Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Escalating Single and Multiple Doses of TAK-653 in Healthy Subjects

NCT Number: NCT02561156

SAP Approve Date: 22 August 2017

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TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-653-1001

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Escalating Single and Multiple Doses of TAK-653 in Healthy Subjects

PHASE 1 TAK-653 ESCALATING SINGLE AND MULTIPLE DOSE STUDY IN HEALTHY SUBJECTS

Version**:** Final

Date: 22 August 2017

Prepared by:

PPD

Prepared by:

PPD

1.1 APPROVAL SIGNATURES

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

2.0 TABLE OF CONTENTS

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

λ_z	terminal disposition phase rate constant
τ	dosing interval
%CV	percent coefficient of variation
Ae_t	amount of drug excreted in urine from time 0 to time t
Ae_τ	amount of drug excreted in urine during a dosing interval
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	AUC from the time 0 to time 24 hours postdose
AUC_{last}	AUC from time 0 to time of the last quantifiable concentration
AUC_∞	AUC from time 0 to infinity
AUC_τ	AUC during a dosing interval
AUEC	area under the effect-time curve
CCI	[redacted]
BMI	body mass index
$C_{av,ss}$	average plasma concentration during a dosing interval, at steady state
CL/F	apparent clearance after extravascular administration
CL_R	renal clearance
CPAP	Clinical Pharmacology Analysis Plan
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration during a dosing interval, at steady state
CSF	cerebrospinal fluid
ECG	electrocardiogram
EEG	Electroencephalogram
E_{max}	maximum observed effect
fe	fraction of administered dose of drug excreted in urine from time 0 to time t
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MR(AUC)	ratio of AUC values of the metabolite compared to parent
MR(C_{max})	ratio of C_{max} values of the metabolite compared to parent
MRD	multiple-rising dose
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
PTE	pretreatment event
qEEG	quantitative electroencephalogram
$R_{ac(AUC)}$	accumulation ratio based on AUC_τ
$R_{ac}(C_{max})$	accumulation ratio based on C_{max}
SAE	serious adverse event

SOC	system organ class
SRD	single-rising dose
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objective

To determine the safety and tolerability of TAK-653 when administered as oral, single and multiple doses at escalating dose levels in healthy subjects.

4.2 Secondary Objective

To determine the pharmacokinetics (PK) of TAK-653 when administered as single and multiple oral doses at escalating dose levels in healthy subjects.

4.3 Exploratory/ Additional Objectives

CCI

[redacted]

4.4 Study Design

This first-in-human, double-blind, placebo-controlled, combined single-rising dose (SRD)/multiple-rising dose (MRD) phase 1 study in healthy subjects is designed to assess the safety, tolerability, and PK of TAK-653. Approximately 112 healthy male and female volunteers will be enrolled.

This study consists of 2 parts: (1) single ascending doses in 5 cohorts (SRD) and (2) single and multiple ascending doses in 4 cohorts (SRD/MRD). Each cohort will consist of 8 subjects (6 active:2 placebo). Subjects will fast for at least 10 hours before dosing. Cohorts may be added or removed. The decision to dose will be based on emerging safety, PK, and PD data.

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[redacted]

Follow-up assessments will occur approximately 14 days after the last dose of study drug to inquire about any ongoing adverse events (AEs) or serious adverse events (SAEs), worsening of AEs or SAEs, or development of new AEs or SAEs, and concomitant medications taken since

final dose. Follow-up will occur by telephone unless abnormal, clinically significant findings are observed upon discharge or at the investigator's discretion. Subjects should then be brought back to the clinic for re-evaluation.

CCI [redacted]

End of trial (study completion date) will be based on the final data collection date for the entire study which is the Follow-up call/visit.

