Title: A Randomized, Double-blind, Placebo-Controlled, 3-Period Crossover Study Followed by 1 Open-label Comparator Period to Evaluate Central Pharmacodynamic Activity of TAK-653 in Healthy Volunteers Using Transcranial Magnetic Stimulation

NCT Number: NCT03792672

SAP Approve Date: 29 May 2019

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

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.

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-653-1003

A Randomized, Double-Blind, Placebo-Controlled, Phase 1, 3-Period Crossover Study Followed by 1 Open-label Comparator Period to Evaluate Central Pharmacodynamic Activity of TAK-653 in Healthy Volunteers Using Transcranial Magnetic Stimulation

TAK-653

PHASE 1

Version**:** 1.2

Date: 29 May 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 01
Protocol Date: 04 April 2019

1.1 Approval Signature

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1, 3-Period Crossover Study Followed by 1 Open-label Comparator Period to Evaluate Central Pharmacodynamic Activity of TAK-653 in Healthy Volunteers Using Transcranial Magnetic Stimulation

Takeda Approval:

PPD

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

2.0 TABLE OF CONTENTS

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
bpm	beats per minute
CV%	percent coefficient of variation
AE	adverse event
ANCOVA	Analysis of Covariance
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{t}	area under the plasma concentration-time curve from time 0 to time t
AUC_{t1-t2}	area under the concentration-time curve from time t1 to time t2
$AUEC_{t}$	Area under the effect concentration-time curve from time 0 to time t
BMI	body mass index
BPM	Beats per minute
C_{max}	maximum observed concentration
CHDR	Center for Human Drug Research
CI	Confidence interval
CPAP	Clinical Pharmacology Analysis Plan
CS	clinically significant
C-SSRS	Columbia - Suicide Severity Rating Scale
DIC	drug-in-capsule
E_{max}	maximum observed effect
ECG	electrocardiogram
eCRF	electronic case report form
ERP	event-related potential
ET	early termination
LICI	long intracortical inhibition
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Motor-evoked potential
N	number of subjects
NCS	not clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PO	single oral
PT	preferred term
EEG	electroencephalography
rMT	Resting motor potential
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SICI	short intracortical inhibition

SOC	system organ class
$t_{1/2z}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
CCI	[redacted]
t_{max}	time to first occurrence of C_{max}
Time to E_{max}	time from dosing to occurrence of E_{max}, taken directly from the change from Baseline data
TMS	Transcranial Magnetic Stimulation
CCI	[redacted]

4.0 OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to determine whether TAK-653, in comparison to placebo, increases central nervous system (CNS) excitability, assessed with TMS-evoked MEP in healthy subjects

4.2 Secondary Objectives

The secondary objectives of this study are as follows:

1. To determine whether TAK-653, in comparison to placebo, modulates responses evoked with paired TMS pulses that capture intracortical circuitry modulation.
2. To determine whether ketamine increases CNS excitability assessed with TMS-evoked MEP in healthy subjects.
3. To determine the safety and tolerability of TAK-653 when administered as single dose in healthy subjects assessing responses evoked by TMS.

4.3 Exploratory/Additional Objectives

CCI

[redacted]

4.4 Study Design

This study consists of a randomized, double blind, placebo-controlled 3-treatment-3-period cross-over study followed by an open-label comparator period. Approximately 24 healthy male and female subjects, aged 18 to 55 years, inclusive, will be enrolled. Each of the first three periods is one day in duration, followed by a washout period of at least 10 days (not to exceed 15 days). Treatment Period 4 begins at the end of the Treatment Period 3 washout. On Day 1 of Period 1, eligible subjects will be randomized with equal probability to 1 of the 6 treatment sequences listed in the table below. The study drug and placebo will be administered orally on

day 1 of each of the first 3 treatment periods. Ketamine 0.5 mg/kg IV will be administered for 40 minutes on day 1 of period 4.

