Title: A Randomized, Open-Label and Double-Blind, Placebo-Controlled, Single- and Multiple-Dose, Phase 1 Study of the Pharmacokinetics of TAK-491 40 mg and 80 mg in Healthy Chinese Subjects

NCT Number: NCT02541669

SAP Approve Date: 28 April 2017

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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.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-491_112

A Randomized, Open-Label and Double-Blind, Placebo-Controlled, Single- and Multiple-Dose, Phase 1 Study of the Pharmacokinetics of TAK-491 40 mg and 80 mg in Healthy Chinese Subjects

Pharmacokinetic Study of TAK-491 in Healthy Chinese Subjects

PHASE I

Version: Amendment 1

Date: 28 April 2017

PPD

Based on:

Protocol Version: Amendment 04

Protocol Date: 05 August 2016

1.1 Approval Signatures

Study Title: A Randomized, Open-Label and Double-Blind, Placebo-Controlled, Single- and Multiple-Dose, Phase 1 Study of the Pharmacokinetics of TAK-491 40 mg and 80 mg in Healthy Chinese Subjects

Pharmacokinetic Study of TAK-491 in Healthy Chinese Subjects

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

λ_z	terminal disposition phase rate constant
%CV	percent coefficient of variation
AE	adverse event
Ae_t	amount of drug excreted in urine from time 0 to time t
Ae_{t1-t2}	amount of drug excreted in urine from time 1 to time 2
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the 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 0 to time of the last quantifiable concentration
BMI	body mass index
bpm	Beats per minute
BUN	blood urea nitrogen
$C_{av,ss}$	average concentration during a dosing interval, at steady state
CI	confidence interval
CL_R	renal clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration during a dosing interval
CPK	creatine phosphokinase
CRF	case report form
C_{trough}	observed concentration at the end of a dosing interval
ECG	electrocardiogram
FAS	full analysis set
f_{et}	fraction of administered dose of drug excreted in urine from time 0 to time t
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
QOL	quality-of-life
PRO	patient-reported outcome
SAE	serious adverse event

SAP	statistical analysis plan
SDB	standard database
TLGs	tables, listings, and graphs
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

To assess the pharmacokinetics (PK) of TAK-491 40 mg and 80 mg in healthy Chinese subjects after both single and multiple dose administration.

4.2 Secondary Objectives

To evaluate the safety and tolerability of TAK-491 40 mg and 80 mg in healthy Chinese subjects after both single and multiple dose administration.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This is a randomized, open-label and double-blind, placebo-controlled, single- and multiple-dose, phase 1 study to evaluate the PK, and safety of TAK-491 or placebo as a single dose followed by multiple doses in healthy adult Chinese subjects.

Sixteen subjects will be randomized 1:1 to TAK-491 40 mg or 80 mg, eight subjects per each TAK-491 arm, in the open-label part of the study; the 2 regimens will be conducted in parallel as shown in Table 4.a.

Table 4.a Open-Label Study Regimen and Subject Allocation

Regimen	Regimen Description	Number of Subjects
A	TAK-491 40 mg as a single dose followed by multiple doses	8
B	TAK-491 80 mg as a single dose followed by multiple doses	8

Forty-eight subjects will be randomized 1:1:1 to TAK-491 40 mg or 80 mg, or placebo, sixteen subjects per each arm, in the double-blind part of the study; the 3 regimens will be conducted in parallel as shown in Table 4.b. To maintain the study blind, subjects in this part of the study will receive a least 1 placebo tablet; the TAK-491 40 mg and TAK-491 80 mg tablets differ in size; therefore, placebo tablets for each size will be utilized as appropriate.

