STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-831-2001

A Phase 2 Randomized, Investigator-Blind, Placebo-Controlled, Cross-Over Study to Evaluate Pharmacodynamic Effects, Safety, Tolerability, and Pharmacokinetics of Multiple Oral Doses of TAK-831 in Adult Subjects With Schizophrenia

PHASE 2

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1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ASL	arterial spin labeling
AST	aspartate aminotransferase
ASSR	auditory steady state response
ANOVA	analysis of variance
ANCOVA	Analysis of covariance
BACS	Brief Assessment of Cognition in Schizophrenia
CDSS	Calgary Depression Scale Score
C-SSRS	Columbia Suicide Severity Rating Scale
Cz	midline central electrode
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBC	eyeblink conditioning
ECG	Electrocardiogram
eCRF	electronic case report form
EEG	electroencephalography
ERP	event related potential
Fz	midline frontal electrode
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MID	monetary incentive delay
MMRM	mixed model for repeated measurements
MMN	mismatch negativity
MRI	magnetic resonance imaging
[redacted]	[redacted]
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	preferred term
Pz	midline parietal electrode
QTcF	QT interval with Frederica correction method
RNA	ribonucleic acid
SAE	serious adverse event
SAS	Simpson Angus Scale
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objective

- To determine whether TAK-831 is superior to placebo in improving cerebellar function as measured with the average % of conditioned responses during the eyeblink conditioning (EBC) test.

4.2 Secondary Objectives

- To determine whether add-on TAK-831 compared to placebo improves sensory processing as measured by event related potentials (ERPs) mismatch negativity (MMN) and p300.
- To determine whether add-on TAK-831 compared to placebo improves the auditory steady-state response (ASSR) to 40 Hz stimulation.
- To determine whether add-on TAK-831 compared to placebo improves the composite score of the BACS battery.
- To assess the safety and tolerability of TAK-831.
- To assess the pharmacokinetics (PK) of TAK-831.
- To assess the pharmacodynamics (PD) of TAK-831 by measurement of plasma D-serine and L-serine levels, as well as plasma D-serine: total serine ratios.

[redacted]

4.4 Study Design

This study is a randomized, double-blind, placebo-controlled, 2-period crossover phase 2 study to evaluate the PD effects, safety, tolerability and PK of multiple daily oral doses of TAK-831 in adult patients with schizophrenia.

Approximately 32 adult male and female subjects between ages 18 and 50, inclusive, with a current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia who are receiving stable antipsychotic therapy (no increase, no decrease >25% in dose in the preceding 2 months) will be randomized in to the study. Subjects will have a [redacted] Subjects with extrapyramidal signs or symptoms or depressive symptoms will be excluded.

Additional screening assessments include a physical and neurological exam, clinical laboratory and ECG measures, a urine drug screen, and screening for suicidality and depression using the Columbia Suicide Severity Rating Scale (C-SSRS) and the Calgary Depression Scale Score (CDSS), respectively. Assessment of extrapyramidal symptoms will be performed with the Simpson Angus Scale (SAS). The presence of dyskinesias will be assessed with the Abnormal Involuntary Movement Scale (AIMS).

During the pretreatment days (Days -2 and -1), subjects will participate in a baseline assessment with a cognitive battery, [redacted] EEG/ERP measures, and the EBC.

Effects of up to 2 dose levels of TAK-831 or placebo will be assessed. Each treatment will be administered daily for a period of 8 consecutive days, separated by a 14 to 21 days washout.

The planned dose levels of TAK-831 to be evaluated will be 500 and 50 mg.

The study will consist of 2 treatment periods, and visits to the clinic at the following times: (1) Screening Period (Days -30 to -3) covering full medical, neurological, and psychiatric examinations; (2) Treatment Visits and in patient stays: On Day -2 of Periods 1 and 2, subjects will be admitted to the clinic for 2-night stays; on Day -2 subjects will undergo baseline clinical assessment procedures and cognitive battery assessment. On Day -1, subjects will receive the baseline EEG and EBC assessments. In Period 1, those who continue to meet all eligibility criteria will be randomized via an interactive response technology (IRT) system to 1 of 2 treatment sequences. On Day 1, subjects will undergo predose blood PK/PD samples, first dosing, and postdose blood draws, after which they will be discharged from the clinic to continue dosing at their residence. Subjects will receive double-blind treatment from Days 1 through 8 (inclusive) with completion of efficacy and PK/PD-related assessments on Days 7 and 8 of each treatment period; and (3), a washout period between Treatment Periods 1 and 2 lasting between 14 to 21 days.