Part 1: SRD

Subjects will be enrolled in SRD Cohorts. Sentinel dosing will be used for each SRD Cohort. The first 2 subjects (1 active: 1 placebo) in each Cohort will receive either TAK-653 or placebo in parallel, followed by a minimum 24-hour gap to ensure adequate evaluation of safety and tolerability prior to administering the same dose of TAK-653 or placebo to the remaining subjects within the Cohort (5 active: 1 placebo). Dosing of the remaining subjects will proceed in a staggered fashion with no more than 3 subjects being dosed at a time and having an approximate 24-hour gap before the next group of subjects is dosed. Each dose cohort will be examined sequentially to ensure adequate evaluation of all available safety, tolerability, PK, and PD data prior to administering the next dose level.

Part 1: SRD Study Schematic

Pretreatment Period		**Treatment Period**				**Follow up (d)**
Screening	Check-in Assessments (a)	TAK-653 Dosing Study Assessments (a) (b) (c)	Safety and PK Assessments (a) (c)	PK Assessments	PK Assessments/ Study Exit (a)	
Day -28 to -2	Day -1	Day 1	Days 2-5	Day 6 (Cohorts 1-5) Days 6-7 (Cohort 6 onward)	Day 7 (Cohorts 1-5) Day 8 (Cohort 6 onward)	Day 14 (±2)
	← Confinement →					

(a) EEG assessments are scheduled on Days -1, 1, 2, and 5, at Study Exit, and at ET.
(b) Study assessments include PK sample collection throughout.
(c) CCI [redacted]
(d) Follow-up will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In this case or at investigator's discretion, subjects should return to the clinic for re-evaluation.

The planned first dose level to be studied is 0.3 mg for SRD Cohort 1. The actual choice of the dose levels in subsequent Cohorts will occur after the full review of all available blinded safety, tolerability, PK, and PD data in the preceding cohorts. If necessary, the sponsor team (Takeda only) may unblind the data and perform additional analyses for an informed dose-escalation

decision. The next dose level may be higher, lower, or remain the same as the preceding dose level. If the dose is not increased in the next Cohort, staggered dosing is not necessary.

Part 1: Summary of SRD Dose Cohorts

Cohort (a)	TAK-653 Single Dose (b) (c)		No. of Subjects
	Planned	Actual	
1	0.3 mg	0.3 mg	6 TAK-653 2 placebo
2	X mg	1.0 mg	6 TAK-653 2 placebo
3 (food-effect cohort) (d)	X mg	3.0 mg	6 TAK-653 2 placebo
4	X mg	5.0 mg	6 TAK-653 2 placebo
5	X mg	9.0 mg	6 TAK-653 2 placebo
6	X mg	18.0 mg	6 TAK-6536 2 placebo

(a) Sentinel dosing will occur at the start of each Cohort in the SRD. After the investigator and sponsor review the 24-hour safety and tolerability data, the remaining subjects can be dosed in a staggered fashion (no more than 3 subjects at a time). A 24-hour gap will follow each subsequent administration to evaluate safety and tolerability data.
(b) Dose escalation to Cohort 2 onward will be based on review of safety, tolerability, and available PK and PD data from the previous cohort(s).
(c) TAK-653 or placebo will be administered orally to subjects after an overnight fast of approximately 10 hours.
(d) Subjects from SRD Cohort 3 (fasted conditions) will return to receive the same dose of TAK-653 following a standard meal.

Subjects in the SRD Cohorts will be kept in the study unit for approximately 96 hours after dosing for safety and PK assessments before discharge. The total confinement period is 5 days. Subjects in Cohorts 1 to 5 will return to the clinic on Days 6 and 7 for additional PK collections. Subjects in Cohort 6 onward will return to the clinic on Days 6, 7, and 8 for additional PK collections. If the $t_{1/2z}$ of TAK-653 for any cohort differs significantly from what was predicted, the duration of confinement may also be adjusted. Subjects in the food effect cohort will be confined twice for 5 days each for a total of 10 days. For SRD Cohort 6 onward, CCI [redacted] ollow-up assessments for all subjects in the SRD study arm will occur on Day 14 (±2).