Sequence	Period 1	Period 2	Period 3	Period 4
1	TAK-653 0.5 mg	TAK-653 6 mg	Placebo	Ketamine 0.5 mg/kg
2	TAK-653 6 mg	TAK-653 0.5 mg	Placebo	Ketamine 0.5 mg/kg
3	TAK-653 0.5 mg	Placebo	TAK-653 6 mg	Ketamine 0.5 mg/kg
4	TAK-653 6 mg	Placebo	TAK-653 0.5 mg	Ketamine 0.5 mg/kg
5	Placebo	TAK-653 0.5 mg	TAK-653 6 mg	Ketamine 0.5 mg/kg
6	Placebo	TAK-653 6 mg	TAK-653 0.5 mg	Ketamine 0.5 mg/kg

5.0 ANALYSIS ENDPOINTS

5.1 Primary endpoints

- The change of peak-to-peak amplitude of the MEP obtained with single-pulse TMS (stimulation intensity: 120% of baseline rMT) at 2½ hours after administration of TAK-653 from pre-dosing baseline compared to placebo.
- The change of rMT obtained with single-pulse TMS at 2½ hour post-dose after administration of TAK-653 from predosing baseline compared to placebo.

5.2 Secondary endpoints

The change from baseline at 2 ½ hours post-dose for the following:

1. Magnitude of long intracortical inhibition (LICI) obtained with paired-pulse TMS (stimulation intensity conditioning pulse and test pulse: 120% of baseline rMT).
2. Magnitude of short intracortical inhibition (SICI) obtained with paired-pulse TMS (stimulation intensity: conditioning pulse 80% of baseline rMT; test pulse: 120% of baseline rMT).
3. The rMT obtained with single-pulse TMS assessing ketamine effects, as well as at 24 hours.
4. The peak-to-peak amplitude of the MEP obtained with single-pulse TMS (stimulation intensity: 120% of baseline rMT) assessing ketamine effects, as well as at 24 hours.

5.3 Safety Endpoints

Safety endpoints include:

1. Number/percentage of subjects with at least 1 AE.
2. Number/percentage of subjects with at least 1 serious adverse event (SAE).
3. Number/percentage of subjects with at least 1 clinically-defined abnormal laboratory value.
4. Number/percentage of subjects with at least 1 clinically-defined abnormal vital sign value.

5.4 Exploratory Endpoints

CCI

[redacted]

CCI

6.0 DETERMINATION OF SAMPLE SIZE

The assumptions used in the sample size determination were based on consideration of a published study on ketamine by di Lazzaro et al. (2003) [4] and the preliminary results of TMS data in a CHDR study of healthy volunteers. Specifically, we assumed an intra-subject correlation of 0.9, a common standard deviation of 9% for rMT and 947 μV for the MEP peak-to-peak amplitude, a correlation coefficient of at least 0.5 between pre- and post-dosing outcome, and a familywise type I error rate of 10%. A sample size of 22 subjects, approximately four subjects for each of the six sequences of the first three treatment periods, will provide at least 80% power in detecting a reduction of 5.3 percentage points in rMT and/or an increase of 560 μV in the MEP peak-to-peak amplitude at the most effective dose level of TAK-653 vs placebo. Subjects who complete at least the first three treatment periods of the study are considered completers. Drop-out rate is expected to be low. Twenty-four subjects will be recruited (4 per sequence) to ensure at least 22 completers. If more than two subjects drop out before completing the first three treatment periods, up to two additional subjects may be enrolled.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This Statistical Analysis Plan (SAP) was developed based on International Conference on Harmonization E3 [2] and E9 [3] Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP was developed using the information provided in Protocol TAK-653-1003 Amendment 01, dated April 4th, 2019 [1].

All study-related raw data, including derived data, will be presented in data listings. 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 at a type-I error rate, α, of 0.10 for significance unless otherwise stated. A p-value less than or equal to α is reported as "significant". All computations will be performed prior to rounding.

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. All data will be presented in data listings regardless.

In case of missing data in the primary and secondary analysis, sensitivity analysis will be conducted using tipping point analysis and by comparing models including and excluding patients who are noncompliant with the dose schedule, or who have incomplete data on parameters in the models.

Plasma concentrations that are below the limit of quantification will be treated as zero in the summarizing of concentration values. 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 1.1 (12 Feb 2016); ADaM Structure for Occurrence Data (OCCDS) Version 1.0 12 Feb 2016).

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.

CCI

For paired pulse TMS-EMG, the SICI and LICI parameters will be derived as follows:

- SICI: the mean peak-to-peak amplitude of the responses to the 50 unconditioned and 50 conditioned test pulses will be calculated. For the unconditioned responses, the single pulse responses will be evaluated. Thereafter, the mean conditioned test response (TR) amplitude, expressed as a percentage of the mean unconditioned response (single pulse MEP; SP_MEP) amplitude, will be calculated as100 · TR/SP_MEP (%).
- LICI: the mean peak-to-peak amplitude of the responses to the 50 conditioning and 50 test pulses will be calculated. Thereafter, the mean test response (TR) amplitude, expressed as a percentage of the mean conditioning response (CR) amplitude, will be calculated as 100 · TR/CR (%).

