Title: Randomized, Double-Blind, Placebo-Controlled, Ascending Oral Single Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-418 in Healthy Subjects

NCT Number: NCT03228433

SAP Approve Date: 07 December 2017

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-418-1001

A Randomized, Double-Blind, Placebo-Controlled, Ascending Oral Single Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-418 in Healthy Subjects

PHASE 1

Version: Final

Date: 07 December 2017

Prepared by:

PPD

Based on:

Protocol Version: Amendment 01

Protocol Date: 07 July 2017

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1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the concentration-time curve
AUC_{24}	area under the serum concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BDNF	brain-derived neurotrophic factor
BL-VAS	Bond-Lader Visual Analogue Scale
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed concentration
CPAP	Clinical Pharmacology Analysis Plan
C-SSRS	Columbia Suicide Severity Rating Scale
%CV	coefficient of variation
DBP	diastolic blood pressure
ECG	Electrocardiogram
eCRF	electronic case report form
F	free base
FAD	flavin adenine dinucleotide
F-FAD	formyl-flavin adenine dinucleotide
FIH	first-in-human
CCI	[redacted]
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	heart rate
CCI	[redacted]
MAV	Markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
miRNA	micro RNA
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PT	preferred term
PTE	Pretreatment adverse event
QTcF	QT interval with Fridericia correction method

RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	Standard deviation
SOC	system organ class
SRD	single rising dose
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this trial is to evaluate the safety and tolerability of TAK-418 following single oral doses in healthy subjects.

4.2 Secondary Objectives

The secondary objective of this trial is to evaluate the PK of TAK-418 free base (F) following a single oral dose (under fasted and fed states) in healthy subjects.

4.3 Exploratory Objectives

Exploratory objectives of the trial include:

CCI

[redacted]

4.4 Study Design

The study is a first-in-human (FIH), randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, and PK of TAK-418 in healthy adult subjects aged from 18 to 55 years, inclusive. The study will also explore the PD of TAK-418 and its effects on selected biomarkers following single oral doses in healthy adult subjects.

This study will involve 40 subjects, equally divided among 5 sequential cohorts of 8 subjects each (with a minimum of 4 male subjects), as shown in Table 4.a. In each cohort, 6 subjects will

receive TAK-418 and 2 will receive matching placebo. To ensure adequate safety and tolerability, sentinel dosing will be used for Cohort 1 with only 2 subjects dosed on Day 1 (1 receiving TAK-418 and 1 receiving placebo). The remaining 6 subjects will be dosed in 2 groups of 3 subjects each after a review of 72-hour postdose safety and tolerability data of the previous group. A staggered dosing regimen will be used for Cohorts 2 to 5. Each cohort will be divided by 2 groups (3 active: 1 placebo), and the second group will be dosed 48 hours after the first group, following assessment of safety and tolerability data.

Additional cohorts may be studied if deemed necessary to fully characterize the pharmacologically active exposure range.

Table 4.a Schematic Doses for Cohorts 1 through 5

Dose 5 mg	Dose 15 mg	Dose 30 mg	Dose 40 mg	Dose 60 mg
Cohort 1 (n=8; 6 active: 2 placebo)	Cohort 2 (n=8; 6 active: 2 placebo)	Cohort 3A and 3B (n=8; 6 active: 2 placebo)	Cohort 4 (n=8; 6 active: 2 placebo)	Cohort 5 (n=8; 6 active: 2 placebo)

TAK-418 and placebo will be administered orally in capsule formulation and will be prepared and dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. Doses planned to be administered range from 5 to 180 mg, but the actual doses administered after the first dose will be based on emerging safety and tolerability data from the previous doses. If needed, a dose higher than 180 mg but less than 300 mg may be evaluated providing its predicted exposure does not exceed the following exposure levels. The highest dose administered will have a predicted mean area under the plasma concentration-time curve (AUC) that does not exceed the monkey AUC at the no-observed-adverse-effect level (NOAEL; males) from the 13-week toxicology study or mean maximum observed concentration (Cmax) that does not exceed one-tenth of the monkey Cmax from the 4-week toxicology study.

