Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single-and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-020 in Healthy Volunteers

NCT Number: TAK-020-1001

Approve Date: 22-May-2017

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black 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-020-1001

TAK-020 SRD/MRD Study

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-020 in Healthy Volunteers

PHASE 1

Version: Final

Date: 22 May 2017

Prepared by:

PPD

Based on:

Protocol Version: Amendment 4

Protocol Date: 27 March 2017

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

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3.0 LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	adverse event
Ae_t	total amount of drug excreted in urine from time 0 to time t
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC_t	area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration
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, where tau (τ) is the length of the dosing interval
CCI	CCI
BMI	body mass index
CCI	CCI
CI	confidence interval
CL/F	apparent clearance after extravascular administration
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
CPAP	Clinical Pharmacology Analysis Plan
%CV	coefficient of variation
CV	conventional units
ECG	electrocardiogram
E_{max}	maximum observed effect
f_e	fraction of drug excreted in urine
LLOQ	lower limit of quantification
MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple rising dose
NOAEL	no observed adverse effect level
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
PTE	pretreatment event
SD	standard deviation
SI	International System of Units
SOC	system organ class
SRD	single rising dose
TDC	Takeda Development Center
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum observed plasma concentration

$t_{max}(E)$	time to reach maximum observed effect
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase after extravascular administration
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to characterize the safety and tolerability of TAK-020 following single and multiple oral doses in healthy subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

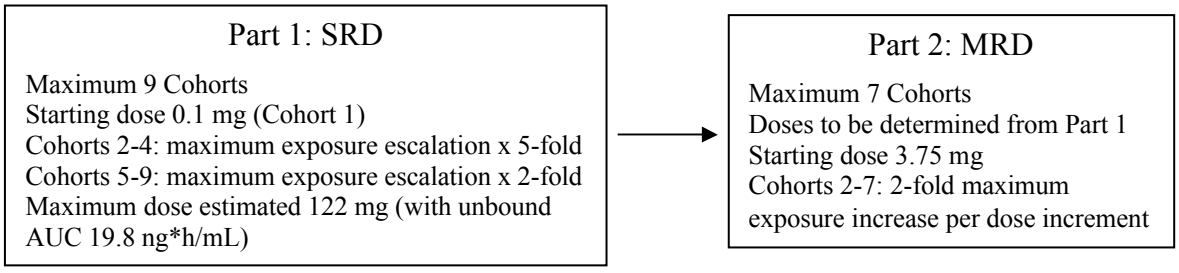
- To characterize the pharmacokinetics (PK) of TAK-020 following single and multiple oral doses.
- To characterize the pharmacodynamics (PD) of TAK-020 following single and multiple oral doses.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple-dose study in healthy volunteers. The study is comprised of 2 parts, each with multiple cohorts and is presented in the Study Schematic below. The study population for each part will be composed of healthy subjects aged 18 to 55 years, inclusive, who weigh at least 45 kg, and have a body mass index (BMI) between 18 and 32 kg/m^2, inclusive, at Screening and Day -1.



SRD=single-rising dose, MRD=multiple-rising dose.

Part 1: Single-Rising Dose (SRD)

This part will comprise a maximum of 9 cohorts. Each cohort will comprise of 8 randomized subjects, with 6 receiving TAK-020 and 2 receiving placebo in the fasted state. Sentinel dosing will be used for Cohort 1 with only 2 subjects dosed on the morning of Day 1 (1 receiving TAK-020 and 1 receiving placebo). The remaining subjects will be dosed following agreement with the investigator and Takeda after reviewing 24-hour postdose safety (adverse events [AEs], vital signs, 12-lead electrocardiograms [ECGs]) and tolerability data. Sentinel dosing will not be necessary for other cohorts provided that exposure is observed in ≥4 subjects receiving active

treatment and in agreement with the investigator and Takeda, otherwise sentinel dosing in the subsequent cohort will be required.

TAK-020 will be orally administered as a solution with a starting dose of 0.1 mg for Cohort 1. Dosing for the subsequent cohorts will only occur after review of the safety, tolerability, and minimum 24-hour PK data from the previous cohort. For each dose escalation, exposures may be increased by a maximum of 5-fold for Cohorts 2-4 and a maximum of 2-fold for Cohorts 5-9. Doses may also be decreased as appropriate.

