STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-831-2002

A Phase 2, 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Evaluate Efficacy, Safety, Tolerability, and Pharmacokinetics of 3 Dose levels of TAK-831 in Adjunctive Treatment of Adult Subjects With Negative Symptoms of Schizophrenia

PHASE 2

Version**:** Amendment 1

Date**:** 01 February 2021

Prepared by:

[redacted]

[redacted]

Based on:

Protocol Version: Amend 04

Protocol Date: 08 June 2020

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
BACS	Brief Assessment of Cognition in Schizophrenia
BNSS	Brief Negative Symptom Scale
CGI-SCH-I	Clinical Global Impression-Schizophrenia-Improvement
CGI-SCH-S	Clinical Global Impression-Schizophrenia-Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	deoxyribonucleic acid
DPAS	Defeatist Performance Attitude Scale
ECG	electrocardiogram
eCRF	electronic case report form
E_{max}	maximum drug-induced effect
[redacted]	[redacted]
FAS	Full Analysis Set
FWER	family-wise error rate
GGT	γ-glutamyl transferase
IPD	important protocol deviation
IRT	interactive response technology
MCP-Mod	Multiple Comparison Procedure-Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
[redacted]	[redacted]
PANSS	Positive and Negative Syndrome Scale
PANSS NSFS	Positive and Negative Syndrome Scale Negative Symptom Factor Score
PD	pharmacodynamic(s)
[redacted]	[redacted]
PK	pharmacokinetic(s)
PPS	Per Protocol Set
PT	preferred term
PTE	pretreatment event
QD	once daily
QTcF	QT interval with Fridericia correction method
RNA	ribonucleic acid
SAE	serious adverse event
SAS	Simpson Angus Scale
SCoRS	Schizophrenia Cognition Rating Scale
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to determine whether add-on TAK-831 is superior to placebo on the Positive and Negative Syndrome Scale Negative Symptom Factor Score (PANSS NSFS).

4.2 Secondary Objectives

- To determine whether add-on TAK-831 is superior to placebo on the Brief Negative Symptom Scale (BNSS) total score.
- To determine whether add-on TAK-831 is superior to placebo on the Brief Assessment of Cognition in Schizophrenia (BACS) composite cognition score.
- To determine whether add-on TAK-831 is superior to placebo on global severity as measured by the Clinical Global Impression-Schizophrenia-Severity (CGI-SCH-S) score.
- To determine whether add-on TAK-831 is superior to placebo on global improvement as measured by the Clinical Global Impression-Schizophrenia-Improvement (CGI-SCH-I) score.
- To determine whether add-on TAK-831 is superior to placebo on the Schizophrenia Cognition Rating Scale (SCoRS) assessment of cognitive functional outcome.
- To determine whether add-on TAK-831 is superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score and additional subscales and factors.
- To assess the safety and tolerability of TAK-831.
- To assess the pharmacokinetics (PK) of TAK-831.

4.3 [redacted]

[redacted]

[redacted]

4.4 Study Design

This is a randomized, double-blind, parallel, placebo-controlled, phase 2 study to evaluate the efficacy, safety, tolerability, and PK of adjunctive treatment with TAK-831 when administered orally once daily (QD) in adult subjects with negative symptoms of schizophrenia. The study will consist of a Screening Period of up to 28 days, a 14-day Single-Blind Placebo Run-in Period, a 12-week Double-Blind Treatment Period, and a Safety Follow-up Visit.

Approximately 234 subjects will be enrolled at approximately 48 sites in North America and Europe.

At the Screening Visit (Visit 1), subjects who provide informed consent will proceed with screening procedures. Subjects who meet a current diagnosis of schizophrenia, as defined by the Mini International Neuropsychiatric Interview (MINI), will then be administered additional psychiatric and neurological rating scale assessments as specified in Protocol Section 9.1.11, and undergo other screening assessments. Subjects must be currently receiving stable treatment on 1 antipsychotic medication at a total daily dose between 2 mg and 6 mg of risperidone equivalents (as outlined in an Antipsychotic Dose Equivalency reference supplied to the sites), with no clinically meaningful change in psychotropic medications (no increase, ≤25% decrease in dose) for the preceding 2 months before the Screening Visit and no dose adjustment is anticipated throughout study participation up to the Day 84/Early Termination Visit. Concomitant treatment

with a subtherapeutic dose of a second antipsychotic may be permitted with sponsor or designee approval if used as a hypnotic, but not if used for refractory positive psychosis symptoms.