Table 4.b Double-Blind Study Regimen and Subject Allocation

Regimen	Regimen Description	Number of Subjects
A	TAK-491 40 mg + placebo as a single dose followed by multiple doses	16
B	TAK-491 80 mg + placebo as a single dose followed by multiple doses	16
C	Placebo (2 tablets) as a single dose followed by multiple doses	16

The pre-dosing study period will consist of a Screening Period (Study Days -28 to -2) and Check-in (Study Day -1). On Day 1, a single dose of TAK-491 or placebo will be administered followed by a pharmacokinetic sampling period through 72 hours postdose (Days 1-4). On Days 4 through 10, subjects will be on a daily dosing regimen, followed by a 24-hour pharmacokinetic assessment period prior to Study Exit (Day 11). The total confinement period for a subject who completes the study will be 12 days. All subjects will return to the site for PK sampling on Days 12 to 13 and follow-up serum chemistry tests on Day 14. A Follow-up telephone call will be made by the site at 14 (±2) days following the last dose of study medication (Day 24±2 days) to inquire for any ongoing adverse events or serious adverse events (SAEs), new adverse events or SAEs, and concomitant medications taken since the final dose of study medication or Early Termination Visit.

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

Figure 4.a Schematic of Study Design

Screening	**Check-in**	**Dosing and PK**	**72-hr PK**	**Dosing (a)**	**Dosing and AM Trough Level (b)**	**Dosing and 24-hr PK**	**Study Exit**	**F/U Visit (c)**	**F/U Call**
Days -28 to -2	Day -1	Day 1	Days 2-4	Day 4	Days 5-9	Day 10	Day 11	Day 14	Day 24 (±) 2
	← Confinement →								

PK=pharmacokinetic.
(a) Dosing will occur after the collection of the 72-hr pharmacokinetic sample.
(b) PK Trough samples will be collected on Days 7 to 9.
(c) Serum chemistry testing.

Table 4.c Schedule of Study Procedures

Study Day	Screening	Check-in	Single and Multiple Dose						Study Exit (o)	PK collection	F/U Visit	ET Visit (a)	F/U Phone Call (b)
	Days -28 to -2	Day -1	Day 1	Days 2-3	Day 4	Days 5-6	Days 7-9	Day 10	Day 11	Days 12-13	Day 14		
Informed consent (c)	X												
Inclusion/exclusion criteria	X	X											
Demographics and medical history	X												
Medication history	X												
Physical examination	X	X							X			X	
Vital signs (d)	X	X	X	X	X	X	X	X	X	X		X	
Weight, height and BMI (e)	X	X							X			X	
Concomitant medications (f)	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions (g)	X	X											
Clinical laboratory tests (h)	X	X			X				X		X	X	
Virology testing (i)	X												
Pregnancy test (hCG) (j)	X	X							X			X	
Urine drug and cotinine screens and breath alcohol	X	X											
12-lead ECG	X	X							X			X	
Study drug dosing (k)			X		X	X	X	X					
PK blood collection (l)			X	X	X		X	X	X	X			
PK urine collection (m)		X	X	X	X			X	X				
PTE assessment (n)	X	X	X										
AE assessment			X	X	X	X	X	X	X	X	X	X	X

Footnotes for Table 4.c are on the next page.