Part 2: Multiple-Rising Dose (MRD)

TAK-020 will be orally administered as a solution. The dose to be used in each cohort will be selected based on data from Part 1 of the study and from the previous cohort in Part 2.

The first cohort for the MRD will receive a dose of 3.75 mg, with a predicted exposure at steady state estimated to be below the no observed adverse effect level (NOAEL) rate (63 ng*h/mL). The predicted steady state exposure in the first MRD cohort will be approximately 10-fold lower than the highest predicted steady state exposure determined from the SRD data. The MRD will comprise a maximum of 7 cohorts, each cohort with 8 subjects randomized with 6 receiving TAK-020 and 2 receiving placebo. In each successive cohort after the first, the dose increments will increase the predicted exposures by no more than 2-fold. The predicted steady state exposure in the MRD will not exceed the maximum exposure observed in the SRD.

A schematic of the study design is included as Table 4.a. A schedule of assessments is listed in Appendix A.

Table 4.a Schematic of Study Design

Study Schematic for Part 1

Screening	Check-in	Dose	Check-out	Follow-up (a)
Day -28 to -2	Day -1	Day 1	Day 5	Day 14 (±2)

(a) A phone call is planned but individual subjects may be asked to return to the unit at this time if abnormal clinical safety laboratory values are obtained at Check-out or TEAEs have not resolved at Check-out.

Study Schematic for Part 2

Screening	Check-in	Dose	Washout	Dose	Check-out	Follow-up (a)
Day -28 to -2	Day -1	Day 1	Day 2	Days 3-9	Day 10	Day 17 (±2)

(a) All subjects will return to the unit and complete hematology and serum chemistry tests, vital signs, concomitant medications, and AE assessment.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary safety endpoints include the number and percentage of subjects who:

- Experience at least 1 treatment-emergent adverse event (TEAE).
- Meet the Takeda Development Center (TDC) markedly abnormal values (MAV) criteria for safety laboratory tests at least once postdose.
- Meet the TDC MAV criteria for vital sign measurements at least once postdose.
- Meet the TDC MAV criteria for safety ECG parameters at least once postdose.

5.2 Secondary Endpoints

The secondary endpoints will be the following PK parameters of TAK-020:

- Maximum observed plasma concentration (C_{max}).
- Time to reach C_{max} (t_{max}).
- Area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration (AUC_t).
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_∞).
- Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_τ).
- $t_{1/2z}$.
- Apparent clearance after extravascular administration (CL/F).
- Apparent volume of distribution during the terminal phase after extravascular administration (V_z/F).
- Total amount of drug excreted in urine from time 0 to time t (Ae_t).
- Fraction of drug excreted in urine (f_e).
- Renal clearance (CL_R).

5.3 Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The sample sizes chosen of 8 subjects per cohort (6 active: 2 placebo) in Part 1 and 2 is considered to be sufficient for evaluation of safety, tolerability, PK and the PD of TAK-020 in each cohort. The sample size was not based on statistical power considerations.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Data for SRD and MRD will be summarized separately over all randomized subjects in each study part. Continuous data will be summarized using descriptive statistics, including the number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. The coefficient of variation (%CV) and geometric mean will be included in the summary of continuous data where indicated. Categorical data will be summarized using the number and percentage of subjects (N[%]) for each category. Missing values will be categorized separately where deemed appropriate and necessary.

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. Means and medians will be presented to 1 more decimal place than the recorded data. SD 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. Percentages will be presented to 1 decimal place (eg, 80.3%). All p-values will be rounded to 3 decimal places. If a p-value is less than 0.001, it will be reported as "<0.001"; if a p-value is greater than 0.999, it will be reported as ">0.999".

All study-related raw data, including derived data, will be presented in data listings.

When no data are available for a table or appendix, an empty page with the title will be produced with suitable text (eg, "There were no subjects with markedly abnormal values of laboratory parameters.").

The Baseline value for a variable is defined as the last observation collected before the first dose of study medication, unless stated otherwise.

Analysis datasets and summary displays will be prepared using SAS version 9.2 or later.

7.1.1 Study Definitions

There are no study-specific definitions.