Study participants will receive daily study drug dosing until Day 8 of each period. Clinical assessments, laboratory tests and ECG will be repeated after dosing on Days 7 and 8 as per the schedule of events. Upon completion of the first dosing period, subjects will enter a wash-out

period lasting between 14 to 21 days and will then return to the study site to undergo Day -2 procedures for the next dosing period.

Approximately 10 to 14 days after the last dose of study drug in the second dosing period, a follow-up safety assessment will be performed.

In the event of a subject prematurely discontinuing the study during one of the study periods, an Early Termination Visit must be conducted, at which the safety, PK, plasma D- and L-serine assessments corresponding to a Final Visit will be performed. If a subject discontinues the study during the washout period, only the procedures corresponding to the follow-up safety assessment will be performed.

Subjects who drop out before completing 2 treatment periods of the study may be replaced at the discretion of the study sponsor.

Subjects who do not meet symptom or medication stability criteria (or other entry criteria that may be met by the subject at a future time) may be considered for rescreening with the approval of the sponsor or designee.

Subjects who have been screened but have exceeded the 28-day Screening Period may proceed in the study after a discussion with the sponsor/designee to obtain approval and to determine whether any screening procedures should be repeated before admission on Day -2 of Period 1.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

- Average % of conditioned responses during the EBC test at Day 8.

5.1.2 Secondary Endpoints

- MMN amplitude at Fz (electroencephalogram [EEG]) at Day 8.
- P300 amplitude at midline parietal electrode (Pz) (EEG) at Day 8.
- ASSR at midline central electrode (Cz) (EEG) at Day 8.
- BACS cognitive battery composite score at Day 7.
- Plasma D-serine and L-serine levels, and plasma D-serine:total serine ratio at Day 8.
- TAK-831 plasma concentrations.

[redacted]

[redacted]

5.1.4 Safety Endpoints

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for safety ECG parameters at least once postdose.
- Percentage of subjects with treatment-emergent suicidal ideation or suicidal behavior as measured using the C-SSRS.

6.0 DETERMINATION OF SAMPLE SIZE

Up to approximately 32 subjects will be enrolled into this 2-period crossover study. Initially 16 subjects will be randomized to 1 of 2 sequences comparing the high dose to placebo. Based on the results of an interim analysis, an additional 16 subjects may be randomized as before or to 1 of the 2 sequences comparing the low dose to placebo.

The expected effect size, defined as the ratio between the mean difference between treatment and placebo divided by the standard deviation of this difference, is 0.6 for the primary endpoint. This effect size is a conservative estimate based on data from [1], which showed an effect size of 0.74 for EBC at 24 hours after initiation of treatment with secretin. In this study of a schizophrenic population, subjects on secretin showed a 24% higher rate of correct responses compared to subjects on placebo (70% vs 46%).

The sample sizes of 16 or 32 subjects have been selected to enable Bayesian analyses to inform dose selection and future drug development under the expected effect size as well as other plausible effect sizes.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Baseline values are defined as the last observed value before the first dose of study medication within each study period.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.10 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

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. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate. For transformed and derived data, summary statistics will be presented to appropriate decimal places.

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 treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Screen failure subjects will be grouped and listed at the end.

For summaries by treatment sequence, the TAK-831 dose level will be summarized separately if the low dose is used.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication within each study period. 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.

7.13 Definition of Study Visit Windows

A windowing convention will be used to determine the analysis value for a given study visit that applies to observed data. For each visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits.

More than 1 result for a parameter may be obtained in a visit window. In such an event, the result with the date closest to the scheduled visit day will be used. In the event of 2 observations equidistant to the scheduled visit day, the later of the observations will be used.