Subjects in Cohort 3 will receive 2 doses (under fasted state [Cohort 3A] and fed state [Cohort 3B]), with at least 7 days washout between dose administrations. Subjects enrolled in Cohort 3A will return to the site to complete Cohort 3B and will be administered TAK-418/placebo under fed condition with a high fat/high calorie breakfast, which must be consumed within 30 minutes and the dose given within 5 minutes after the end of the meal. All assessments from Day -1 to Day 4 in Cohort 3B will be same as in Cohort 3A; however, there will be no follow-up for CCI after Cohort 3A and the Day 14 follow-up assessment for Cohort 3B. For male subjects, CCI days will be adjusted based on dosing in Cohort 3B.

CCI [redacted]

CCI [redacted]

The trial schedule is detailed in Table 4.b.

Table 4.b Trial Schedule

Screening Period	Pretreatment (a)	Treatment		Posttrial (c)
		Dose Administration (b)	Postdose Procedures (b)	
Days -28 to -2	Day -1	Day 1	Days 1 to 4	Day 14 (±2) (c) Days 91, 93, 182, and 184 (±7)

(a) CCI [redacted]
(b) Subjects will remain in the phase 1 unit for a minimum of 48 hours following the dose of trial drug and may be released after 48 hours and complete the 72 hour and later procedures at an outpatient visit. Subjects may be kept in the clinic for longer time at PI's discretion.
(c) CCI [redacted]

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint of the study is a composite of safety variables and dose-limiting effects of TAK-418 that will be evaluated after dosing on Day 1 by the number and percentage of subjects who:

- Experience at least 1 treatment-emergent adverse event (TEAE).
- Discontinue because of an adverse event (AE).
- Meet the markedly abnormal criteria for neurological assessment measurements at least once postdose.
- Meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Meet the markedly abnormal criteria for safety 12-lead ECG parameters at least once postdose.

5.2 Secondary Endpoints

The secondary endpoints include:

Evaluation of the following PK parameters in healthy subjects after dosing on Day 1:

- Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
- Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).
- Maximum observed concentration (C_{max}).
- Time of first occurrence of C_{max} (t_{max}).

5.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters in healthy subjects after dosing on Day 1:

CCI

CCI

6.0 DETERMINATION OF SAMPLE SIZE

The sample size of 8 subjects per cohort (6 active: 2 placebo) chosen is based upon precedents from other FIH trials rather than a formal assessment of statistical power.

Subjects who drop out for nonsafety reasons may be replaced on a case-by-case basis at the discretion of the sponsor in consultation with the investigator. Subjects who replace dropouts will be allocated to the same dose as the subject they replace. Subjects who drop out for safety reasons will not be replaced.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the coefficient of variation (%CV) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percentage of subjects (N[%]) for each category, where applicable. Missing values will be categorized separately where deemed appropriate and necessary.

Baseline values are defined as the last observed values before the first dose of study drug, unless otherwise stated; baseline values for Cohort 3 are defined as the last observed values before the first dose of study drug in each period.

In general, the presentation of decimal points will follow the following rules as appropriate: minimum and maximum values will be presented using the same number of decimal places as the recorded data. Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data. The confidence interval (CI) for a parameter estimate will be presented using the same number of decimal places as the parameter estimate. Percentage will be presented to 1 decimal place (eg, 80.1%). All p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. In addition, the actual day relative to the first dose will be presented, where applicable.

As applicable, summaries for the study will be presented by pooled placebo, each TAK-418 dose level, TAK-418 overall and overall total. Data from the food effect cohort (Cohort 3) will be summarized separately by placebo fed, placebo fasted, TAK-418 fed, and TAK-418 fasted.

All statistical analyses will be performed using the SAS System® Version 9.4 or higher.

7.1.1 Study Definitions

There are no study-specific definitions.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the electronic case report form (eCRF) dosing page. Other study days are defined relative to Study Day 1, with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug}. Study days on or after the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug + 1}.

7.1.3 Definition of Study Visit Windows

There will be no visit windowing.

7.1.4 Conventions for Missing Adverse Event Dates

There will be no imputation of incomplete or missing adverse event dates.

7.1.5 Conventions for Missing Concomitant Medication Dates

There will be no imputation of incomplete or missing concomitant medication dates.

7.1.6 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

Plasma or urine concentrations that are below the limit of quantification (< BLQ) will be treated as zero in the summarization of concentration values and derivation of PK parameters.