7.1.2 Definition of Study Days

Study day will be calculated relative to the date of first dose of study medication for each subject. Study Day 1 is defined as the date on which a subject takes the first dose of study medication, as recorded on the CRF dosing page. Study days prior to the date of first dose of study medication will be calculated as: date of assessment (or event) - date of first dose of study medication. Study days after the date of first dose of study medication will be calculated as: date of assessment (or event) - date of first dose of study medication + 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 concentrations that are below the lower limit of quantification (< LLOQ) 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:

- All randomized subjects will consist of all subjects who are randomized to a treatment.
- The safety analysis set will consist of all subjects who are randomized to a treatment and receive 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.
- The PK analysis set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration or amount of drug in the urine. Subjects in this analysis set will be used for all PK summaries and statistical analyses.
- The PD analysis set will consist of all subjects who receive study drug and have at least 1 predose and postdose PD measurement. Subjects in the analysis set will be used for all PD summaries and statistical analyses.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but all randomized subjects will be presented in the subject listings.

7.3 Disposition of Subjects

Disposition of all screen 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-020 dose level and TAK-020 overall. The categories will include:

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

- Subjects who prematurely discontinued study visits.

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

Disposition information for randomized subjects will be listed. The status of the 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 entrance criterion.

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

7.4 Demographic and Other Baseline Characteristics

Demographic characteristics, including age at informed consent, gender, ethnicity and race will be summarized and listed for screen failure subjects, along with the reason(s) for failure.

Demographic and study baseline characteristics, including age at informed consent, gender, ethnicity, race, baseline height (cm), baseline weight (kg), baseline BMI (kg/m^2), smoking history, alcohol history, caffeine/xanthine history and female reproductive status will be summarized for all subjects in the safety analysis set by pooled placebo, each TAK-020 dose level, TAK-020 overall and total overall. Subjects who identify themselves as belonging to more than 1 race on the eCRF will be classified as multiracial for summaries and each race selected will be listed. In addition, demographic and baseline characteristics will be summarized for all subjects in the safety analysis set (i.e. SRD and MRD combined) by pooled placebo, TAK-020 and overall.

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 stopped prior to the signing of informed consent. Concurrent medical conditions are defined as significant conditions that are present or ongoing at or after the signing of informed consent.

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

Medical history and concurrent medical conditions will be listed separately by site and subject number.

There will be no summary or 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 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 (WHODrug) version 01MAR2016 Expanded or higher.

Separate listings for medication history and concomitant medications will be produced by site and subject number.

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

7.7 Study Drug Exposure and Compliance

Each subject will be given a single dose 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 for SRD and MRD 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

The schedule of blood samples for PK analysis of TAK-020 is listed in Table 7.a and the schedule of urine samples is listed in Table 7.b.

Plasma concentrations of TAK-020 will be summarized by treatment over each scheduled sampling time using descriptive statistics. The amount of TAK-020 excreted in urine will also be summarized by treatment over each scheduled sampling interval using descriptive statistics. Plasma concentrations and the amount of study drug excreted in urine will be summarized separately for the SRD and MRD portions of the study. Subjects randomized to placebo will not be included in these summarizes but will be listed. Individual plasma concentrations and urine amounts will be listed separately.

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis

Part 1 (SRD)

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose

Part 2 (MRD)

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
Plasma	9	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose

Table 7.b Collection of Urine Samples for Pharmacokinetic Analysis

Part 1 (SRD)

Sample Type	Dosing Day	Time Postdose (hours)
Urine	1	Predose (-12-0), and 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 hour postdose intervals

Part 2 (MRD)

Sample Type	Dosing Day	Time Postdose (hours)
Urine	1	Predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals
Urine	9	Predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals

PK parameters of TAK-020 are listed in Table 7.c and will be determined from the concentration-time profiles for all evaluable subjects.

Table 7.c Plasma and Urine PK Parameters

The following plasma PK parameters will be determined:

Symbol/Term	Definition
Plasma/Blood/Serum	
AUC_{24}	Area under the plasma concentration-time curve from the time 0 to time 24 hours.
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval.
AUC_t	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty}=AUC_t+C_{last}/\lambda_z$
R	Accumulation ratio (index) calculated as AUCτ at steady state/AUC∞ after a single dose.
$R_{ac(AUC)}$	Accumulation ratio (based on AUC), calculated as AUC_{τ} at steady state/AUC_{τ} after a single dose.
C_{max}	Maximum observed plasma concentration.
$C_{max,ss}$	Maximum observed steady-state plasma concentration during a dosing interval.
CL/F	Apparent clearance after extravascular administration, calculated as =Dose/AUC_{∞} after a single dose and as Dose/AUC_{τ} after multiple dosing (at steady state).
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal disposition phase half-life, calculated as $\ln(2)/\lambda_z$.
t_{lag}	Lag time.
t_{max}	Time of first occurrence of C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.

