consent. Concurrent medical conditions are defined as significant conditions ongoing or present at the time of informed consent.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0) coding system.

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

7.6 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped prior to signing of informed consent. Concomitant medications are recorded on the eCRF and include any medications, other than the study drug, taken at any time between informed consent and on or prior to the last dose of study drug.

Medication history and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO Drug) version 2016Q1 or higher.

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

7.7 Efficacy Analysis

Not applicable.

7.8 Pharmacokinetic/Pharmacodynamic Analysis

7.8.1 Pharmacokinetic Analysis

Plasma Concentrations of TAK-438F and Its Metabolites M-I, M-II, M-III and M-IV-Sul

Analysis Set:	PK Analysis Set
Analysis Variable:	Plasma Concentrations of TAK-438F and Its Metabolites M-I, M-II, M-III and M-IV-Sul
Time Point:	Visit: Days 1 and 9 Pre–morning dose (0 hours) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16*, 24*, 36*, 48* hours post–morning dose (relative to start time of morning dose at Day 1 or 9) * Blood samples collection at these time points on Day 9 is not scheduled for Cohort 3, ie, subjects assigned to the 20 mg BID regimen. Visit: Days 4-8 Pre–morning dose (0 hours)
Analytical Methods:	The following summaries will be provided for each analyte by cohort. **(1) Summary of Plasma Concentrations by Time Point** Descriptive statistics for observed values will be provided for each time point. In addition, geometric mean, 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 scales and common log scales for Days 1-9, Day 1 and Day 9 respectively.

Plasma PK Parameters of TAK-438F and Its Metabolites M-I, M-II, M-III and M-IV-Sul

Analysis Set:	PK Analysis Set		
Analysis Visit and Variable:	Plasma PK Parameters of TAK-438F and Its Metabolites M-I, M-II, M-III and M-IV-Sul		
	Visit: Day 1		
	C_{max}	t_{max}	AUC_{∞}
	AUC_{τ}	$t_{1/2z}$	λ_z
	CL/F	V_z/F	
	Visit: Day 9		
	$C_{max,ss}$	$t_{max,ss}$	$AUC_{\tau,ss}$
	$t_{1/2z}$	λ_z	CL/F_{ss}
	V_z/F_{ss}	$R_{ac(AUC)}$	$R_{ac(Cmax)}$
Analytical Methods:	The following summaries will be provided for each analyte by cohort.		
	(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.		

Urine PK Parameters of TAK-438F and Its Metabolites M-I, M-II, M-III and M-IV-Sul

Analysis Set:	PK Analysis Set		
Analysis Visit and Variable:	Urine PK Parameters of TAK-438F, Its Metabolites M-I, M-II, M-III and M-IV-Sul, and the Total of TAK-438F and Its Metabolites		
	Visit: Day 1		
	Ae_t	$f_{e,t}$	CL_R
	Visit: Day 9		
	Ae_{τ}	$f_{e,\tau}$	CL_R
Analytical Methods:	The following summaries will be provided for each analyte by cohort.		
	(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-438F and its metabolites.		

7.8.2 Pharmacodynamic Analysis

Not applicable.

7.9 Other Outcomes

Not applicable.

7.10 Safety Analysis

7.10.1 Adverse Events

7.10.1.1 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 for each cohort.

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

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

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

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

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

10) Significant Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

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

TEAEs will be counted according to the rules below.

<u>Number of subjects</u>

- Summaries for 2), 5), 7) and 11)
  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), 5), 7) and 11)
  A subject with multiple occurrences of TEAE will be counted only once.

<u>Number of events</u>

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

7.10.1.2 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 for each cohort.

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

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

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

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

(12) Drug-Related Significant 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.

7.10.1.3 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.

7.10.2 Clinical Laboratory Evaluations

Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variables : Hematology

Red blood cells ($\times 10^{12}$/L)	White blood cells ($\times 10^{9}$/L)	Hemoglobin (g/L)
Hematocrit (%)	Platelets ($\times 10^{9}$/L)	
White blood cell differential (Neutrophils (%), Eosinophils (%), Basophils (%), Monocytes (%), Lymphocytes (%))		
PT/INR	PT (sec)	aPTT (sec)
Reticulocyte percentage (%)		

Serum Chemistry

Alanine aminotransferase (U/L)	Alkaline phosphatase (U/L)	Aspartate aminotransferase (U/L)
GGT (U/L)	Total bilirubin (µmol/L)	Direct bilirubin (µmol/L)
Lactose dehydrogenase (U/L)	Creatine kinase (U/L)	Albumin (g/L)
Total protein (g/L)	Serum creatinine (umol/L)	Blood urea (mmol/L)
Uric Acid (mmol/L)	HDL Cholesterol (mmol/L)	LDL Cholesterol (mmol/L)
Triglycerides (mmol/L)	Glucose (mmol/L)	Potassium (mmol/L)
Sodium (mmol/L)	Magnesium (mmol/L)	Calcium (mmol/L)
Chloride (mmol/L)	Amylase (U/L)	

Visit: Baseline, Days 3, 9 and 11.

Analytical Methods: The following summaries will be provided for each cohort. Liver function testing measurements at local laboratories are not used for the summaries.