Part 2: SRD/MRD

Progression into the SRD/MRD Part 2 will occur only after review of all available safety, tolerability, PK, and PD data collected in at least the first 3 SRD cohorts. The actual dose in the SRD/MRD Cohorts will not be administered unless there is acceptable safety, tolerability, PK, and PD data at the same or higher dose level after a single dose in the SRD Cohorts. If necessary, the sponsor team (Takeda only) may unblind the data and perform additional analyses for an informed dose-escalation decision. The potential for accumulation, and its

impact on the likelihood of reaching the no-observed-adverse-effect level exposure cap, will be taken into account when selecting doses for the MRD.

A single dose of TAK-653 or placebo will be administered on Day 1 followed by approximately 120 hours for safety, tolerability, PK, and PD assessments. Once daily (QD) multiple dosing will begin on Day 6 and continue through Day 18 (13 days). Initiation of the multiple-dose phase on Day 6 may be adjusted based on emerging safety, PK, and/or PD data. Neither sentinels nor staggered dosing are used in the SRD/MRD. Subjects in the SRD/MRD Cohorts will be kept in the study unit for at least 72 hours after the last dose for safety assessments before discharge. The total confinement period planned is 21 days. Cohort 4 as well as any additional cohorts are optional (Note: at the time of this SAP, Cohort 4 has been initiated), to be used if emerging safety and/or PK or PD data warrant further study at a different dose. Follow-up assessments will occur on Day 31 (±2).

Each dose cohort will be examined sequentially to ensure adequate evaluation of all available safety, tolerability, PK, and PD data prior to administering the next dose level

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[redacted]

Part 2: SRD/MRD Study Schematic

Pretreatment Period		**Treatment Period**					**Follow-up (e)**
Screening	Check-in Baseline Assessments	TAK-653 Single Dose Study Assessments (a) (b) (d)	Safety and PK Assessments (d)	TAK-653 QD dosing Study Assessments (a) (b) (c) (d)	Safety and PK Assessments	Study Exit	
Day -28 to -2	Day -1	Day 1	Days 2-5	Days 6-18	Days 19-20	Day 21	Day 31 (±2)
	◄---------- Confinement ----------►						

(a) Study assessments include PK sample collection throughout.
(b) EEG assessments are scheduled on Days 1, 11, 18, and ET.
(c) CCI [redacted]
(d) CCI [redacted]
(e) The Follow-up assessments will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In this case or per investigator's discretion, subjects should return to the clinic for re-evaluation.

Part 2: Summary of SRD/MRD Dose Cohorts

	Planned TAK-653 Dose (a) (b) (c)		
Cohort	**Planned**	**Actual**	**Subjects**
1	X mg	0.3 mg	6 TAK-653
			2 placebo
2	X mg	1.0 mg	6 TAK-653
			2 placebo
3	X mg	3.0 mg	6 TAK-653
			2 placebo
4	X mg	6.0 mg	6 TAK-653
			2 placebo
5	X mg	9.0 mg	6 TAK-653
			2 placebo

(a) Dosing for the first SRD/MRD Cohort will not begin until there is acceptable safety, tolerability, and available PK and PD data at the same or higher dose level after a single dose from at least the first 3 SRD Cohorts. Dose escalation to subsequent Cohorts will be based on review of safety, tolerability, and available PK and PD data from previous Cohorts. The subsequent dose level may be higher, lower, or the same as the preceding dose level.
(b) In each Cohort, a single dose will be administered on Day 1 followed by 120 hours of safety, tolerability, PK, and PD assessments. QD multiple doses will proceed from Day 6 through Day 18.
(c) TAK-653 or placebo tablets will be administered orally to subjects after an overnight fast of at least 10 hours.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints will be the following safety variables:

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who discontinue due to an AE.
- Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once post-dose.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post-dose.
- Percentage of subjects who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once post-dose.
- Percentage of subjects who experience clinically significant abnormal changes in EEG measurements at least once post-dose.
- Columbia-Suicide Severity Rating Scale (C-SSRS):
  - Treatment-emergent suicidal ideation compared to Baseline, as measured by an increase in suicidal ideation category (1-5 on the C-SSRS) during treatment from the maximum suicidal ideation category at Baseline, or any suicidal ideation during treatment if there was none at Baseline.
  - Treatment-emergent suicidal behavior compared to Baseline, as measured by an increase in suicidal behavior category (6-10 on the C-SSRS) during treatment from the maximum suicidal behavior category at Baseline, or any suicidal behavior during treatment if there was none at Baseline.