The following urine PK parameters of TAK-020 will be determined:

Urine	
Ae_{t1-t2}	Amount of drug excreted in urine from time 1 to time 2, calculated as $C_{ur}\times V_{ur}$, where C_{ur} is the concentration of drug excreted in urine and V_{ur} is the volume of urine excreted.
Ae_t	Total amount of drug excreted in urine from time 0 to time t.
Ae_{τ}	Amount of drug excreted in urine during a dosing interval (τ) at steady state.
f_e	Fraction of drug excreted in urine, calculated as $(Ae_t/dose)\times 100$. Molecular weight adjustment needed for metabolites.
CL_R	Renal clearance, calculated as Ae_{0-24}/AUC_{24}.

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

PK parameters of TAK-020 will be summarized by treatment using descriptive statistics. In addition, geometric mean and coefficient of variation will be computed for C_{max} and AUCs. PK

parameters will be summarized separately for the SRD and MRD portions of the study. Individual PK parameters will be listed.

Dose proportionality will be tested for C_{max} and AUCs of both SRD and MRD using a power model. The power fit will be assumed as described by the following equation:

$$\ln(PK\ Parameter) = \beta_0 + \beta_1 \ln(Dose) + \varepsilon$$

where β_0 is the intercept, β_1 is the slope and ε is the random error. The 90% CI for β_1 will be presented and dose proportionality would be declared when this CI 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 lowest dose in the study. This criterion implies that the 90% CI for the ratio of the central values of the PK parameter of interest from the highest dose to the lowest dose is contained completely within the bioequivalence range of (0.80, 1.25) [2].

For SRD, the effect of dose on Tmax and λz will be evaluated using analysis of variance (ANOVA) with treatment as a fixed effect. Means and standard deviations will be presented for all treatments along with a p-value of overall treatment effect. A similar analysis will be completed for Tmax within the MRD portion of the study. This analysis will be done separately for Day 1 and Day 9.

ANOVA will be used to assess time dependency for Part 2 (MRD). The natural log-transformed AUCs and Cmax will be used as response variable and dose level, Day and the interaction of dose level and Day will be fixed factors. Within the frame work of ANOVA, 90% CIs for the ratio of AUCs and Cmax central values between Day 9 and Day 1 will be presented.

7.9.2 Pharmacodynamic Analysis

Sampling times for collection of CCI [redacted] samples are listed in Table 7.d.

Table 7.d Pharmacodynamic Sample Collection

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety analyses include evaluations of AEs, clinical laboratory results, vital signs results and 12-lead ECG results. All summaries of safety data are based on subjects included in the Safety Analysis Set. The safety data will be summarized by placebo, each TAK-020 dose level and TAK-020 overall, where appropriate, for the SRD and MRD portions of the study. Placebo data will be pooled across the cohorts in each part.

7.11.1 Adverse Events

A TEAE is defined as any AE, regardless of relationship to study drug, which occurs on or after the first dose of study drug and no more than 30 days after receiving the last dose of study drug (onset date – date of last dose + 1 $\leq$ 30). A TEAE may also be an event or condition reported prior to the date of first dose, which worsens in intensity after administration of study drug. A PTE is defined as any adverse event that occurs or worsens after the subject has signed informed consent and before the first dose of study drug.

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

Summary tables will be generated for AEs. TEAEs and PTEs will be presented by pooled placebo, each TAK-020 dose level and TAK-020 overall. The following summary tables will be generated separately for SRD and MRD:

- Overview 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.
- Non-Serious TEAEs by SOC and PT.
- Relationship of TEAEs to study drug by SOC and PT.
- Drug related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.
- Intensity of drug related TEAEs by SOC and PT.
- PTEs by SOC and PT.
- Serious PTEs by SOC and PT.

If a subject has more than 1 AE that codes to the same level of a MedDRA term, the subject will be counted only once for that level, where applicable, using the most extreme incidence (related or more severe in intensity).

All AEs will be presented in the data listings.

7.11.2 Clinical Laboratory Evaluations

All clinical laboratory evaluations (hematology, chemistry and urinalysis) will be summarized. Renal safety biomarkers will be summarized separately.