(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) 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.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Test results
Overall frequency distributions of MAV during treatment phase 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	[Negative, Positive]
	Glucose	[Negative, Positive]
	Nitrites	[Negative, Positive]
	Bilirubin	[Negative, Positive]
	Ketones	[Negative, Positive]
	Urobilinogen	[Normal, Abnormal]
	Microscopic Analysis	
	RBC (/HPF)	[Negative, Positive]
	WBC (/HPF)	[Negative, Positive]
	Hyaline casts (/LPF)	[Not Found, Positive]
	Granular casts (/LPF)	[Not Found, Positive]
	Epithelial cells ($\times 10^6$/L)	[Min<= - <2.0, 2.0<= - <=10.0, 10.0< - <=Max]
Visit:	Baseline, Days 3, 9 and 11.	
Analytical Methods:	The following summaries will be provided for each cohort.	

(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.

7.10.3 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:	Baseline, Days 2-11
Analytical Methods:	For each variable, following summary will be provided by cohort.
	(1) Summary of Vital Signs Parameters 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) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters Overall frequency distributions of MAV during treatment phase 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.

7.10.4 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:	Baseline, Days 1-11	

Analytical Methods: For each variable other than 12-lead ECG interpretations, summary (1) will be provided by cohort.

For 12-lead ECG interpretations, summary (3) will be provided by cohort.

(1) Summary of ECG Parameters 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) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
Overall frequency distributions of MAV during treatment phase 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.

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

7.10.5 Other Observations Related to Safety

Not applicable.

7.11 Interim Analysis

Not applicable.

7.12 Changes in the Statistical Analysis Plan

From the SAP version 1.0, the following parts were updated. In 7.3.4, the subject flow chart was mentioned clearly. In 7.8.1, common log scales were applied to semi-log graphs for mean concentration-time profiles instead of natural log scales, and Ae was removed from the summary table for the total of TAK-438F and its metabolites. In 7.10.1.1 and 7.10.1.2, several tables for drug-related TEAEs were added. In 7.10.2, PT and microscopic analysis parameters were added to the analysis variables. In 9.1.1, the MAV criteria of blood urea was removed.

8.0 REFERENCES

Not applicable.

9.0 APPENDIX

9.1 Criteria for Markedly Abnormal Values

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

For each parameter, all evaluable data (ie, non-missing data) obtained up to Day 11 will be classified as a MAV or not. The criteria in the table below will be used.

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 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 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	MAV Criteria	
	Lower Criteria	Upper Criteria
Red blood cells ($\times 10^{12}$/L)	<0.8×LLN	>1.2×ULN
White blood cells ($\times 10^{9}$/L)	<0.5×LLN	>1.5×ULN
Hemoglobin (g/L)	<0.8×LLN	>1.2×ULN
Hematocrit (%)	<0.8×LLN	>1.2×ULN
Platelets ($\times 10^{9}$/L)	<75	>600
Neutrophils (%)	<0.5×LLN	>1.5×ULN
Eosinophils (%)	-	>2×ULN
Basophils (%)	-	>3×ULN
Monocytes (%)	-	>2×ULN
Lymphocytes (%)	<0.5×LLN	>1.5×ULN
aPTT (sec)		>1.5×ULN
PT/INR		>1.5

Serum Chemistry

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Alanine aminotransferase (U/L)	-	>3×ULN
Alkaline phosphatase (U/L)	-	>3×ULN
Aspartate aminotransferase (U/L)	-	>3×ULN
GGT (U/L)	-	>3×ULN
Total bilirubin (µmol/L)	-	>34.2
Direct bilirubin (µmol/L)	-	>2×ULN
Creatine kinase (U/L)	-	>5×ULN
Albumin (g/L)	<25	-
Total protein (g/L)	<0.8×LLN	>1.2×ULN
Uric Acid (mmol/L)	-	>0.773
Triglycerides (mmol/L)	-	>2.5×ULN
Glucose (mmol/L)	<2.8	>19.4
Potassium (mmol/L)	<3.0	>6.0
Sodium (mmol/L)	<130	>150
Magnesium (mmol/L)	<0.5	>1.2
Calcium (mmol/L)	<1.75	>2.88
Chloride (mmol/L)	<75	>126
Amylase (U/L)	-	>2×ULN
Serum creatinine (µmol/L)	-	>177

Vital Signs

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Body Temperature (°C)	<35.6	>37.7
Systolic Blood Pressure (mmHg)	<85	>180
Diastolic Blood Pressure (mmHg)	<50	>110
Pulse (bpm)	<50	>120

12-lead ECG

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Heart Rate (bpm)	<50	>120
QT Interval (msec)	<=50	>=460
QTcF Interval (msec)	<=50	-

9.1.2 12-lead ECG (Upper MAV Criteria of QTcF Interval)

All evaluable data (ie, non-missing data) obtained up to Day 11 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 baseline 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 baseline 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 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 baseline 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	MAV Criteria	
	Lower Criteria	Upper Criteria
QTcF Interval (msec)	-	If either of the following conditions is met: • observed value >=500 • change from baseline >= 30 and observed value >=450

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	04-Sep-2017 01:41 UTC
PPD	Clinical Pharmacology Approval	04-Sep-2017 04:06 UTC
PPD	Biostatistics Approval	04-Sep-2017 13:13 UTC
PPD	Clinical Approval	06-Sep-2017 04:56 UTC
PPD	Pharmacovigilance Approval	19-Sep-2017 12:11 UTC