Values below 100% represent inhibition and values above 100% facilitation.

7.1.3 Definition of Study Days and Baseline

For pharmacodynamic and safety endpoints, pre-dosing baseline is generally defined as the last non-missing measurement prior to the dosing of study drug in the respective treatment period. But when more than one measurement is taken predose during the same visit, the average will be used as baseline value.

For pharmacodynamic and safety endpoints, study day will be calculated relative to the date of dosing in the respective treatment period. Study day prior to the treatment in the respective

treatment period will be calculated as: date of assessment/event – date of treatment; study day on or after the dose of treatment in the respective treatment period will be calculated as: date of assessment/event – date of treatment + 1.

7.2 Analysis Sets

Safety Set

The safety analysis set consists of all subjects who are randomized and received at least 1 dose of study drug. Subjects in this analysis set are used for demographic, Baseline characteristics, and safety summaries.

Pharmacokinetic Set

The PK set consists of all subjects who receive study drug and have at least 1 measurable plasma concentration.

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 PK analysis but will be presented in the subject listings.

Pharmacodynamic Set

The PD set consists of all subjects who receive study drug and have at least 1 post-dose PD measurement.

The primary and the first two secondary endpoints will be based on subjects who have completed the first three treatment periods. In case not all subjects have completed the first three periods, sensitivity analysis will be conducted by including the entire PD set in the model and tipping point analysis will be performed. The third and fourth secondary analyses on the effect of ketamine will be based on subjects who have completed period 4.

7.3 Disposition of Subjects

The number and percentage of subjects who complete study drug, prematurely discontinue study drug and study visits will be summarized by treatment sequence and overall. If not all patients finished the four treatment periods, the summary will also be provided for the first three treatment periods. In addition, the number and percentage of subjects will be summarized for each reason of discontinuation of study drug and study visits. Subjects' study completion data, including reasons for premature termination, will be listed by study part for all subjects.

The number and percentage of subjects who are included in each analysis set will be summarized for the first three periods (by treatment sequence and overall) and period 4 separately.

7.4 Protocol Deviations

The protocol deviations will be provided in a data listing and summarized for first three periods (by treatment and overall) and for period 4 separately.

7.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects in safety analysis set in the first three periods (by treatment sequence and overall). If not all patients finished the four treatment periods, the summary will also be provided for period 4 separately. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (e.g., age, height, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (e.g., gender, race, ethnicity, caffeine consumption, alcohol use, and smoking status).

7.6 Medical History and Concurrent Medical Conditions

Medical history obtained includes determining whether the subjects has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions.

Medical history and concurrent medical condition verbatim reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No summaries for medical history and concurrent medical conditions will be provided. All medical history and concurrent medical conditions will be listed.

7.7 Concomitant Medications

Medications used from signing of informed consent through the end of study will be considered as concomitant medications. Concomitant medications will be coded using World Health Organization Drug Dictionary. No summaries for concomitant medications will be provided. All concomitant medications data will be listed.

7.8 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 and PD data will be provided by treatment. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic Analysis

TAK-653 plasma and ketamine concentrations will be tabulated and summarized by descriptive statistics at each scheduled time point (arithmetic mean, median, SD, percent coefficient of variation [%CV], minimum, and maximum) for each treatment. Individual subject plasma concentration data will be listed.

7.11 Pharmacodynamic Analysis

The following pharmacodynamics parameters will be estimated for each timepoint, including pre-dosing baseline and all post-dose measurements, in each of the four treatment periods:

- Peak-to-peak amplitude of the MEP obtained with single-pulse TMS (stimulation intensity: 120% of baseline rMT).
- Resting motor threshold obtained with single-pulse TMS.
- Magnitude of LICI obtained with paired-pulse TMS (stimulation intensity conditioning pulse and test pulse: 120% of baseline rMT).
- Magnitude of SICI obtained with paired-pulse TMS (stimulation intensity: conditioning pulse 80% of baseline rMT; test pulse: 120% of baseline rMT).