Clinical laboratory tests will be summarized using descriptive statistics (N, mean, median, SD, minimum, and maximum) for baseline, post-baseline, and change from baseline values by treatment regimen and study visit for both SRD and MRD using the Safety Analysis Set. Unscheduled laboratory assessments that are collected post first dose of study drug will be excluded from the summary statistics. Only the scheduled safety laboratory results within 7 days of the last dose of study drug will be included in the summary. Note that urinalysis parameters with character results, such as protein and nitrite, will only be listed.

Individual results for hematology and chemistry laboratory tests that meet the Takeda predefined laboratory markedly abnormal value (MAV) criteria in Appendix B will be presented in a data listing. If a subject has a MAV for a particular laboratory parameter at a visit, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 postdose MAV during treatment will be summarized for each laboratory parameter by pooled placebo, each TAK-020 dose level and TAK-020 overall. The mapping of subjects who meet the MAV criteria will also be presented. All postdose observations, including those at unscheduled visits, will be considered to determine if a subject had a MAV during treatment.

Clinical laboratory tests will be summarized using Takeda Standard International System of Units (SI) units. For test results not in SI units, the conversion to SI units will be done in ADaM datasets using the known conversion factors. All laboratory test parameters will be displayed in individual subject data listings using both SI and conventional units (CV).

Clinical laboratory results for all subjects in the safety analysis set will be summarized separately for the SRD and MRD portions of the study.

7.11.3 Vital Signs

Vital signs measurements include systolic and diastolic blood pressure, pulse, body temperature and respiratory rate. Each vital signs measurement will be summarized using descriptive statistics (N, mean, SD, median, minimum and maximum) for baseline, postdose, and change from baseline to postdose values. Summaries will be presented separately for SRD and MRD by pooled placebo and each TAK-020 dose level.

Individual results for vital sign measurements that meet the Takeda predefined vital signs MAV criteria in Appendix C will be presented in a data listing. If a subject has a MAV for a particular vital sign parameter at a visit, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 postdose markedly abnormal vital sign

measurement during treatment will be summarized by pooled placebo, each TAK-020 dose level and TAK-020 overall. The mapping of the subjects who meet the MAV criteria will also be created. All postdose observations, including those at unscheduled visits, will be considered to determine if a subject had a MAV during treatment.

All vital sign measurements will be listed by subject in the data listings and markedly abnormal values will be flagged.

Vital signs results for all subjects in the safety analysis set will be summarized separately for the SRD and MRD portions of the study.

7.11.4 12-Lead ECGs

Triplicate 12-lead ECGs will be collected at the scheduled 12-lead ECG measurement visits and time points. The average of the triplicate values will be used as analysis endpoint in summaries.

ECG measurements include heart rate, RR interval, PR interval, QRS interval, QT interval, QTcF interval (Fredericia's method) and QTcB interval (Bazett's method). Each ECG measurement will be summarized with descriptive statistics (N, mean, SD, median, minimum and maximum) for baseline, postdose, and change from baseline to postdose values. Summaries will be presented separately for SRD and MRD by pooled placebo and each TAK-020 dose level.

Individual results for 12-lead ECG measurements that meet the Takeda predefined 12-lead ECG MAV criteria in Appendix D will be presented in a data listing. If a subject has a MAV for a particular ECG parameter at a visit, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 postdose markedly abnormal ECG measurement during treatment will be summarized by pooled placebo, each TAK-020 dose level and TAK-020 overall. If any ECG result in a set of triplicate ECG measurements meets the MAV criteria, the subject will be counted as having a MAV ECG result. The mapping of the subjects who meet the MAV criteria will be also be created. All postdose observations, including those at unscheduled visits, will be considered to determine if a subject had a MAV during treatment

A shift table showing the number of subjects with status changes from baseline to postdose (normal, abnormal not clinically significant and abnormal clinically significant) according to investigator interpretations will be created.

All ECG measurements will be listed by subject in the data listings and markedly abnormal values will be flagged.

ECG results for all subjects in the safety analysis set will be summarized separately for the SRD and MRD portions of the study.

7.11.5 Other Observations Related to Safety

Cardiac monitoring telemetry will be performed at different scheduled times from approximately 2 hours predose until 12 hours postdose on Day 1 for SRD and both Day 1 and Day 9 for MRD. Ten second triplicate ECG parameters will be summarized using descriptive statistics for

baseline, postdose and change from baseline to postdose using the average of the triplicate values. All cardiac monitoring telemetry results will be listed by subject in the data listings and markedly abnormal values will be flagged.

