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

NCT Number: NCT03501069

SAP Approve Date: 28 January 2019

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-418-1003

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

PHASE 1

Version: Final

Date: 28 January 2019

Prepared by:

PPD

Based on:

Protocol Version: Original

Protocol Date: 05 March 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 TABLES

LIST OF APPENDICES

3.0   LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CPAP	Clinical Pharmacology Analysis Plan
CPK	creatine phosphokinase
CRF	case report form
ECG	electrocardiogram
FAS	full analysis set
GGT	γ-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PK	pharmacokinetics
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SDB	standard database
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

4.0   OBJECTIVES

4.1   Primary Objectives

To characterize the safety and tolerability of TAK-418 in non-Japanese and Japanese healthy female subjects when administered at single or multiple (once daily [QD]) oral escalating doses.

4.2   Secondary Objectives

To characterize the PK of TAK-418 in non-Japanese and Japanese healthy female subjects when administered at single or multiple (QD) oral escalating doses.

4.3   Trial Exploratory Objectives

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4.4   Study Design

This phase 1, randomized, double-blind, placebo-controlled trial is designed to evaluate the safety, tolerability, PK, and PD of single and multiple (QD) rising oral doses of TAK-418 (capsule formulation) in healthy adult female subjects.

Approximately 48 subjects are planned for enrollment in 6 cohorts (n=8 per cohort). In SRD cohort 1, subjects will receive a single oral dose of study drug (TAK-418 or matching placebo) in a double-blind manner in period A. After a washout interval of at least 14 days after the dose of study drug and following the review of the safety, tolerability, and PK data from period A, subjects in cohort 1 may receive a second single dose of study drug in period B. In multiple-rising dose (MRD) cohorts 2 to 6, subjects will receive study drug QD for 10 days in a double-blind manner. In each SRD and MRD cohort, 6 subjects will be randomly assigned to receive TAK-418 and 2 to receive placebo. The cohorts will be enrolled in a consecutive, staggered, or parallel manner (see the protocol [1]).

For all SRD and MRD cohorts, blood samples will be collected for PK (TAK-418), CCI and CCI . For MRD cohort 3 only, serial lumbar CSF samples will be collected through an indwelling temporary catheter for 48 hours after the last dose of study drug for PK (TAK-418) and CCI . Urine samples will be collected from selected non-Japanese MRD cohorts.

The planned TAK-418 dosing regimens and ethnicity of subjects are presented in Table 4.a. Non-Japanese subjects will be enrolled in cohorts 1 to 4 and Japanese subjects in cohorts 5 and 6. Planned doses range from 20 to 160 mg, but the actual doses administered after cohort 1 (period A) and cohort 2 will be based on emerging safety, tolerability, and PK data available from the previous doses.

The trial may be conducted at multiple phase 1 units to support both CSF collection and recruitment of Japanese subjects.

Due to the early termination of the study, cohort 6 was not run. For cohorts 4 and 5, 4 subjects, instead of 8 were recruited. The actual doses for cohorts 3 and 4 are CCI mg and CCI mg, respectively.

Table 4.a - Planned Dosing Regimens and Ethnicity of Subjects

Cohort	Ethnicity	Planned TAK-418 Dosing Regimen		Comments
1 (period A)	Non-Japanese	CCI	single dose	Cohort 1 (period A) may receive a second single dose (period B).
1 (period B)			single dose	
2			D (10 days)	Cohort 2 may run in parallel with cohort 1 (period A or period B).
3			D (10 days)	Serial CSF samples will be collected.
4			D (10 days)	
5	Japanese		D (10 days)	Cohort 5 may run in parallel with cohort 1, 2, or 3.
6			D (10 days)	

5.0   ANALYSIS ENDPOINTS

5.1   Primary Endpoints

For All Cohorts

- Number and percentage of subjects with at least 1 TEAE.

- Number and percentage of subjects with at least 1 serious adverse event (SAE).

- Number and percentage of subjects who meet the markedly abnormal criteria for clinical laboratory values at least once postdose.

- Number and percentage of subjects who meet the markedly abnormal criteria for vital signs at least once postdose.

- Number and percentage of subjects who meet the markedly abnormal criteria for safety 12-lead ECG parameters at least once postdose.

5.2   Secondary Endpoints

For SRD Cohort 1 (Periods A and B)

- AUC_∞ after a single dose of TAK-418.