5.2 Secondary Endpoints

The secondary endpoints include the following PK parameters of TAK-653:

- C_{max} (Day 1 for all Cohorts and Day 6 for SRD/MRD Cohorts).
- Maximum observed steady-state plasma concentration during a dosing interval ($C_{max,ss}$) (Day 18 for SRD/MRD Cohorts).
- Time to reach C_{max} (t_{max}) (Day 1 for all Cohorts and Day 18 for SRD/MRD Cohorts).
- Area under the plasma concentration-time curve (AUC) from time 0 to time of the last quantifiable concentration (AUC_{last}) (Day 1 for all Cohorts).
- AUC from time 0 to infinity (AUC_{∞}) (Day 1 for all Cohorts).
- AUC during a dosing interval (AUC_{τ}) (Day 6 and Day 18 for SRD/MRD Cohorts).

5.3 Exploratory/ Additional Endpoints

CCI

[redacted]

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6.0 DETERMINATION OF SAMPLE SIZE

The sample size chosen of 8 subjects in each Cohort (6 active: 2 placebo) is considered to be sufficient for evaluation of safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All study-related raw and derived data will be presented in data listings as appropriate. Continuous data will be summarized using number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, 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 for each category where appropriate.

All statistical tests will be 2-tailed at α=0.05 level for significance unless otherwise stated. The p-values less than or equal to α (when rounded to 3 digits) are reported as "significant". The phrase "no significant difference" indicates that all p-values for the tests are greater than α. All computations will be performed prior to rounding.

Subjects who take placebo in each cohort group will be pooled together in all safety summaries for each part (Part 1 and Part 2) and will be analyzed as one placebo group.

7.1.1 Missing Data

There will be no imputation of incomplete or missing data. Decisions regarding inclusion or exclusion of data from an analysis for subjects who are noncompliant with the dose schedule, or who have incomplete data, will be made on a case-by-case basis, but the data will be presented in data listings regardless.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for summarizing concentration values and deriving PK parameters. These values will be flagged in the data listings, and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

7.1.2 Derived Datasets and Variables

Derived datasets will be generated according to CDISC guidance documents: Analysis Data Model (ADaM) Implementation Guide, Version 1.0 (17 Dec 2009); ADaM Data Structure for Adverse Event Analysis, Version 1.0 (10 May 2012).

7.1.3 Definition of Study Days and Baseline

For all safety endpoints, Baseline is defined as the last non-missing measurement prior to first dose of study drug for Part 1 SRD Cohorts and Part 2 SRD/MRD Cohorts. Baseline is defined as the last non-missing measurement prior to the first dose of study drug in each period (fed and fasted) for Part 1 Food Effect Cohort. Study day will be calculated relative to the date of the first dose in the study. Study day prior to the first dose of treatment will be calculated as: date of assessment/event – date of treatment; study day on or after the date of first dose of treatment will be calculated as: date of assessment/event – date of treatment + 1.

7.2 Analysis Sets

Safety Set	The safety set will consist of all subjects who are enrolled and received 1 dose of study drug. Subjects in this analysis set will be used for demographic, other baseline characteristic, and safety summaries.
Randomized Set	The randomized set will consist of all subjects who are enrolled and randomized.
PK Set	The PK 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.
PD Set	The PD set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

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

7.3 Disposition of Subjects

Number of subjects randomized by site will be summarized separately by pooled placebo, each TAK-653 dose level, pooled TAK-653, and overall total for each part.