Footnotes for Table 4.c
ET=early termination.
(a) Conduct procedures for subjects discontinued early. The PK sample collection should not be collected at the Early Termination Visit if a PK sample is not scheduled. Additional procedures may be performed at the discretion of the investigator to assess safety.
(b) A Follow-up telephone call will be made by the site at 14 (±2) days following the last dose of study medication (Day 24 ± 2) to inquire for any ongoing adverse events or serious adverse events (SAEs), new adverse events or SAEs, and concomitant medications taken since final dose of study medication or Early Termination Visit. Any spontaneously reported AEs will continue to be collected for 30 days after the last dose of study medication or Early Termination.
(c) ICF must be signed before any study specific procedures are performed.
(d) Sitting blood pressure, pulse, respiration rate and oral temperature will be measured on Day -1, and on confinement days, vitals are to be measured pre-dose or upon morning rising. Vitals will be collected prior to the PK blood collection.
(e) Height (for calculation of BMI) will only be measured at Screening. Weight will be measured at Screening, Check-in (Day -1), and Study Exit or Early Termination Visit.
(f) Record all ongoing medications.
(g) Concurrent conditions are medical conditions that are present at Screening (time of informed consent).
(h) Hematology, serum chemistries, and urinalysis tests. Blood and urine samples to be obtained before study drug dosing on Day 4. On Day 14, serum chemistry only; subjects with ALT/AST elevations on Day 11 and/or 14 will be followed-up every 5-7 days until resolution.
(i) HBsAg, anti-HCV, anti-HIV, Anti-HBsAb, HBeAg, anti-HBeAb, anti-HBcAb, EBV VCA IgG, EBV VCA IgM, Anti-CMV IgG, and Anti-CMV IgM. HBsAg, anti-HCV, and anti-HIV test results will be collected for all subjects. The results for Anti-HBsAb, HBeAg, anti-HBeAb, anti-HBcAb, EBV VCA IgG, EBV VCA IgM, Anti-CMV IgG, and Anti-CMV IgM tests performed at Screening will be recorded in the (e)CRF for randomized subjects only.
(j) Women of childbearing potential.
(k) Study drug will be administered on Day 1 and Day 10 with 240 mL of water after a fast of at least 8 hours. On Day 1 and Day 10, subjects will also continue to fast for an additional 4 hours after dosing and subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. For Days 4 to 9, fasting is not required for dosing.
(l) TAK-536 plasma PK: 6 mL blood samples will be collected on Day 1 at Predose (up to 15 minutes prior to dose [0 hour]) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. On Days 7, 8, and 9 at predose (up to 15 minutes prior to dose [0 hour]) and on Day 10 at predose (up to 15 minutes prior to dose [0 hour]) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 hours postdose.
(m) TAK-536 urine PK: urine will be collected starting on Day 1 at Predose (-12 to 0 hour) and at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours postdose and on Day 10 at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours postdose.
(n) PTEs will be collected from the time of the informed consent to immediately prior to dosing on Day 1 of Period 1.
(o) Subjects will be discharged from the clinic after completion of all scheduled procedures and at the investigator's discretion.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

Primary endpoints for TAK-536 (the active moiety derived from TAK-491) of this study are as follows:

- Maximum observed concentration (C_{max}).
- Time of first occurrence of C_{max} (t_{max}).
- Area under the concentration-time curve from time 0 to infinity (AUC_{∞}) (single dose only).
- Area under the concentration-time curve from time 0 to 24 hours (AUC_{24}) (multiple dose only)
- Terminal disposition phase half-life ($t_{1/2z}$) (single dose only).

5.2 Additional Endpoints

Additional endpoints for TAK-536 are as follows:

- Area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}) (single dose only).
- Terminal disposition phase rate constant (λ_z) (single dose only).
- Observed concentration at the end of a dosing interval (C_{trough}) (multiple dose only).
- Minimum observed concentration during a dosing interval (C_{min}) (multiple dose only).
- Average concentration during a dosing interval, at steady state ($C_{av,ss}$) (multiple dose only).
- Amount of drug excreted in urine from time 1 to time 2 ($Aet_{1\text{-}t2}$).
- Renal clearance, (CL_R).
- Fraction of administered dose of drug excreted in urine from time 0 to 72 hr ($f_{e0\text{-}72}$) in single dose and time 0 to 24 hours ($fe_{0\text{-}24}$) for multiple dose. Molecular weight adjustment needed from TAK-491 to TAK-536,

5.3 Safety Endpoints

The safety and tolerability endpoints of TAK-491 40 mg and 80 mg for the study will be determined from the primary safety variables that will include: physical examination findings, vital signs, 12-lead electrocardiogram (ECG) results, laboratory evaluations (hematology, serum chemistry, and urinalysis), and adverse events (AEs).

6.0 DETERMINATION OF SAMPLE SIZE

Total sample size of 64 subjects will be enrolled in this study. Sixteen subjects, 8 per regimen (TAK-491 40 mg and 80 mg), will be randomized to the open-label part of the study. Forty-eight subjects, 16 per regimen (TAK-491 40 mg, 80 mg and placebo), will be randomized to the double-blind part of the study. The sample size is considered sufficient for evaluation of safety, tolerability and PK of each part of the study, and was not based on statistical analysis power considerations.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Summary Statistics and Precision

All tabulations of analysis results will include summaries by following regimens: TAK-491 40 mg (open-label), TAK-491 80 mg (open-label), TAK-491 40 mg (double-blind), TAK-491 80 mg (double-blind) and placebo (double-blind).