7.1.4 Conventions for Missing Adverse Event Dates

Incomplete adverse event (AE) start dates will be imputed to determine the relationship between the start date and the informed consent date, as well as the start date and the first dose date of a given Period. All references to ***first dose*** in this section should be understood relative to each treatment Period.

Incomplete AE dates will be presented as they are in the listings.

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

- If only the month and year of the start date are available and the month and year are different than the month and year of the first dose (of double-blind study medication) or the stop date is prior to the first dose, then the first day of the month will be used for the start date. If only

the month and year of the start date are available and the month and year are the same as the month and year of the first dose and the stop date is not prior to the date of first dose, then the date of first dose will be used for the start date.

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

If the above instructions indicate conflicting start dates for an AE, then the earliest date indicated shall be used.

7.1.5 Conventions for Missing Concomitant Medication Dates

If start date and stop date are missing, medication will be assumed to occur both prior and concomitantly. Also see Section 7.6.

7.2 Analysis Sets

7.2.1.1 Safety Set

The Safety Set will include all randomized subjects who receive at least 1 dose of double-blind study medication. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries. Subjects will be analyzed according to the actual treatment received.

7.2.1.2 PK Set

The PK Set will include all randomized subjects who receive at least one dose of double-blind study medication and who have any available plasma concentration data. Subjects will be analyzed according to the actual treatment received.

7.2.1.3 PD Set

The PD set will consist of all subjects who receive at least 1 dose of study drug and have at least 1 postdose PD result. Subjects will be analyzed according to the randomized treatment.

7.3 Disposition of Subjects

Study Information, including date first subject signed ICF, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, MedDRA Version, WHODrug Version, SAS Version, will be listed.

Disposition of all screened subjects (denominator) will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

Disposition of all randomized subjects will be tabulated:

- All subjects received at least one dose of study drug (denominator).

- Subjects who completed the study.
- Subjects who prematurely discontinued study.

Primary reasons for discontinuation of study as entered on the electronic case report form (eCRF), will be tabulated. Reasons for discontinuation include adverse event, liver function test, significant protocol deviation, lost to follow-up, voluntary withdrawal, study termination, and other. The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

Disposition of screen failure subjects will be summarized descriptively. Primary reasons for failure will be summarized and will be presented in a data listing.

Significant protocol deviations will be summarized and listed.

All summaries will be presented by treatment sequence and overall.

7.4 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics including age, gender, race, and body mass index will be listed and summarized by randomized treatment sequence and overall based on the Safety Set.

Baseline values for primary and secondary PD assessments (including average % of conditioned responses during the EBC test at Day 8, MMN amplitude at Fz at Day 8, P300 amplitude at Pz at Day 8, ASSR at Cz at Day 8, BACS cognitive battery composite score at Day 7, plasma D-serine, L-serine levels and the ratio of the two at Day 8) will also be summarized by treatment sequence and overall based on the Safety Set.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 18 or higher) coding system. Ongoing conditions are considered concurrent medical conditions.

All medical history and concurrent medical condition data will be listed by site (study center) and subject number. The listing will contain subject identifier, treatment sequence, system organ class (SOC), preferred term (PT), whether there was any medical history or concurrent condition, and, if yes, a detail of the medical history or concurrent condition.

Medical history and concurrent medical conditions will be listed and summarized by each treatment sequence and overall based on the Safety Set.

7.6 Medication History and Concomitant Medications

All medication history and concomitant medications will be listed by site (study center) and subject number. The listings will contain subject identifier, treatment, World Health Organization Drug Dictionary (WHODrug) preferred medication name, dose, unit, frequency, route, start date, stop date, whether the medication was ongoing, and reason for use. No inferential statistics will be presented.

Medication history and concomitant medications will be coded using the WHODrug Version 01March 2017 or higher.

7.7 Study Drug Exposure and Compliance

The duration of exposure will be summarized as a continuous variable.

The percentage of study drug compliance will be defined as {(number of tablets dispensed – number of tablets returned) / [5*(date of last dose – date of first dose +1)]} x 100%. For each treatment group, study medication compliance will be summarized by compliance category (<80%, 80 to 120%, and >120%) and the number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment group.