The number and percentage of subjects, who are randomized but not treated, complete study drug, prematurely discontinue study drug and study visits will be summarized by pooled placebo, each TAK-653 dose level, pooled TAK-653, and overall total for each part for subjects in the Randomized Set. In addition, the number and percentage of subjects will be summarized for each reason of discontinuation of study drug and study visits by pooled placebo, each TAK-653 dose level, pooled TAK-653, and overall total for each part. Subjects' study completion data, including reasons for premature termination, will be listed by dose level for all subjects.

The number and percentage of subjects who comprised each analysis set will be summarized by pooled placebo, each TAK-653 dose level, pooled TAK-653, and overall total for each part.

7.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics (caffeine consumption, smoking status, and female reproductive status) will be summarized by pooled placebo, each TAK-653 dose level, pooled TAK-653, and overall total for each part, and by overall total for combined Part 1 and Part 2. 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, and ethnicity).

For each part, demographic variables of screen failure subjects and reasons for screen failure 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 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 plasma concentration and exposure data will be provided by TAK-653 dose level as well as listed in data listings. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.6 Efficacy Analysis

Not applicable.

7.7 Pharmacokinetic/Pharmacodynamic Analysis

7.7.1 Plasma Pharmacokinetic Concentrations

Collection of Blood Samples for PK Analysis (All SRD Cohorts)

Sample Type	Dosing Day	Scheduled Time (hours)
Plasma	1	Predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours postdose. Additional collection at 168 hours postdose for Cohort 6 onward.

Collection of Blood Samples for PK Analysis (All SRD/MRD Cohorts)

Sample Type	Dosing Day	Scheduled Time (hours)
Plasma	1	Predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 (a) hours postdose.
Plasma	6	0.5, 1, 2, 4, 6, 8, 12, 16, and 24 (b) hours postdose.
Plasma	12, 14, 16	Predose (within 15 minutes prior to dosing) (and following CCI collection procedure on Day 12 (SRD/MRD Cohort 3 only).
Plasma	18	Predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose.

(a) The 120-hour sample must be collected before dosing on Day 6.
(b) The 24-hour sample must be collected before dosing on Day 7.

For each part, the concentration of TAK-653, CCI [redacted] in plasma will be summarized by TAK-653 dose level, Day, and period (fasted vs fed) over each scheduled sampling time using descriptive statistics (N, arithmetic mean, SD, median, minimum, and maximum). Individual plasma concentration data versus time will be presented in a data listing.

Blood samples for placebo will not be analyzed by the bioanalytical laboratory except for 2 samples per subject receiving placebo, 1 predose and the other around the expected time at which C_{max} occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional subjects were on active treatment. These data will be listed but not summarized.

For each part, individual concentrations of TAK-653, CCI [redacted] in plasma will be plotted by actual time on linear and semilogarithmic scales. Plots of mean TAK-653, CCI [redacted] plasma concentrations versus nominal time will also be provided on linear and semilogarithmic scales.

7.7.2 Plasma Pharmacokinetic Parameters

The PK parameters of plasma TAK-653 and its metabolites CCI [redacted] will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated using non-compartmental analysis using Phoenix WinNonLin version 6.4 or higher.

PK Parameters for TAK-653, [redacted]

Symbol/Term	Definition
AUC_{24}	Area under the plasma concentration-time curve from the time 0 to time 24 hours postdose.
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
AUC_{last}	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 using the observed value of the last quantifiable concentration.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
$C_{av,ss}$	Average plasma concentration during a dosing interval, at steady state.
C_{max}	Maximum observed plasma concentration.
$C_{max,ss}$	Maximum observed plasma concentration during a dosing interval, at steady state.
CL/F	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration (TAK-653 only).
λ_z	Terminal disposition phase rate constant.
[redacted]	[redacted]
t_{max}	Time of first occurrence of C_{max}.
[redacted]	[redacted]

(a) [redacted].

Dose-normalized AUC, C_{max}, and $C_{max,ss}$ will also be calculated. Additional information regarding the plasma PK analysis and plasma PK parameter calculation and presentation will be provided in the Clinical Pharmacology Analysis Plan (CPAP). Additional plasma PK parameters may be calculated if necessary, in accordance with the CPAP.