No formal statistical test will be performed in this study. Summaries will be based on descriptive analysis.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Exceptions may be made for derived data in the database where decimal precision is beyond necessary.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by regimen. Percentages will be reported to 1 decimal place. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

The data summaries will be accompanied by individual subjects data listings sorted by study part, regimen, and subject number. All data available from raw data will be listed. The actual day relative to the start of study drug will be determined and included in the listing.

Derived analysis datasets will be produced from raw data. This allows for convenient review of the data as well as any necessary supplemental analyses. All data from the raw data will be included in the derived datasets. Derived dataset specifications will be developed to include the names and definitions of derived variables in the derived SAS datasets. All analyses and data listings will be performed using the derived datasets.

Screen failure subjects will be grouped and listed.

7.1.2 Derived Datasets and Variables

Derived datasets will be generated according to GDDB Implementation Guide (G-SPEC-RD-004), version 01 (30 April 2011). Following are definitions of derived variables:

- Body mass index (BMI) will be calculated as weight (kg)/(height (m))^2 and will be presented to 1 decimal place. BMI will be calculated for Screening.

7.1.3 Definition of Study Days and Baseline

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

- If the date of the event is on or after the date of first dose:
  Study Day = date of event – date of first dose +1.
- If the date of the event is prior to the date of first dose:
  Study Day = date of event – date of first dose.

Baseline values are defined as the last observed value before the first dose of study medication (including a screening value and unscheduled assessments if necessary). In the case where the last observed value and the first dose coincide, that value will be considered as baseline value, unless actual time (hour: minute) indicate otherwise. Unless otherwise specified, AEs and medications commencing on the first dose date (i.e. Study Day 1) will be considered as post baseline events, unless actual time (hour : minute) indicate otherwise.

7.1.4 Statistical Software

All statistical analyses will be conducted using SAS® Version 9.2, or higher.

7.2 Analysis Sets

Randomized Set: The randomized set will include all subjects who are randomized.

Safety Set: The safety set will include all randomized subjects who received at least 1 dose of study drug, including subjects who do not complete the study.

Pharmacokinetic Set: The pharmacokinetic set will consist of all subjects who received study drug and have at least 1 measurable plasma concentration for TAK-536. If any subjects are found to have incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis, but will be presented in the subject listings.

7.3 Disposition of Subjects

Study Information, including date first subject signed ICF, date of first and last open-label dose, date of first and last double-blind dose, date of last subjects' last visit/contact for open-label part and double-blind part, Medical Dictionary for Regulatory Activities (MedDRA) Version, World Health Organization (WHO) Drug Dictionary Version, and SAS Version will be presented.

All screened subjects will be presented, number of subjects who signed informed consent, number of subjects who were or not randomized and primary reason for screen failure (pretreatment event/adverse event, significant protocol deviation, lost to follow-up, voluntary withdrawal, study termination, did not meet entrance criteria or other) will be summarized as recorded on the eCRF.

Disposition of all randomized subjects will be tabulated by randomized regimen and study part.

Subjects with significant protocol deviations will be summarized, and categories will be tabulated as entered on the eCRF. Number of subjects within each analysis set will be tabulated.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized and listed by regimen for each part and overall using the Randomized Set. Demographic and baseline characteristics will include age (years) at date of informed consent, gender, race, height (cm), baseline weight (kg), baseline body mass index (BMI) (kg/m^2), smoking classification, and female reproductive status.

Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age, height, weight and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, race, ethnicity, smoking classification and female reproductive status). Individual demographic and baseline characteristics will be listed by study part and regimen.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized for all 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 failure will also be presented in the data listing.

7.5 Medical History and Concurrent Medical Conditions

Medical history (significant conditions or diseases that stopped at or prior to the time of informed consent) and concurrent medical conditions will be listed. Medical history and concurrent medical conditions will be coded as system organ class (SOC) and preferred term (PT) using the MedDRA, Version 19.0, or higher coding system.

All medical history and concurrent medical condition data will be listed by study part, regimen, site number and subject number.

7.6 Medication History and Concomitant Medications

Medication history and concomitant medications will be listed

Medication history information to be obtained 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 medication other than study drug taken at any time between time of informed consent through the end of the study (including the follow-up visit).