7.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

- Safety Set: The safety set will consist of all subjects who receive at least 1 dose of trial drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.
- Pharmacokinetic (PK) Set: The PK set will consist of all subjects who receive at least 1 dose of trial drug and have at least 1 measurable plasma concentration or amount of drug in the urine for TAK-418. All subjects with valid PK parameter estimates will be included in the summaries and analyses for that parameter.
- CCI [redacted]

If any subject is found to be noncompliant with the dosing schedule or has incomplete data, a decision will be made on a case-by-case basis as to whether that subject should be included in the PK and PD analyses; however, data for all subjects will be presented in the data listings.

7.3 Disposition of Subjects

Disposition of all screened failure subjects will be summarized according to the primary reason for screen failure. Additionally, disposition information for screen failures will be listed.

Disposition of all randomized subjects will be summarized by pooled placebo, each TAK-418 dose level, TAK-418 overall and overall. The categories will include:

- Subjects who were randomized but not treated, if applicable.
- Subjects who completed the study drug.
- Subjects who prematurely discontinued the study drug.
- Subjects who completed all study visits.

- Subjects who prematurely discontinued study visits.

Primary reasons for discontinuing study drug and/or visits, as recorded on the eCRF, will be summarized.

Disposition information for randomized subjects will be listed. The status of blind for randomized subjects will also be listed. A listing of inclusion/exclusion criteria not met will be provided for randomized subjects who did not meet at least one inclusion criterion.

Significant protocol deviations captured on the eCRF will be listed and summarized.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for subjects in the Safety Set. Summaries will be presented by pooled placebo, each TAK-418 dose level, TAK-418 overall, and overall total. Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables (eg, age, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristic data will be provided in the data listings.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, any available safety data and reason for screen failures will also be presented in the data listing.

There will be no inferential analysis of demographic and baseline characteristics.

7.5 Medical History and Concurrent Medical Conditions

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

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 19 or higher) coding system.

Medical history and concurrent medical conditions will be listed by site and subject number. The listing will contain subject identifier, treatment, system organ class (SOC), preferred term (PT), whether there was any medical history or concurrent condition, and, if yes, a detail of the medical history or concurrent condition.

There will be no inferential 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 at or within 28 days prior to signing of informed consent. Concomitant medications are recorded on the eCRF and include any medications, other than study drug, taken at any time from signing of informed consent through the end of the study.

All medication history and concomitant medications will be listed by site and subject number. The listings will contain subject identifier, treatment, World Health Organization Drug Dictionary (WHODrug) preferred medication name, dose, unit, frequency, route, start date, stop date, whether the medication was ongoing, and reason for use. No inferential statistics will be presented.

Medication history and concomitant medications will be coded using the WHODrug Version 01 March 2016 or higher.

7.7 Study Drug Exposure and Compliance

Each subject will be given a single dose as per the study design. Since all doses of study medication will be administered during confinement, study drug compliance will not be summarized. Dosing administration as well as study drug concentration data will be provided by subject and visit in the listings. Meal time and meal consumption will be listed as collected on the eCRF.

There will be no inferential analysis of study drug exposure.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/ Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

All PK summaries and analyses will be based on the PK Set. PK parameters of TAK-418 will be derived using noncompartmental analysis methods and will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times for plasma PK parameters. Nominal time intervals will be used for computations of urine PK parameters.

PK blood and urine samples for TAK-418F concentrations will be collected as specified in the Schedule of Trial Procedures (See Appendix D). Plasma and urineTAK-418F concentrations will be measured by liquid chromatography with tandem mass spectrometry method.

Plasma concentrations of TAK-418F will be summarized by dose over each scheduled sampling time using descriptive statistics. The amount of TAK-418F excreted in urine will also be summarized by dose using descriptive statistics. Subjects randomized to placebo will not be included in these summarizes but will be listed. Individual plasma concentration and urine concentration versus time and PK parameters will be presented in a data listing.

The following pharmacokinetic parameters will be calculated for plasma concentration values of TAK-418F:

Symbol/Term	Definition
t_{max}	Time of first occurrence of C_{max}.
C_{max}	Maximum observed concentration.
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
CCI	[redacted]

Descriptive statistics (N, arithmetic mean, SD, %CV, median, minimum, and maximum) will be used to summarize the plasma PK parameters for TAK-418 by dose. In addition, geometric mean will be computed for C_{max} and AUCs. Individual plasma PK parameters will be presented in a data listing.