Liver function test results will be presented in the data listings. No summary tables will be provided.

Physical examination findings will be presented in the data listings. No summary tables will be provided.

Pharmacogenomic sample collection data will be presented in the data listings. No summary tables will be provided.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

1. Protocol: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-020 in Healthy Volunteers, Protocol Amendment 3, 31 October 2016.
2. Brian P. Smith, etc. (2000): Confidence Interval Criteria for Assessment of Dose Proportionality. Pharmaceutical Research; Vol. 17, No. 10: 1278-1283.

Appendix A Schedule of Study Procedures

Part 1 (SRD)

Study Day:	Screening Days -28 to -2	Check-in Day -1	Treatment Day 1	 Day 2	 Day 3	 Day 4	Check-out Day 5	Early Termination (a)	Follow-up Day 14 (±2) (b)
Confinement		X	X	X	X	X	X		
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics and medical history	X	X							
Medication history	X								
Physical examination	X		X(c)	X	X	X	X	X	
Vital signs (d)	X	X	X	X	X	X	X	X	
Weight, height, and BMI (e)	X	X					X	X	
Concurrent medical conditions	X	X							
Concomitant medications (f)	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (g)	X	X		X	X		X	X	
Hepatitis panel	X								
HIV screening	X								
TB screening	X								
Pregnancy test (hCG) (h)	X	X					X	X	
Urine drug/alcohol/cotinine screen	X	X							
CCI [redacted]									
ECG (j)	X	X	X	X	X	X	X	X	
Telemetry (k)			X						
PGx DNA sample collection (l)			X						
PGx RNA sample collection (m)			X	X					
PK blood collection (n)			X	X	X	X	X	X	
PK urine collection (o)			X	X	X	X	X	X	
CCI [redacted]									
CCI [redacted]									
Dispense study medication			X						
PTE assessment (q)	X	X	X						
AE assessment			X	X	X	X	X	X	X

Footnotes are on the next page.

(a) Conduct procedures for subjects discontinued early. The PK sample collection should be collected at the Early Termination Visit, if possible. For example, collect samples if early withdrawal is due to an AE, and/or if several hours elapsed since last blood draw.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.
(c) The physical examination can be conducted within 24 hours prior to study drug administration.
(d) Vital signs (oral temperature, sitting pulse, and blood pressure) will be collected at Screening and Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, 24, 48, 72, 96 hours postdose or Early Termination.
(e) Height will only be collected at Screening.
(f) Record all medications (other than study drug) from Screening and throughout the study.
(g) Clinical laboratory tests (hematology, serum chemistries, and urinalysis) will be collected at Screening, Day -1, Days 2 and 3, and prior to check-out (Day 5) or Early Termination. Laboratory samples will be taken following a minimum 10-hour overnight fast.
(h) Pregnancy test (hCG) will be performed for all female subjects.
CCI [redacted]
(j) Triplicate 12-lead ECGs printed in standard format, will be collected at Screening, Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, 24, 48, 72 and 96 hours postdose or Early Termination.
(k) Telemetry will be performed approximately 2 hours predose until 12 hours postdose on Day 1. Ten (10) sec triplicate ECGs will be extracted at PK time-points for manual reading and precise ECG reading including QT interval measurement.
(l) One blood sample (6 mL) will be collected prior to dosing on Day 1.
(m) Two whole blood samples (2.5 mL per sample) will be collected on Days 1 (predose) and 24 hours postdose.
(n) Blood samples for PK analysis will be collected on Day 1 at predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose.
(o) Urine samples for PK analysis will be collected on Day 1 at predose (-12-0) and 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 hour postdose intervals.
(p) Blood samples for PD analysis will be collected on Day 1 at predose (within 30 minutes prior to dosing) and at 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose.
(q) PTEs will be collected from signing of informed consent up until dosing on Day 1.