All study drug administration and compliance data will also be summarized in a listing(s).

7.8 PD Analysis

7.8.1 Primary PD Endpoint

The primary endpoint is the average % of conditioned responses in the EBC task at Day 8.

The primary endpoint will be summarized for baseline, post-dose, and change from baseline by treatment.

Pairwise comparisons between active treatments and placebo will be generated within the framework of analysis of variance (ANOVA), with treatment sequence, period, and treatment as fixed effects. Subject nested within sequence is included as a random effect. The dependent variable is the change in response from the period baseline assessment to the final treatment day for each period, and the response data will be logit transformed before the change is calculated. The analysis will be performed using observed data. Potential carryover effects will be investigated. P-values and confidence intervals will be reported. The following SAS code may be used:

```
proc mixed data=XXXX;

class sequence treatment period subject;

model response = sequence treatment period / ddfm=kr;

random subject (sequence);

estimate 'Treatment Difference' treatment -1 1 / al alpha = 0.10 E;

lsmeans treatment;

run;
```

The primary endpoint will be tested individually for each of the two doses against 5% (one-sided) level of significance.

As a supplementary analysis, an ANCOVA (analysis of covariance) model will be applied to the primary endpoint with (period) baseline as a covariate, treatment sequence, period, treatment effect, baseline-by-treatment as fixed effects, and subject as a random effect. The dependent variable is the change in response from the period baseline assessment to the final treatment day for each period, and the response data will be logit transformed before the change is calculated. Based on a missing at random assumption, this analysis will be performed using observed data only. P-values and confidence intervals for this model will be provided.

In addition, as a supporting analysis and in the interim analysis (see Section 7.12), the primary endpoint will be analyzed using a Bayesian normal linear model with treatment sequence, period, and treatment as fixed effects, subject within sequence as a repeated factor, and (period) baseline as a covariate. The dependent variable is the change in response from the period baseline assessment to the final treatment day for each period. The response data will be logit transformed before the change is calculated. A diffuse normal distribution will be used as a prior for the regression coefficients and a diffuse inverse gamma for the residual variance. The Bayesian model will be used to estimate the posterior distribution of the treatment effect from each dose (as applicable). The posterior mean, standard deviation and the 90% credible interval (highest posterior density interval) for each treatment, along with the posterior mean treatment difference, corresponding standard deviation and 90% credible interval (highest posterior density interval) will be reported. The following SAS code may be used for the analysis:

```
proc genmod data = XXXX;
class Sequence Period Treatment Subject;
model Response = Sequence Period Treatment Subject Baseline / dist = Normal link=identity alpha=0.1;
bayes seed = 666 coeffprior=normal dispersionprior = igamma(shape=0.001, scale=0.001) nbi=2000 nmc=10000 maxit=2000 outpost=post diagnostics=all stats=all;
lsmeans Treatment / pdiff alpha = 0.1;
run;
```

7.8.2 Secondary PD Endpoint(s)

The secondary EEG endpoints will be analyzed using an ANOVA model similar to that used for the primary endpoint, as described in Section 7.8.1.

The cognitive battery composite score, the BACS, will be analyzed as follows. The primary measure from each test is standardized by creating z-scores whereby the mean of the test session of a healthy participant is set to 0 and the standard deviation set to 1 [2]. A composite score will be calculated by averaging the 4 measures from the BACS used in the study, and then calculating a z-score of the composite. The composite z-score indicates how much higher or lower the participant's cognition is compared to a healthy person. An ANOVA will be performed on the change from baseline for the composite BACS score, using a similar model to that used for primary endpoint.

For each regimen, the concentrations of D-serine, L-serine, and the ratio of D-serine to total serine with change and percent change from Baseline will be summarized at each time point of each dose level using descriptive statistics. In addition, a mixed model for repeated measures (MMRM) will be used on the change from baseline in these concentrations, with sequence, period, treatment and visit as fixed effects, and subject nested within sequence as a random effect. Based on a missing at random assumption, this analysis will be performed using observed case data only. The effect at each time point for each subject is allowed to vary freely and an unstructured covariance matrix is assumed. If the model does not converge, other covariance structures will be considered. Pairwise comparisons between the test regimens (high dose, low dose and placebo) will be made and the CIs for the difference in the LS means will be constructed for Day 8 assessments.