Derived PD parameters will be listed by subject and summarized using descriptive summary statistics (including N, arithmetic mean, SD, median, minimum, maximum, and CV% where appropriate) by treatment group. The change from baseline (CFB) will be calculated for all continuous endpoints. Descriptive summary statistics of CFB will be provided by treatment group. The PD parameters will also be presented graphically as mean over time, with standard deviation as error bars.

A mixed model for repeated measures will be used for the primary analysis, with fixed factors for treatment, period, sequence, and treatment by period interaction, and subject nested in sequence as a random effect. The baseline measure will be included in the model as a covariate. Treatment differences, 2-sided 90% CIs, and *p*-values will be presented for change of measures at 2 ½ hours post-dose from pre-dosing baseline. Hochberg's step-up procedure will be used in the primary analysis to adjust for multiple testing due to two primary endpoints. One-sided t-tests comparing each of the primary endpoints for placebo vs. treatment at each dose level will be conducted as secondary analyses, adjusted for multiple testing to ensure type 1 error control at the 10% level.

The mean conditioned test response amplitude of LICI and the mean test response amplitude of SICI will be analyzed using linear mixed effect models analogous to the model used to analyze the primary endpoints. One-sided t-tests (alpha = 0.05) will be used for the comparison of placebo versus one of the TAK-653 treatment groups.

The relationship between time-matched TAK-653 plasma concentrations and PD effects observed with TMS such as rMT, the peak-to-peak amplitude of the MEP, and the magnitude of LICI and SICI will be explored graphically. CCI [redacted]

Additional analyses may also be considered as data permitted.

CCI [redacted]

CCI

CCI

[redacted]

7.12 Safety Analysis

The safety of TAK-653 will be assessed through AEs, clinical laboratory results, physical examination findings, ECG findings, vital signs, and suicidal assessments. All safety summary tables are presented by treatment groups.

7.12.1 Adverse Events

A TEAE is defined as an adverse event or an SAE that starts or increases in intensity after receiving the first dose of study drug until the Follow-up Visit/Call or Early Termination. A TEAE may also be a pretreatment adverse event 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 event verbatim reported terms will be coded by system organ class, high-level term and preferred term using MedDRA.

TEAE summary tables will include numbers and percentages of subjects experiencing at least one AE by system organ class (SOC) and preferred term (PT) and will be tabulated by treatment groups. TEAEs will be summarized according to the treatment most recently received prior to the onset of the event, unless an AE increases in intensity in a subsequent treatment period, in which case it will be handled as a new TEAE on the treatment received prior to the increase in intensity.

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

- Overview of TEAEs.
- TEAEs by SOC and PT at subject and event level.
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Most Frequent TEAEs by PT.
- Most Frequent 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.

- Pretreatment Events by SOC and PT.

If a subject has more than one AE that codes to the same PT, the subject will be counted only once for that PT. If a subject has more than one AE within an SOC category, the subject will be counted only once for that SOC. For the intensity or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary.

Most frequent TEAEs are defined as the AEs occurring in more than 5% subjects in any treatment. Note the cutoff point will be applied before any rounding. For example, for a safety population of 22, most frequent TEAEs are AEs occurring in at least 2 subjects.

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

7.12.2 Clinical Laboratory Evaluations

All samples are collected in accordance with acceptable laboratory procedures. During the treatment period, laboratory samples are taken following a minimum 8 hour overnight fast on the days stipulated in the Schedule of Study Procedures.

Individual results for hematology, chemistry, and coagulation laboratory tests are evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix A) using the result and criteria in SI units.

Clinical laboratory tests (hematology, chemistry, and urinalysis) will be listed. The results that meet MAV criteria will be flagged in the listing. Baseline, post-dose and change from Baseline to post-dose laboratory data will be summarized. Baseline is defined as the last non-missing measurement prior to first dose of study drug in each period.

The percentage of subjects who meet MAV criteria at least once postdose will be summarized.

7.12.3 Vital Signs

Vital signs include body temperature (auricular) respiratory rate, (semi-recumbent) blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute [bpm]).

All measurements are recorded on the source documents and in the eCRF.

When vital signs are scheduled at the same time as blood draws, the blood draw takes priority and vital signs are obtained within 0.5 hour before or after the scheduled blood draw.