Part 2 (MRD)

Study Day:	Screening Days -28 to -2	Check-in Day -1	Treatment Day 1	Washout Day 2	Treatment Day 3-9	Check-out Day 10	Early Termination (a)	Follow-up Visit Day 17 (±2) (b)
Confinement		X	X	X	X	X		
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics and medical history	X	X						
Medication history	X							
Physical examination	X		X (c)	X	X	X	X	
Vital signs (d)	X	X	X	X	X	X	X	X
Weight, height, and BMI (e)	X	X				X	X	
Concurrent medical conditions	X	X						
Concomitant medications (f)	X	X	X	X	X	X	X	X
Clinical laboratory tests (g)	X	X		X	X	X	X	X (s)
Hepatitis panel	X							
HIV screening	X							
TB screening	X							
Pregnancy test (hCG) (h)	X	X				X	X	
Urine drug/alcohol/cotinine screen	X	X						
ECG (i)	X	X	X	X	X	X	X	
Telemetry (j)			X		X			
PGx DNA sample collection (k)			X					
PGx RNA sample collection (l)			X		X			
PK blood collection (m)			X	X	X	X	X	
PK urine collection (n)			X	X	X	X	X	
CCI [redacted] CCI [redacted] CCI [redacted]								
Dispense study medication			X		X			
PTE assessment (r)	X	X	X					
AE assessment			X	X	X	X	X	X

Footnotes are on the next page.

(a) Conduct procedures for subjects discontinued early. The PK sample collection should be collected at the Early Termination Visit, if possible. For example, collect samples if early withdrawal is due to an AE, and/or if several hours elapsed since last blood draw].
(b) All subjects will return to the unit and complete Hematology and Serum Chemistry tests, vital signs, concomitant medications, and AE assessment.
(c) The physical examination can be conducted within 24 hours prior to study drug administration.
(d) Vital signs (oral temperature, sitting pulse, and blood pressure) will be collected at Screening and Check-in (Day -1) and on Day 1 at predose (0 hours) and 1, 4, 12, 24 hours postdose, then twice daily until Study Exit (Day 10) or Early Termination and once during the Follow-up visit.
(e) Height will only be collected at Screening.
(f) Record all medications (other than study drug) from Screening and throughout the study.
(g) Clinical laboratory tests (hematology, serum chemistries, and urinalysis) will be collected at Screening, Day -1, Days 2, 3, 5, 8 and prior to check-out (Day 10) or Early Termination. Laboratory samples will be taken following a minimum 10-hour overnight fast
(h) Pregnancy test (hCG) will be performed for all female subjects.
(i) Triplicate 12-lead ECGs printed in standard format, will be collected at Screening, Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, and 24 hours postdose, Days 3, 5, 9, 10 at predose (0 hours) or Early Termination.
(j) Telemetry will be performed approximately 2 hours predose until 12 hours postdose on Days 1 and 9 only. Ten (10) sec triplicate ECGs will be extracted at PK time-points for manual reading and precise ECG reading including QT interval measurement.
(k) One blood sample (6 mL) will be collected prior to dosing on Day 1.
(l) Two whole blood samples (2.5 mL per sample) will be collected at predose on Days 1, 3 and 9.
(m) Blood samples for PK analysis will be collected at predose on Day 1 (within 30 minutes prior to dosing) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose and at predose on Day 9 (within 30 minutes prior to dosing) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose.
(n) Urine samples for PK analysis will be collected on Day 1 and Day 9 at predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals.
(o) CCI [redacted]
CCI [redacted]
(p) CCI [redacted]
CCI [redacted]
(q) CCI [redacted]
CCI [redacted]
(r) PTEs will be collected from signing of informed consent up until dosing on Day 1
(s) Hematology and Serum Chemistry only.

Appendix B 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 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/μL	>600 x 10^3/μL
	SI	<75 x 10^9/L	>600 x 10^9/L
Fibrinogen	Both	< 0.8 × LLN	> 1.2 × ULN

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
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI		>177 μmol/L
Blood urea nitrogen	Conventional		>30 mg/dL
	SI		>10.7 mmol/L
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
CPK	Both	--	>5x ULN
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Lipase	Both	--	>3x ULN
Triglycerides	Both	--	>2.5x ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix C Criteria for Identification of Markedly Abnormal Vital Signs Parameters

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 D Criteria for Identification of Markedly Abnormal 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤80 milliseconds	≥200 milliseconds
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcB Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	25-May-2017 14:32 UTC
	Statistical Approval	25-May-2017 14:35 UTC
	Pharmacovigilance Approval	25-May-2017 15:04 UTC
	Clinical Pharmacology Approval	25-May-2017 20:02 UTC
	Clinical Approval	28-May-2017 08:45 UTC