Medication history and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version 01March2014, Enhanced, or higher) coding system.

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

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects. Summaries of PK data will be provided by regimen. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Concentrations

Serial blood samples for determination of TAK-536 will be collected according to Table 7.a.

Table 7.a Collection of Blood Samples for TAK-536 Pharmacokinetic Analysis

Matrix	Dosing Day(s)	Scheduled Time
Plasma	1	Predose (up to 15 minutes prior to dose [0 hour]) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose
Plasma	7, 8, 9	Predose (up to 15 minutes prior to dose [0 hour])
Plasma	10	Predose (up to 15 minutes prior to dose [0 hour]) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose

Serial urine samples for determination of TAK-536 will be collected according to Table 7.b.

Table 7.b Collection of Urine Samples for TAK-536 Pharmacokinetic Analysis

Matrix	Dosing Day	Scheduled Time
Urine	1	Predose (-12 to 0 hour) and at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours postdose
Urine	10	0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose

All pharmacokinetic analyses will be based on Pharmacokinetic Set.

Concentrations of TAK-536 in plasma and the amount of TAK-536 excreted in urine will be summarized by regimen over each scheduled sampling time using descriptive statistics (N, mean, SD, SE, median, minimum and maximum) for the open-label and double-blind parts separately. Individual plasma and urine concentrations data will be listed.

7.9.2 Pharmacokinetic Parameters

Plasma and urine PK parameters of TAK-536 are listed in Table 7.c.

Table 7.c Pharmacokinetic Parameters

Symbol/Term	Definition
Plasma	
AUC_{24} (h* ng /mL)	Area under the concentration-time curve from time 0 to 24 hours (multiple dose only).
AUC_{last} (h*ng/mL)	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (single dose only).
AUC_{∞} (h*ng/mL)	Area under the concentration-time curve from time 0 to infinity (single dose only), calculated using the observed value of the last quantifiable concentration.
$C_{av,ss}$ (ng/mL)	Average concentration during a dosing interval at steady state (multiple dose only).
C_{max} (ng/mL)	Maximum observed concentration.
C_{min} (ng/mL)	Minimum observed concentration during a dosing interval (multiple dose only).
C_{trough} (ng/mL)	Observed concentration at the end of a dosing interval (multiple dose only).
λ_z (1/h)	Terminal disposition phase rate constant (single dose only).
$t_{1/2z}$ (h)	Terminal disposition phase half-life (single dose only).
t_{max} (h)	Time of first occurrence of C_{max}.
Urine	
Ae_{t1-t2} (mg)	Amount of drug excreted in urine from time 1 to time 2.
Ae_t (mg)	Amount of drug excreted in urine from time 0 to time t.
f_{et} (%)	Fraction of administered dose of drug excreted in urine from time 0 to time t. Molecular weight adjustment needed for metabolites
CL_R (L/h)	Renal clearance.

Plasma and urine PK parameters of TAK-536 will be summarized by regimen using descriptive statistics (N, mean, SD, SE, %CV, median, minimum and maximum) for each part separately. Geometric means (GM) and %GM CV will also be computed for AUCs, C_{max} and C_{min}. All individual PK parameters data will be listed.

Additional plasma PK parameters and/or analyses may be added in the presentation as considered appropriate.

7.9.3 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety summaries will be based on the Safety Set. All safety assessments, including AEs, clinical laboratory evaluations, 12-lead ECG results, physical examination, and vital signs will be summarized with descriptive statistics by regimen for each part separately and overall, where appropriate, and presented in the data listings.

7.11.1 Adverse Events

Pretreatment events (PTEs) and AEs will be coded using MedDRA Version 19.0 or higher.

A 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 medication; 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 pharmaceutical product, including placebo; it does not necessarily have to have a causal relationship with this regimen.

Treatment-emergent adverse events (TEAE) are defined as any AEs, regardless of relationship to study drug, which occurred or worsened in severity on or after the first dose of study medication and until 30 days after the last dose of study medication is received.