For MRD Cohorts 2 to 6

- Area under the plasma concentration-time curve during a dosing interval (AUC_τ) on Day 1 and after the final dose following multiple (QD) dosing of TAK-418.

For All Cohorts

- C_{max}.

- Time of first occurrence of C_{max} (t_{max}).

5.3   Exploratory Endpoints

5.3.1   Exploratory PK Endpoints

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5.3.2 Exploratory PD Endpoints

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5.3.3 Exploratory Biomarker Endpoints

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5.3.4 Other Exploratory Endpoints

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6.0   DETERMINATION OF SAMPLE SIZE

The sample sizes chosen are considered sufficient for evaluation of safety, tolerability, PK, and PD of each cohort but are not based on statistical considerations.

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 1 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 for SRD and MRD parts. Data from Cohort 1 will be summarized separately by treatment regimen.

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

All data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

7.1.4 Conventions for Missing Adverse Event Dates

Incomplete adverse event (AE) start dates will be imputed to determine the relationship between the start date and the informed consent date, as well as the start date and the first dose date of the double-blind study medication. Incomplete AE dates will be presented as they are in the listings.

The following methods will be used to impute incomplete start dates of AEs:

- If only the month and year of the start date are available and the month and year are different than the month and year of the first dose of double-blind study medication or the stop date is prior to the first dose of study medication, then the first day of the month will be used for the start date. If only the month and year of the start date are available and the month and year are the same as the month and year of the first dose of double-blind study medication and the stop date is not prior to the date of first dose, then the date of first dose will be used for the start date.

- If only the year of the start date is available and the year is different than the year of the first dose of double-blind study medication or the stop date is prior to the first dose of study medication, then January 1st will be used for start date. If only the year of the start date is available and the year is the same as the year of the first dose of double-blind study medication and the stop date is not prior to the date of first dose, then the date of first dose will be used for start date.

7.1.5 Conventions for Missing Concomitant Medication Dates

If start date and stop date are missing, medication will be assumed to occur both prior and concomitantly.

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 include all subjects who were enrolled and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristic, and safety summaries.

- Pharmacokinetic (PK) Set: The PK set will include all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma or CSF concentration or amount of drug in urine for TAK-418.

- CCI

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 for SRD and MRD parts. The categories will include:

- Subjects who were randomized but not treated, if applicable.

- Subjects who completed the study.

- Subjects who prematurely discontinued the study.

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. 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 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. Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic and other baseline characteristic variables (eg, age, height, weight, BMI) for the pooled placebo group, each TAK-418 dose level, and TAK-418 overall. The number and percentage of subjects in each class of the categorical demographic and other baseline characteristic variables (eg, sex, ethnicity, race) will be tabulated for the pooled placebo group, each TAK-418 dose level, and TAK-418 overall. Data from subjects who received placebo will be pooled across cohorts, as appropriate to each analysis. Individual subject demographic and other baseline characteristic data will be listed.

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 for each period in SRD and multiple doses in MRD 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.

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. The PK parameters of TAK-418 will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in computations involving sampling times, except where otherwise noted. Nominal time intervals will be used for computations of urine PK parameters.

PK blood, urine and CSF samples for TAK-418 concentrations will be collected as specified in the protocol. Plasma, urine, and CSF concentrations of TAK-418 free base will be measured by a

validated high-performance liquid chromatography with tandem mass spectrometry assay. Free base TAK-418 concentrations are used for all PK summaries and analyses.

TAK-418 concentrations in plasma (including trough concentrations for the MRD cohorts) and CSF will be summarized by dose over each scheduled sampling time point using descriptive statistics. The amount of TAK-418 excreted in urine will be summarized by dose over each scheduled sampling interval using descriptive statistics. Plasma concentrations will be summarized separately for the SRD and MRD portions of the study. Subjects randomized to placebo will not be include in these summaries but will be listed. Individual plasma concentrations versus time, CSF concentration versus time and individual urine TAK-418 excretion by collection interval and individual will be listed separately.