Descriptive statistics (N, arithmetic mean, SD, median, minimum, maximum and %CV) will be used to summarize the plasma PK parameters for TAK653, [redacted] by TAK-653 dose level, Day, and period (fasted vs fed) for each part. In addition, geometric mean

and %CV will be computed for C_{max} and AUCs. Individual plasma PK parameters will be presented in a data listing for each part.

For each part, scatter plots of individual plasma TAK-653 ln-transformed Cmax and AUCs versus ln-transformed dose will be provided (fasted cohorts only).

Additionally, box plots of TAK-653 dose-normalized C_{max} and AUCs versus dose will be provided for each part (fasted cohorts only). Box plots of TAK-653 C_{max} and AUCs comparing fasted versus fed cohorts will also be provided.

Dose proportionality will be tested for SRD cohorts (fasted cohorts only) on Day 1 and for SRD/MRD cohorts after multiple dosing on Day 18 for TAK-653 C_{max} and AUCs 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 and β_1 is the slope. The dose proportionality will be declared when the 90% confidence interval 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 this study. This criterion implies that the 90% CI for the ratio of the central values of 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]. Plots of ln(AUC) or ln(C_{max}) vs ln(Dose) may also be used to illustrate dose proportionality or lack of it.

A power model will be performed to test whether the slope=1 in the power model and whether the point estimate of the slope is significantly different from 0 or not.

The effect of food on the PK of TAK-653 will be evaluated via a paired t-test. The point estimates and 90% CIs for the ratio of C_{max} and AUC central values for TAK-653 tablets administered after fed conditions vs those obtained in the fasted state will be determined. The food effect on t_{max} will also be evaluated using a non-parametric Wilcoxon rank sum test.

7.7.3 CCI [redacted]

All attempts will be made to have a distribution of CCI [redacted] times within the prescribed window of 2 to 6 hours postdose on Day 12 for SRD/MRD Cohort 3; for example, the CCI [redacted] may be collected at 2 hours postdose from the first subject, 3 hours postdose from the

second subject, 4 hours postdose from the third subject, and 6 hours postdose from the fourth subject with a collection window of +1 hour for each subject.

The [redacted], if available, will be presented in a data listing. The ratio of TAK-653 [redacted] on Day 12 to the TAK-653 plasma concentration on Day 12 will also be listed. TAK-653, [redacted] and TAK-653 [redacted] plasma ratios will be summarized using descriptive statistics (N, arithmetic mean, SD, median, minimum, and maximum).

7.7.4 Urine Pharmacokinetic Concentrations

Collection of Urine Samples for PK Analysis (All SRD/MRD Cohorts)

Sample Type	Dosing Day	Time post-dose (hours)
Urine	1	Predose (-12 to 0 hours) and at (0 to 6), (6 to 12), (12 to 24), (24 to 48), and (48 to 72) hour intervals postdose
Urine	18	(0 to 6), (6 to 12), and (12 to 24) hour intervals postdose.

The amount of TAK-653, [redacted] in urine will be summarized by TAK-653 dose level and Day over each scheduled sampling interval using descriptive statistics (N, arithmetic mean, SD, median, minimum, and maximum). Individual urine concentration data versus time interval along with urine volume will be presented in a data listing.

7.7.5 Urine Pharmacokinetic Parameters

The PK parameters of urine TAK-653, [redacted] will be determined from urine concentrations for all evaluable subjects. The following PK parameters will be calculated using SAS version 9.3:

Symbol/Term	Definition
Ae_t	Amount of drug excreted in urine from time 0 to time t.
Ae_τ	Amount of drug excreted in urine during a dosing interval.
$f_{e,t}$	Fraction of administered dose of drug excreted in urine from time 0 to time t. Molecular weight adjustment needed for metabolites (a).
[redacted]	[redacted]

(a) [redacted].