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. Thus, if a subject has two distinct AEs, each of which corresponds to a distinct PT but both of which correspond to the same SOC, then that subject will be counted once at that SOC subject-count summary level and once at each of the two PTs subject-count summary levels. For the intensity summaries, if a subject reports multiple TEAE coded to the same SOC or PT, the TEAE with maximum intensity will be included in the summary. For the relationship summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE most related to study drug will be included in the summary.

Adverse events will be summarized by study part, regimen and TAK-491 overall for double blind part, which will include the number and percentage of subjects as follows:

- Overview of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Subject Mappings for Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by Preferred Term
- Non-Serious Treatment-Emergent Adverse Events by and Preferred Term
- Relationship of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Pretreatment Adverse Events (PTE) by System Organ Class and Preferred Term
- Pretreatment Serious Events by System Organ Class and Preferred Term

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be evaluated by central laboratory and presented using the International System of Units (SI) units unless otherwise stated. Table 4.c shows the scheduled measurements for clinical laboratory tests and Table 7.d shows a list of all clinical laboratory tests.

Table 7.d Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells White blood cells with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes) Hemoglobin Hematocrit Platelets	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase γ-Glutamyl transferase Potassium Sodium Glucose Chloride Triglycerides HDL-C LDL-C Total cholesterol	pH Specific gravity Protein Glucose Blood Ketones Microscopic Analysis (a): RBC/high power field WBC/high power field Epithelial cells, casts etc.
Diagnostic Screening:		
Serum	**Urine**	**Breath**
HBsAg, anti-HCV, anti-HIV (b) Additional Virology Tests: Anti-HBsAb, HBeAg, anti-HBeAb, anti-HBcAb, EBV VCA IgG, EBV VCA IgM, Anti-CMV IgG, and Anti-CMV IgM (c) **Female Subjects only:** Serum hCG at Screening, Check-in, and Study Exit or Early Termination	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine	Breath alcohol test

EBV= Epstein-Barr virus viral capsid antigen, hCG=human chorionic gonadotropin, RBC=red blood cell, WBC=white blood cell.
(a) Microscopic analysis should be performed only if urine evaluations are abnormal.
(b) HBsAg, anti-HCV, and anti-HIV test results will be collected for all subjects.
(c) The results for the additional virology tests performed at Screening will be recorded in the (e)CRF for randomized subjects only.

The following summaries will be provided for laboratory data by part and regimen:

- Baseline, postdose, and, change from baseline to postdose values for quantitative measurements.
- Number and percent of urine parameters results for categorical measurements.
- Number and percent of subjects with markedly abnormal value (MAV) which identified by the criteria in Appendix A.
- Shift from baseline of high/low/normal values according to normal range criteria (baseline versus each post-baseline visit).

If a subject has multiple values within a particular visit window, the most abnormal result will be used for summary.

All clinical laboratory results data will be presented by subject in listing.

7.11.3 Vital Signs

Vital signs' (including pulse rate, weight, SBP, DBP, body temperature and respiratory rate) collection schedule is presented in Table 4.c, and baseline, postdose, and changes from baseline to each post-dose values will be summarized using descriptive statistics by visit and regimen for each part.

Number and percentage of subjects with markedly abnormal value (MAV) will also be tabulated based on the criteria listed in Appendix B.

All vital signs data will be presented in the listings.

7.11.4 12-Lead ECGs

ECG data collection schedule is presented in Table 4.c. and will be summarized with descriptive statistics by regimen for baseline, postdose and change from baseline to postdose value for each part.

Overall ECG interpretation category (within normal limits, not clinically significant abnormal, clinically significant abnormal) is collected by eCRF according to the scheduled measurements. Shifts in ECG interpretation will be presented as cross-tabulations of numbers of subjects with normal, not clinically significant abnormal, and clinically significant abnormal ECG interpretation results and will include categories for missing and totals.

ECG parameters with markedly abnormal value (MAV) will be tabulated based on the value categories listed in Appendix C.

Summary of Subjects with QTcF in various pre-defined categories will also be tabulated. Categories are listed in Appendix C.

ECG data will be presented in the subject data listings.

7.11.5 Other Observations Related to Safety

All physical examination findings will be listed by study part, and regimen. Data on study drug overdose and interruption will be listed.