The following pharmacokinetic parameters of TAK-418 will be derived from urine concentrations of TAK-418F:

Symbol/Term	Definition
CCI	[redacted]

Descriptive statistics (N, arithmetic mean, SD, median, minimum, and maximum) will be used to summarize the urine PK parameters for TAK-418. Individual urine PK parameters will be presented in a data listing.

Specific or additional PK parameters may be added as appropriate per the Clinical Pharmacology Analysis Plan (CPAP).

If sufficient data are available, the does proportionality for cohorts (fasted cohorts only) on Day 1 for key PK parameters (C_{max} and AUCs) will be assessed using the power model. The power model can be described by the following equation:

$$\ln(PK\ Parameter) = \beta_o + \beta_1 \ln(Dose) + \varepsilon$$

where β_o is the intercept and β_1 is the slope with random error ε. Dose proportionality will be declared if the 90% confidence interval (CI) for β_1 lies entirely within the critical region,

$$\left(1 + \frac{\ln(0.80)}{\ln(r)}, 1 + \frac{\ln(1.25)}{\ln(r)}\right)$$

where r is the ratio of the highest and the lowest dose in the study. [3]

For evaluation of potential food effect on TAK-418F PK, log-transformed C_{max} and AUC values for Cohort 3 will be compared between the treatments (Reference=fasting administration; Test=fed administration) using an analysis of variance (ANOVA) with fixed effect for treatment and a random effect for subject. The geometric mean for relative bioavailability and 90% CIs of geometric mean ratio for C_{max}, AUC_{last}, and AUC_{∞} will be calculated.

7.9.2 Pharmacodynamic Analysis

PD samples will be collected as specified in the Schedule of Trial Procedures (See Appendix D).

CCI

Additional analyses will be performed if useful and appropriate.

7.10 Other Outcomes

CCI

Additional analyses will be performed if useful and appropriate. Detailed statistical methods for biomarker will be specified in a separate biomarker analysis plan.

7.11 Safety Analysis

Safety analyses include AEs, clinical laboratory parameters, vital sign results, 12-lead ECG results, and other safety parameters. The Safety Set will be used for all summaries of safety parameters. These summaries will be presented by pooled placebo, each TAK-418 dose level, and TAK-418 overall (as appropriate). These summaries will not contain data from the fed portion. Data from the food effect cohort will be summarized separately by placebo fed, placebo fasted, TAK-418 fed, and TAK-418 fasted.

7.11.1 Adverse Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study, but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

A TEAE is defined as any sign, symptom, syndrome, or new illness, regardless the relationship to study drug, which occurs on or after the administration of the study drug and no more than 30 days after receiving the last dose of study drug (onset data-last date of dose +1 ≤30). A TEAE may also be a pretreatment AE or a concurrent medical condition diagnosed prior to the date of first dose of study drug that increases in severity after the start of dosing. Any event with partially or completely missing onset date information will be considered treatment emergent unless the available information indicates that the onset occurred outside the window (onset data-last date of dose +1 ≤30).

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA, version 19 or higher).

TEAEs are recorded in the eCRF as being related or not related to study drug and study procedure. TEAEs that are recorded as related to study drug and/or study procedure will be summarized separately. TEAEs will also be presented by intensity/severity (mild, moderate, and severe). Serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death will also be summarized using SOC and PT.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary.

AEs with missing intensity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. If the relationship of an event is missing, the relationship for the event will be considered to have been related.

TEAEs will be presented by pooled placebo, each TAK-418 dose level and TAK-418 overall. The tables will include the number and percentage (N[%]) of subjects. The following summary tables will be generated:

- Overviews of TEAEs, including number of subjects and events.
- TEAEs by SOC and PT, including number of subjects and events.
- Subject mappings for TEAEs by SOC and PT.
- TEAEs by PT.

- Serious TEAEs by SOC and PT.
- Relationship of TEAEs to study drug by SOC and PT.
- Drug related TEAEs by SOC and PT.
- Drug related TEAEs by PT.
- Intensity of TEAEs by SOC and PT.
- Intensity of drug related TEAEs by SOC and PT.
- Pretreatment Adverse Events (PTE) by SOC and PT.

Data listings will be provided for PTEs, TEAEs, TEAEs leading to study drug discontinuation, SAEs, and AEs that resulted in death.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be assessed using the Safety Set and will be evaluated and presented using International System of Units (SI) units unless otherwise stated. Refer to Appendix D for scheduled clinical laboratory test measurements.