Additional information regarding the urine PK analysis and urine PK parameter calculation and presentation will be provided in the CPAP. Additional urine PK parameters may be calculated if necessary, in accordance with the CPAP.

Descriptive statistics (N, arithmetic mean, SD, median, minimum, maximum and %CV) will be used to summarize the urine PK parameters for TAK-653, [redacted] by TAK-653 dose level and Day. Individual urine PK parameters will be presented in a data listing.

7.7.6 CCI Pharmacodynamic Analysis

Collection of Blood Samples for PD Analysis of CCI

Sample Type	Study Day	Time Points
SRD (Cohort 6 onward) and SRD/MRD (Cohort 3 onward)		
Serum	1	Predose and at 4, 8, and 12 hours postdose
Serum	2-5	24, 48, 72, and 96 hours postdose
SRD/MRD (Cohort 3 onward)		
Serum	18	Predose and at 4, 8, and 12 hours postdose
Serum	19	24 hours postdose

Note: Hemolyzed PD samples will not be redrawn.
Note: A single dose is administered on Day 1. No additional doses are administered until Day 6 when QD dosing begins from Day 6 through 18.

CCI

PD Parameters for CCI

Symbol/Term	Definition
AUEC	Area under the effect-time curve over 96 hours after a single dose and over 24 hours after multiple dosing.
E_{max}	Maximum observed effect.

CCI

CCI

[redacted]

7.7.7 CCI Pharmacodynamic Parameters

All the analyses, including data listings, for this section will be performed independently outside this document.

7.8 Other Outcomes

Not applicable.

7.9 Safety Analysis

For each part, data for all subjects in the safety analyses set will be summarized by pooled placebo and each TAK-653 dose level for clinical laboratory, vital signs, ECG, and C-SSRS results, and by pooled placebo, each TAK-653 dose level, pooled TAK-653, and overall total for other safety variables. These summaries will not contain data from the food effect cohort (SRD Cohort 3); data from this cohort will be summarized separately by placebo fed, placebo fasted, TAK-653 fed, and TAK-653 fasted.

7.9.1 Adverse Events

A TEAE will be defined as an AE or a SAE that occurs or gets worse after receiving the first dose of study drug and within 30 days (onset date – last date of dose + 1 ≤ 30) after the last dose of study drug. A TEAE may also be a pretreatment event (PTE) 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. Adverse events data with onset occurring more than 30 days after last dose of study drug (AE start date – last dose date >30) will be listed, but not included in the summary tables.

AE verbatim reported terms will be coded by system organ class (SOC), high-level term (HLT) and preferred term (PT) using MedDRA.

The following is a list of AE summary tables that will be generated:

- Overview of TEAE.
- TEAEs by SOC and PT at subject and event level.
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Non-Serious TEAEs by 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.

A subject with 2 or more different AEs within the same level of the MedDRA term will be counted only once in that level using the most extreme incident for the intensity tables, and relationship to study drug for the causality tables.

Data listings will be provided for all AEs (including PTEs for enrolled subjects), AEs leading to study drug discontinuation, AEs leading to study visit discontinuation, SAEs, and AEs resulting in death.

7.9.2 Clinical Laboratory Evaluations

Clinical laboratory tests include hematology, serum chemistry and urinalysis.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical laboratory variables in SI units will be summarized for Baseline, postdose, and change from Baseline at each visit. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for hematology and chemistry laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (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 postdose 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 clinical laboratory results within 7 days of the last dose, including scheduled and unscheduled measurements, will be included in the MAV summaries.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

7.9.3 Vital Signs

Vital signs will include body temperature (oral), supine blood pressure (resting more than 5 minutes), respiration rate, and heart rate. Heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of these vital signs will be summarized for Baseline, postdose, and change from Baseline at each visit. Only the vital signs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed vital signs.