There will be no adjustment for the multiplicity of secondary endpoints.

All secondary PD endpoints will be summarized for baseline, post-dose, and change from baseline by treatment.

7.9 Pharmacokinetic Analysis

Plasma concentrations of TAK-831 will be listed for each subject and summarized by each time point for each dose and period of the study.

Individual concentration-time data will be pooled to describe the population PK of TAK-831. As data permit, a nonlinear mixed effects modeling approach (NONMEM software) will be used to assess TAK-831 exposure. PK information generated in this study will be further utilized in subsequent population PK-PD analyses. The relationships between TAK-831 plasma concentrations and drug response will be explored. As appropriate, historical data may be used in

this analysis to increase the robustness of the model and precision of estimated parameters. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses may be reported separately.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

The Safety Set will be used for all summaries of safety parameters. These summaries will be presented by placebo, each TAK-831 dose level, and TAK-831 overall (as appropriate).

7.11.1 Adverse Events

Verbatim terms will be coded by SOC and PT using MedDRA (version 20.0 or later).

TEAEs will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occur after the first dose of study drugs. TEAEs with onset occurring within 30 days (onset date – last date of dose +1≤30) after study drug administration will be included in the summary tables. All AEs will be included in the listings.

TEAEs will be summarized by treatment. TEAE will only be included for the treatment administered in the Period of its start date, unless it increases in intensity in the following Period, in which case will be handled as a new TEAE on the second treatment.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary. An exception to the previous rule is if the TEAE begins in Period 1 but increases in intensity in Period 2, in which case it will be summarized as separate TEAEs.

AEs with missing intensity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. If the relationship of an event is missing, the relationship for the event will be considered to have been related.

In general, AEs will be tabulated at the following levels: overall summary (subjects with at least 1 AE in any dose or regimen), the MedDRA SOC, and the MedDRA PT. The tables will include the number and percentage (N[%]) of subjects. Summary tables that will be generated will include, but may not be limited to:

- Overview of Treatment-Emergent Adverse Events.
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, including number of subjects and events.
- Treatment-Emergent Adverse Events by Preferred Term.

- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, including number of subjects and events.
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by Preferred Term.
- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Pretreatment Adverse Events by System Organ Class and Preferred Term.
- Most Frequent (>5%) Non-Serious Adverse Events by System Organ Class and Preferred Term.
- Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term.

In addition, subject mappings for the TEAEs by SOC and PT will be generated.

Data listings will be provided for pretreatment AEs, TEAEs, TEAEs leading to study drug discontinuation, liver function abnormalities, serious adverse events (SAEs), and AEs that resulted in death. AEs happened after 31 days post the last dose of the study drug will be listed as well.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be assessed using the Safety Set and will be evaluated and presented using International System of Units (SI) units unless otherwise stated. Refer to Protocol Section 9.2.17 as well as the schedule of the events for a list of all clinical laboratory tests.

All laboratory test parameters will be displayed in individual subject data listings. For test results not in SI units, the conversion to SI units will be done in the derived SDTM and ADaM datasets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived SDTM and ADaM datasets. All summaries and analyses will be based on the values using these preferred SI units.

Only observations within 3 days of the last dose of study drug will be included in the tables, with the exception of observations from the Early Termination Visit. No inferential statistics will be presented unless otherwise stated.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed and change from baseline values will be presented by treatment. Baseline from each period will be used for change from baseline. Note that "character" urinalysis tests will only be listed.

Laboratory markedly abnormal values (MAVs), identified by the criteria defined in Appendix A, will be tabulated. If a subject has a MAV for a particular laboratory test, all visits for that subject

for that parameter will be listed. The number and percentage of subjects with at least 1 postdose markedly abnormal laboratory test result will be summarized by treatment. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

Also, the elevated hepatic parameters will be summarized by treatment.