Data related to liver function test will be listed, including signs and symptoms, event history, test results and reports, and additional comments.

7.12 Interim Analysis

No formal interim analysis is planned for the study. However, Takeda will designate an external hepatologist as an independent assessor of any liver enzyme elevation in the study. Takeda will also designate a Pharmacovigilance physician who is not involved in the study conduct as a

sponsor liaison to participate and facilitate the safety communication between the external expert, the study site and Takeda.

7.13 Changes in the Statistical Analysis Plan

PK data will not be summarized for combining open-label and double blind parts of the study.

8.0 REFERENCES

1. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.
2. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.
3. A Randomized, Open-Label and Double-Blind, Placebo-Controlled, Single- and Multiple-Dose, Phase 1 Study of the Pharmacokinetics of TAK-491 40 mg and 80 mg in Healthy Chinese Subjects, Pharmacokinetic Study of TAK-491 in Healthy Chinese Subjects, Takeda Development Center Asia, Pte. Ltd., Protocol No. TAK-491_112, Amendment Number 4, 05 August 2016.
4. Guidance for Defining Markedly Abnormal Values Used in Statistical Analyses, Takeda Development Center Asia, Pte. Ltd.m C-GUID-PV-001, Version 1.2, 02-Jun-2016.
5. Guidelines for Statistical Reporting, Takeda Development Center Asia, Pte. Ltd., C-GUID-DO-812, Version 1.0, 02-Apr-2014.
6. Guideline for Data Handling Rules for Analysis, Takeda Development Center Asia, Pte. Ltd., Version 1.0, 20-Sep-2011.

APPENDIX

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	SI	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	SI	< 0.8 × LLN	> 1.2 × ULN
RBC count	SI	< 0.8 × LLN	> 1.2 × ULN
WBC count	SI	<0.5 x LLN	>1.5 x ULN
Platelet count	SI	<75 x 10^9/L	>600 x 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
ALT	SI	--	>3x ULN
AST	SI	--	>3x ULN
GGT	SI	--	>3x ULN
Alkaline phosphatase	SI	--	>3x ULN
Total bilirubin	SI	--	>34.2 μmol/L
Albumin	SI	<25 g/L	--
Total protein	SI	<0.8x LLN	>1.2x ULN
Creatinine	SI	--	>177 μmol/L
Blood urea nitrogen	SI	--	>10.7 mmol/L
Sodium	SI	<130 mmol/L	>150 mmol/L
Potassium	SI	<3.0 mmol/L	>6.0 mmol/L
Creatine Kinase	SI	--	>5x ULN
Glucose	SI	< 2.8 mmol/L	>19.4 mmol/L
Chloride	SI	<75 mmol/L	>126 mmol/L
Triglycerides	SI	--	>2.5x ULN
HDL-C	SI	--	--
LDL-C	SI	--	--
Total cholesterol	SI	--	>7.72 mmol/L

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

Urinalysis—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Blood	SI	--	≥1+
Glucose	SI	--	≥1+
Ketones	SI	--	≥2+
Casts	SI	--	>1/1pf
Microscopic RBCs*	SI	--	≥5/hpf
Microscopic WBC	SI	--	≥20/hpf
pH	SI	≤4	≥8
Protein	SI	--	≥1+
Specific Gravity	SI	--	--
Epithelial Cells	SI	--	--

Hpf=high power field.
*Markedly abnormal if repeated values both meet the criteria: ie, if two values are greater than or equal to 5/hpf within 30 days of one another.

Appendix B Criteria for Markedly Abnormal Values for 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 Out-of-Range Values for the 12-Lead ECG Parameters

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

QTcF interval in pre-defined various criteria categories:

- Increase from baseline ≥30 msec
- Increase from baseline ≥60 msec
- > 500 msec
- > 500 msec and increase from baseline ≥60 msec

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	01-May-2017 16:28 UTC
	Pharmacovigilance Approval	01-May-2017 18:16 UTC
	Clinical Science Approval	01-May-2017 19:10 UTC
	Statistical Approval	01-May-2017 20:14 UTC
	Clinical Pharmacology Approval	02-May-2017 01:15 UTC