All individual vital signs that meet Takeda's predefined MAV criteria (Appendix B) will be listed. The number and percentage of subjects with at least one postdose markedly abnormal vital sign measurement will be summarized. The mapping of the subjects who meet the MAV criteria after dosing will be listed as a table. All postdose vital signs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

7.9.4 12-Lead ECGs

ECG measurements include clinical interpretation, heart rate, and PR, QRS, RR, QT, and QTcF intervals.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of the quantitative ECG will be summarized for Baseline, postdose, and change from Baseline at each visit. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed ECGs.

All individual ECGs that meet Takeda's predefined MAV criteria (Appendix C) will be listed. The number and percentage of subjects with at least one postdose markedly abnormal ECG measurement will be summarized. Subjects who meet the MAV criteria after dosing will be mapped to their respective qualifying ECG result. All postdose MAV ECGs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

For ECG interpretation data, shift tables will be provided for the number and percentage of subjects who change status on the interpretation from Baseline to each scheduled postbaseline measurement.

All ECG data will be presented in data listings.

7.9.5 Safety EEG

For EEG interpretation data, shift tables will be provided for the number and percentage of subjects who change status on the interpretation from Baseline to each scheduled postbaseline measurement.

All safety EEG data will be presented in data listings.

7.9.6 Other Observations Related to Safety

All results for the physical examination, neurological examination, meal time, telemetry, C-SSRS, and pregnancy avoidance counseling will be presented in data listings.

The C-SSRS has 2 domains, Suicidal Ideation, and Suicidal Behavior.

Treatment-emergent suicidal ideation compared with Baseline and treatment-emergent suicidal behavior compared with Baseline will be summarized by category, visit, and TAK-653 dose level.

7.10 Interim Analysis

Not applicable.

7.11 Changes in the Statistical Analysis Plan

The analysis for EEG pharmacodynamic parameters outlined in the Section of 13.1.4 in Protocol TAK-653-1001 [1] will be performed outside this SAP.

8.0 REFERENCES

1. Protocol: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Escalating Single and Multiple Doses of TAK-653 in Healthy Subjects Amendment 6, 24 March 2017.
2. Brian P. Smith, etc. (2000), Confidence Interval Criteria for Assessment of Dose Proportionality, Pharmaceutical Research, Vol. 17, 10:, 1278-1283.
3. Hedges, L. and Olkin, I. (1985) Statistical Methods for Meta-Analysis. New York: Academic Press, Page 86.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 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
Neutrophils (Absolute)	Both	<0.5 x LLN	>1.5 x LLN
Neutrophils (Relative)	Both	<0.5 x LLN	>1.5 x LLN
Lymphocytes (Absolute)	Both	<0.5 x LLN	>1.5 x LLN
Lymphocytes (Relative)	Both	<0.5 x LLN	>1.5 x LLN
Monocytes (Absolute)	Both	--	>2 x ULN
Monocytes (Relative)	Both	--	>2 x ULN
Eosinophils (Absolute)	Both	--	>2 x ULN
Eosinophils (Relative)	Both	--	>2 x ULN
Basophils (Absolute)	Both	--	>3 x ULN
Basophils (Relative)	Both	--	>3 x 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
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Direct bilirubin	Both	--	>2 ULN
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
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Bicarbonate	Conventional	<8.0 mEq/L	
	SI	<8.0 mmol/L	
Creatine kinase	Both	--	>5x ULN

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

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<40	>110
Systolic blood pressure	mm Hg	<85	>160
Diastolic blood pressure	mm Hg	<45	>100
Body temperature	^{o}C	< 35.6	>37.7

Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	< 50	> 120
PR	msec	≤ 110	≥ 220
RR	msec	≤ 600	≥ 1440
QRS	msec	≤ 75	≥ 110
QT Interval	msec	≤ 50	≥ 460
QTcF Interval	msec	≤ 50	>=450 or >=30 change from Baseline or >=60 change from Baseline

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	28-Aug-2017 16:40 UTC
	Statistical Approval	28-Aug-2017 17:04 UTC
	Clinical Pharmacology Approval	28-Aug-2017 17:57 UTC
	Pharmacovigilance Approval	28-Aug-2017 18:42 UTC
	Clinical Science Approval	11-Sep-2017 16:38 UTC