The central laboratory will perform laboratory tests, including hematology, urinalysis, chemistry and other tests.

For hematology, urinalysis and chemistry tests, descriptive statistics (N, mean, median, SD, minimum and maximum) will be summarized for baseline, post-baseline, and change from baseline values by treatment regimen and study visit. Only the scheduled measurements will be included in the summary.

Individual results for hematology and chemistry laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (see Appendix A) using the result and criteria in SI units. All subjects with results that meet the MAV criteria will be presented in a data listing. The number and percentage of subjects with at least one post dose markedly abnormal laboratory test result will also be summarized. The mapping of the subjects who meet the MAV criteria after dosing will be listed as a table. All postdose observations, including scheduled and unscheduled measurements will be included in the MAV summaries.

Listings of all clinical safety laboratory data will be provided and will be presented in both SI and CV units. Laboratory data outside of the normal reference range will be indicated in the listings. In addition, MAVs will be flagged. The listing will include site number, subject identifier, age (at informed consent), gender, treatment group, study visit, and sample collection date. CCI parameters will be listed separately.

7.11.3 Vital Signs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize vital sign parameters at baseline, each post-baseline visit, and change from baseline

to each post-baseline visit. Summaries will be presented by pooled placebo and each TAK-418 dose level.

Individual results of vital signs that meet Takeda's markedly abnormal criteria (see Appendix B) will be summarized and provided in the data listings. If a subject has a MAV for a particular vital sign parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 postdose MAV signs measurement will be summarized by pooled placebo, each TAK-418 dose level and TAK-418 overall. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

All vital sign results for all subjects in the Safety Set will be listed by subject in the data listings and markedly abnormal values will be flagged.

7.11.4 12-Lead ECGs

The scheduled 12-lead ECG data will be collected according to Appendix D. The ECG parameters include heart rate, PR-interval, QRS-duration, QT-interval, and QTcF interval, and the interpretation of the ECG profile by the principal investigator.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters will be presented for baseline, each post-baseline visit, and changes from Baseline in quantitative ECG parameters to each post-baseline visit. Only the scheduled measurements will be included in the summary. No inferential statistics will be presented.

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet Takeda's markedly abnormal criteria (see Appendix C) will be summarized and provided in the data listings. Shift tables will be generated to show the investigator's ECG interpretations at each postdose collection by the interpretation at Baseline.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Physical examination findings will be presented in the data listings.

Columbia-Suicide Severity Rating Scale results will be presented in the data listings.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

1. A Randomized, Double-Blind, Placebo-Controlled, Ascending Oral Single Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-418 in Healthy Subjects, Takeda Development Center Americas, Inc., Amendment 01, Trial No. TAK-418-1001, dated 07 July, 2017.
2. CCI [redacted]
3. Brian P. Simith, etc. (2000), Confidence Interval Criteria for Assessment of Dose Proportionality, Pharmaceutical Research; Vol 17, No. 10, pp 1278-1283.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 × LLN	>1.5 × ULN
Platelet count	Conventional	$<75 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$
	SI	$<75 \times 10^9/L$	$>600 \times 10^9/L$

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Alkaline Phosphatase	Both	--	>3 × ULN
ALT	Both	--	>3 × ULN
AST	Both	--	>3 × ULN
Blood urea nitrogen	Conventional	--	>30 mg/dL
	SI	--	>10.7 mmol/L
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L
Carbon dioxide (Bicarbonate)	Conventional	<8.0 mEq/L	--
	SI	<8.0 mmol/L	--
Chloride	Both	<75 × LLN	>126 × ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI	--	>177 μmol/L
Glucose	Conventional	<50 mg/dL	>350 mg/dL
	SI	<2.8 mmol/L	>19.4 mmol/L
Gamma-glutamyl transferase	Both	--	>3 × ULN
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Total protein	Both	<0.8 × LLN	>1.2 × ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	<35.6	>37.7

Appendix C Criteria for Identification of Markedly Abnormal 12-Lead ECG Parameters

Parameter	Unit	Lower Criteria	Upper Criteria
HR	bpm	<50	>120
QT-interval	msec	≤50	≥460
QTcF-interval	msec	≤50	≥500 OR ≥30 change from baseline and ≥450