Individual vital signs is evaluated against Takeda's predefined criteria for MAV (Appendix B). All vital signs will be listed. The results that meet MAV criteria will be flagged in the listing. Baseline, postdose and change from Baseline to postdose vital signs parameters will be summarized. Baseline is defined as the last non-missing measurement prior to first dose of study drug for subjects in each period.

The percentage of subjects who meet MAV criteria of vital signs at least once postdose will be summarized.

7.12.4 12-Lead ECGs

A standard 12-lead ECG is recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. The following parameters will be recorded from the subject's ECG trace: heart rate, RR interval, PR interval, QRS interval, and QTcF (QT interval with Fridericia correction method).

If an ECG is scheduled at the same time as blood draws or vital signs, the ECG is obtained within 0.5 hours before the scheduled blood draw/vital sign assessment. Predose ECGs may be done within 1 hour prior to dosing. If an ECG coincides with a meal, the ECG takes precedence followed by the meal.

Individual ECGs are evaluated against Takeda's predefined criteria for MAV (Appendix C). The all ECGs will be listed. The results that meet MAV criteria will be flagged in the listing. Baseline, postdose and change from Baseline to postdose ECG parameters will be summarized. Baseline is defined as the last non-missing measurement prior to first dose of study drug in each period.

The percentage of subjects who meet MAV criteria of ECGs at least once postdose will be summarized.

7.12.5 Other Observations Related to Safety

7.12.5.1 Physical Examination

A Baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the study drug must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF.

The physical examination findings will be presented in a data listing. No summary tables will be provided.

7.12.5.2 Columbia - Suicide Severity Rating Scale (C-SSRS)

The C-SSRS was developed by researchers at Columbia University as a tool to systematically assess suicidal ideation and behavior in subjects during participation in a clinical trial of centrally-acting drugs. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with sub-questions assessing the severity. The tool is administered via interview with the subject.

C-SSRS data will be presented in data listings. No summary tables will be provided.

7.13 Interim Analysis

After at least 18 subjects have completed the first three periods of the study, an unblinded data analysis may be conducted on the change of primary endpoints. An unblinded team not involved in the study conduct or the program will perform the unblinded analysis. A firewall will be set up between the unblinded team and the study team. No decision on the trial or modification of sample size will be made based on the analysis. The investigator and study site will not have access to the analysis results until the final unblinding of the study. This early data review will be conducted only for the purpose of sponsor programmatic forward planning that is unrelated to the conduct of the present study.

The primary endpoints in the first three treatment periods will be summarized using descriptive summary statistics (including N, arithmetic mean, SD, median, minimum, maximum, and CV% where appropriate) by treatment group.

A mixed model for repeated measures will be used, with fixed factors for treatment, period, sequence, and treatment by period interaction, and subject nested in sequence as a random effect, for the analysis of primary endpoints. The baseline measure will be included in the model as a covariate. Treatment differences, 2-sided 90% CIs, and p-values will be presented for change of measures at 2 ½ hours post-dose from pre-dosing baseline. Hochberg's step-up procedure will be used to adjust for multiple testing.

7.14 Changes in the Statistical Analysis Plan

This SAP contains no changes to the planned analyses described in the Protocol.

8.0 REFERENCES

1. Protocol Amendment 031: A Randomized, Double-Blind, Placebo-Controlled, Three-Period Crossover Study Followed by One Open-label Comparator Period to Evaluate Central Pharmacodynamic Activity of TAK-653 in Healthy Volunteers Using Transcranial Magnetic Stimulation, April 4th 2019.
2. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.
3. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.
4. Di Lazzaro V, Oliviero A, Profice P, Pennisi MA, Pilato F, Zito G, et al. Ketamine increases human motor cortex excitability to transcranial magnetic stimulation. J Physiol 2003;547(Pt 2):485-96.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

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

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

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3 × ULN
AST	Both	--	>3 × ULN
GGT	Both	--	>3 × ULN
Alkaline phosphatase	Both	--	>3 × ULN
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	<0.8 × LLN	>1.2 × 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	Conventional	--	>5 × ULN
	SI	--	>5 × ULN
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L

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	<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 Markedly Abnormal Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<50	>120
PR	msec	≤80	≥200
QT Interval	msec	≤50	≥460
QTcB Interval	msec	≤300	≥500 OR ≥30 change from baseline and ≥450
QTcF Interval	msec	≤300	≥500 OR ≥30 change from baseline and ≥450
QRS	msec	≤80	≥180

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	03-Jun-2019 20:21 UTC