Listings of all clinical safety laboratory data will be provided in Appendix 16.2 Laboratory data outside of the normal reference range will be indicated in the listings. In addition, MAVs will be flagged. The listing will include site number, subject identifier, age, gender, treatment sequence, study period/visit, and sample collection date.

7.11.3 Vital Signs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize vital sign parameters at baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Summaries will be by treatment. Baseline from each period will be used for change from baseline. Only observations within 3 days of the study drug will be included in the tables, with the exception of observations from the Early Termination Visit.

Vital sign MAVs, identified by the criteria defined in Appendix B, will be tabulated. If a subject has a MAV for a particular vital signs parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 postdose markedly abnormal vital signs measurement will be summarized by treatment. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

Listings of all vital signs data will be provided in Appendix 16.2. Vital sign MAVs will be flagged in the listings. The listing will include site number, subject identifier, age, gender, treatment sequence, study period/visit, and sample collection date.

7.11.4 12-Lead ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet Takeda's markedly abnormal criteria will be summarized by treatment and provided in the data listings. Baseline from each period will be used for change from baseline. Baseline, postdose, and changes from Baseline in quantitative ECG parameters will be summarized. Shift tables will be generated to show the investigator's ECG interpretations at each postdose collection by the interpretation at Baseline.

All ECG data will be provided in the data listings.

7.11.5 Other Observations Related to Safety

Physical examination findings will be presented in the data listings. C-SSRS will be summarized by treatment.

7.12 Interim Analysis

A planned unblinded interim analysis of the primary PD endpoints will be conducted when approximately 14 patients have been completed the primary endpoint. The site will be allowed to continue enrollment to the high/placebo comparison, with the goal that approximately 16 patients will be randomized by the time the interim analysis is complete. (The additional approximately 2 subjects will be included in the final analysis but not the interim analysis.) The interim PD analysis will be to determine whether to continue enrolling subjects to the high-dose/placebo comparison or switch enrollment to the low-dose/placebo comparison.

The Bayesian normal linear model described in Section 7.8.1 will be performed for the primary endpoint. “Success Stop criteria” at interim analysis is 70% posterior probability (or greater) of a difference between 500 mg TAK-831 and placebo >0.6 (on logit scale), and a decision of switching to the low dose will be made when “Success Stop criteria” are met. “Futility Stop criteria” will be met if the posterior probability of a difference between 500 mg TAK-831 and placebo >0.1 (on logit scale) is less than 30%, and a decision of switching to the low dose will be made. If none of the aforementioned criteria are met, a decision of continuing enrolling high-dose/placebo subjects (“Continue” decision) will be made.

In addition, a decision to switch to the low dose may be made based on the safety or tolerability of the high dose.

7.13 Changes in the Statistical Analysis Plan

The primary endpoint will be tested individually for each of the two doses against 5% (one-sided) level of significance.

The summaries of safety parameters will be presented by placebo, each TAK-831 dose level, and TAK-831 overall (as appropriate), rather than by cohort as stated in the protocol.

To increase statistical efficiency, baseline will be used as a covariate in the Bayesian normal linear model described in Section 7.8.1.

8.0 REFERENCES

[1] A. R. Bolbecker, W. P. Hetrick, J. K. Johannesen, B. F. O'Donnell, J. E. Steinmetz and A. S. Shekhar, "Secretin effects on cerebellar-dependent motor learning in schizophrenia," *Am J Psychiatry,* vol. 166, no. 4, pp. 460-6, 2009.

[2] R. S. Keefe, P. D. Harvey, T. E. Goldberg, J. M. Gold, T. M. Walker, C. Kennel and K. Hawkins, "Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS)," *Schizophr Res,* vol. 102 , no. 1-3, pp. 108-115, 2008.

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

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

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI		>177 μmol/L
Blood urea nitrogen	Conventional		>30 mg/dL
	SI		>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
CPK	Both	--	>5x ULN
Glucose	Conventional	<50 mg/dL	>350 mg/dL
	SI	<2.8 mmol/L	>19.4 mmol/L

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

Appendix B Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	<35.6	>37.7

Appendix C Criteria for 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
PR	≤80 milliseconds	≥200 milliseconds
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcB Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]		