Appendix D Schedule of Trial Procedures

Schedule of Activities

	Day(s) (a)		Scheduled Time (a)															Follow-up/ ET (b)	CCI
	-28 to -2	-1	Hours															Days	
	Screening		Predose Day 1	0	0.25	0.5	1	1.5	2	3	4	8	12	24	36	48	72	14 (±2)	91, 93, 182, 184 (±7)
Administrative Procedures																			
Informed consent	X																		
Inclusion/exclusion criteria	X	X	X																
Medical history/ demographics	X																		
Prior and concomitant medication review	X----------Continuous Review----------X																		
Clinic Procedures/Assessments																			
Full physical examination	X		X (d)															X	
Neurological examination	X		X (d)											X			X	X	
Height	X																		
Weight	X		X											X				X	
BMI	X																		
Semirecumbent vital signs (HR, SBP, and DBP)	X		X (e)				X		X					X				X	
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature)	X		X (e)				X		X					X				X	
12-lead ECG	X	X	X (e)				X		X					X				X	

	Day(s) (a)		Scheduled Time (a)															Follow-up/ ET (b)	CCI
	-28 to -2	-1	Hours															Days	
	Screening		Predose Day 1	0	0.25	0.5	1	1.5	2	3	4	8	12	24	36	48	72	14 (±2)	91, 93, 182, 184 (±7)
TAK-418/placebo administration				X															
C-SSRS	X		X											X		X	X	X	
BL-VAS			X				X							X					
CCI																			
AE monitoring	X----------Continuous Monitoring----------X																		
Laboratory Procedures/Assessments																			
Hematology	X		X											X				X	
Urinalysis	X		X											X				X	
Serum chemistry	X		X											X				X	
hCG (females)	X	X															X	X	
CCI																			
CCI																			
CCI																			
Urine/breath alcohol test (j)	X	X																	
Hepatitis screen	X																		
HIV	X																		
PK Evaluations																			
Blood for plasma PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine for PK (k)			X----------X																

	Day(s) (a)		Scheduled Time (a)															Follow-up/ ET (b)	CCI
	-28 to -2	-1	Hours															Days	
	Screening		Predose Day 1	0	0.25	0.5	1	1.5	2	3	4	8	12	24	36	48	72	14 (±2)	91, 93, 182, 184 (±7)
Biomarker Evaluations																			
CCI																			
CCI																			
CCI																			
PGx Evaluations																			
Blood sample for DNA PGx (n)			X																
Blood sample for RNA PGx (o)			X											X					
Other																			
CCI																			
Confinement		X----------X																	

Footnotes are on the last table page.

AE=adverse event, BL-VAS=Bond-Lader Visual Analogue Scale, BMI=body mass index, C-SSRS=Columbia–Suicide Severity Rating Scale, DBP=diastolic blood pressure, ECG=electrocardiogram, ET=early termination, F-FAD=formyl-flavin adenine dinucleotide, CCI , hCG=human chorionic gonadotropin, HIV=human immunodeficiency virus, HR=heart rate, CCI , PBMC=peripheral blood mononuclear cell, PGx=pharmacogenomics, PK=pharmacokinetic, SBP=systolic blood pressure.

(a) For Cohort 3, there will be a 7 day washout between Cohorts 3A and 3B, starting from TAK-418 administration on Day 1 for Cohort 3A. For Cohort 3B, all assessments on Days -1 through Day 4 will be same as Cohort 3A.

(b) CCI

(c) CCI

(d) Predose physical and neurological examinations may be done within approximately 24 hours predose.

(e) Vital signs and a 12-lead ECG will be performed within approximately 1 hour predose on Day 1.

(f) CCI

(g) CCI

(h) CCI

(i) CCI

(j) A urine alcohol test may be performed at the discretion of the investigator.

(k) Urine sample for TAK-418F concentrations may be collected at a dose level projected to produce therapeutic exposure at the following time intervals: Predose (spot collection), 0 to 12 hours, 12 to 24 hours, 24 to 48 hours.

(l) CCI

(n) Blood for DNA PGx will be collected within 60 minutes predose.

(o) Blood for RNA PGx will be collected within 60 minutes predose and 24 hours postdose.

(p) CCI

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	12-Dec-2017 16:07 UTC
	Clinical Pharmacology Approval	12-Dec-2017 16:37 UTC
	Pharmacovigilance Approval	12-Dec-2017 16:51 UTC
	Statistical Approval	12-Dec-2017 16:54 UTC
	Clinical Approval	12-Dec-2017 20:45 UTC