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

The following PK parameters will be calculated from plasma concentrations of TAK-418:

For SRD cohort 1 (periods A and B) after a single dose on Day 1

- AUC_∞
- C_{max}
- t_{max}
- AUC_t
- $t_{1/2z}$
- CL/F
- V_z/F

For MRD cohorts 2 to 6 on Day 1

- AUC_τ
- AUC_∞
- C_{max}
- t_{max}

For MRD cohorts 2 to 6 at steady state (after the final dose)

- AUC_τ
- C_{max}
- t_{max}
- AUC_t
- $t_{1/2z}$
- CL/F
- V_z/F

- $R_{ac(AUC)}$

- $R_{ac(Cmax)}$

Descriptive statistics (N, arithmetic mean, SD, %CV, median, minimum, and maximum) will be used to summarize the plasma PK parameters for TAK-418 by cohort, day and period (period A vs period B). In addition, geometric mean will be computed for C_{max} and AUCs. Individual plasma PK parameters will be listed.

The following PK parameters will be calculated from urine concentrations of TAK-418:

For selected MRD cohorts after a single dose on Day 1 and at steady state (after the final dose)

- Ae_t

- $f_{e,t}$

- CL_R

Descriptive statistics (N, arithmetic mean, SD, %CV, median, minimum, and maximum) will be used to summarize the urine PK parameters for TAK-418 by cohort and day. Individual urine PK parameters will be listed.

The following PK parameters will be calculated from CSF concentrations of TAK-418:

For MRD cohort 3 only at steady state (after the final dose)

- CSF t_{max}

- CSF C_{max}

- CSF AUC_{24}

- CSF AUC_{48}

- CSF AUC_{24}:plasma AUC_{24}

- CSF AUC_{48}:plasma AUC_{48}

Descriptive statistics (N, arithmetic mean, SD, %CV, median, minimum, maximum, and/or geometric mean) will be used to summarize the CSF PK parameters for TAK-418 by cohort, as appropriate. Individual CSF PK parameters will be listed.

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

For the MRD part, an analysis of variance (ANOVA) model may be used to assess time dependency in the PK of plasma TAK-418 between Day 1 and Day 10. Specifically, time invariance will be assessed by comparing AUC_τ for Day 10 to the AUC_∞ for Day 1, separately for each dose. The model will include dose level, day, and interaction of dose level by day as fixed factors and the natural logarithmic AUCs as the responses. Using the ANOVA model, the point estimates for the ratios of AUC central values and their 90% CIs between Day 10 and Day 1 will also be provided for each dose level.

For non-Japanese MRD cohorts, dose proportionality for C_{max} and AUCs will be tested using a power model. The power fit will be assumed as 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]

7.9.2 Exploratory Pharmacodynamic Analysis

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7.10 Other Outcomes

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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, where appropriate, for the SRD and MRD portions of the study. Data for subjects who received placebo will be pooled across all cohorts, as appropriate to each analysis. All safety data will be presented in data listings.

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 $+1 \leq 30$). 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 $+1 \leq 30$).

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, AEs, 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 B 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 for both SRD and MRD using the Safety Set. 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. 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. Semen analysis 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 for SRD and MRD parts.

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 the protocol. The ECG parameters include heart rate, PR-interval, QRS-interval, QT-interval, 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, neurological examination and fundoscopic 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

Dose proportionality for C_{max} and AUCs will be assessed for non-Japanese MRD cohorts.

8.0 REFERENCES

1. A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-418 in Healthy Female Subjects, Millennium Pharmaceuticals, Inc, Original Protocol, Trial No. TAK-418-1003, dated 20 March, 2018.

2. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th ed. Cooper TG, editor. Geneva, Switzerland: World Health Organization; 2010.

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	$<0.8 \times$ LLN	$>1.2 \times$ ULN
Hematocrit	Both	$<0.8 \times$ LLN	$>1.2 \times$ ULN
RBC count	Both	$<0.8 \times$ LLN	$>1.2 \times$ ULN
WBC count	Both	$<0.5 \times$ LLN	$>1.5 \times$ 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	--	$>3 \times$ ULN
ALT	Both	--	$>3 \times$ ULN
AST	Both	--	$>3 \times$ 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	>126
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	--	$>3 \times$ 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	$<0.8 \times$ LLN	$>1.2 \times$ 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	29-Jan-2019 17:51 UTC
	Clinical Pharmacology Approval	29-Jan-2019 18:05 UTC
	Clinical Science Approval	29-Jan-2019 19:40 UTC
	Biostatistics Approval	29-Jan-2019 20:19 UTC