Subjects must have a BNSS total score (12-item, excluding item number 4) ≥28 and limited PANSS symptoms as outlined in the study inclusion criteria, and must demonstrate stable BNSS total scores (≤20% change from the Screening score) at the Single-Blind Placebo Run-in Visit (Day -14; Visit 2) and Baseline Visit (Day 1; Visit 3). Subjects with extrapyramidal signs/symptoms or depressive symptoms based on study assessments, as outlined in the study entry criteria, will be excluded.

During the Screening Period (Days -42 to -15), subjects will visit the clinic and receive full medical, neurological, and psychiatric examinations as well as be familiarized with study procedures. Additional screening procedures include diagnostic assessments, safety assessments, and other clinical assessments. An adult informant capable of providing information about the subject's symptoms and function for the PANSS and SCoRS must attend the Screening or Placebo Run-in Visit for evaluation by site staff and to provide written informed consent for informant study participation. Alternatively, a site staff member may also go to the informant's location to obtain informed consent and, if a qualified rater, obtain the informant interview; or the informant interview may be conducted by phone if the site staff is not a rater. If the informant is unavailable for an in-person interview at the screening visit, the initial informed consent may be obtained in a telephone discussion (as permitted by local ethics and regulatory policy) so that the informant information may be included in the screening assessments requiring informant input.

Subject eligibility for the study will be confirmed by a centralized vendor that will also provide rater qualification, training, and ongoing rater quality monitoring throughout the conduct of the study. For the Screening Visit, the centralized vendor will review documentation and recordings of the diagnostic and selected symptom assessment interviews as well as collected information addressing key study entry criteria. The study site must receive documentation of approval of subject eligibility before the subject can be enrolled into the Single-Blind Run-in Period.

The 2-week Single-Blind Placebo Run-in Period (Days -14 to -1) will be used to evaluate compliance with study drug intake and stability of BNSS and PANSS scores. During this period, all subjects will receive placebo tablets that appear identical to the study drug to be used during the randomized Double-Blind Treatment Period. Note: If the scheduling of the Day 1 visit is delayed for any reason, the subject should be instructed to continue treatment with run-in medication until the Day 1 visit is reschedule.

At Baseline (predose Day 1; Visit 3), subjects who continue to meet all eligibility criteria, including placebo run-in drug compliance requirements, will be randomized via an interactive response technology (IRT) system to 1 of the following treatments: TAK-831 50 mg QD, TAK-831 125 mg QD, TAK-831 500 mg QD, and placebo QD. Randomization will be followed by a 12-week Double-Blind Treatment Period (Days 1 to 84), during which subjects will undergo assessments as outlined in Protocol Appendix A. Efforts will be made to perform cognition testing at approximately the same time of day throughout the Double-Blind Treatment Period (postbaseline assessments must be administered ±2 hours from the time of Baseline assessment

administration). A Safety Follow-up Visit (between Days 94 and 98; Visit 11) will be scheduled for all subjects 10 to 14 days after the last dose of study drug.

[redacted]

Subjects will be instructed to take 5 tablets QD during the Single-Blind Placebo Run-in and Double-Blind Treatment Periods, during which time study drug compliance will be monitored with a mobile technology system. Subjects will be instructed to take their study drug with water or milk and to avoid drinking juices 1 hour before and 1 hour after taking study drug.

Subjects who have been screened but have exceeded the 28-day screening period may proceed to the placebo run-in visit after a discussion with the sponsor/designee to obtain approval and to determine whether any screening procedures should be repeated before that study visit.

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.

In the event that a subject prematurely discontinues the study, an Early Termination Visit must be conducted, at which time all the assessments scheduled for the Final Visit will be performed.

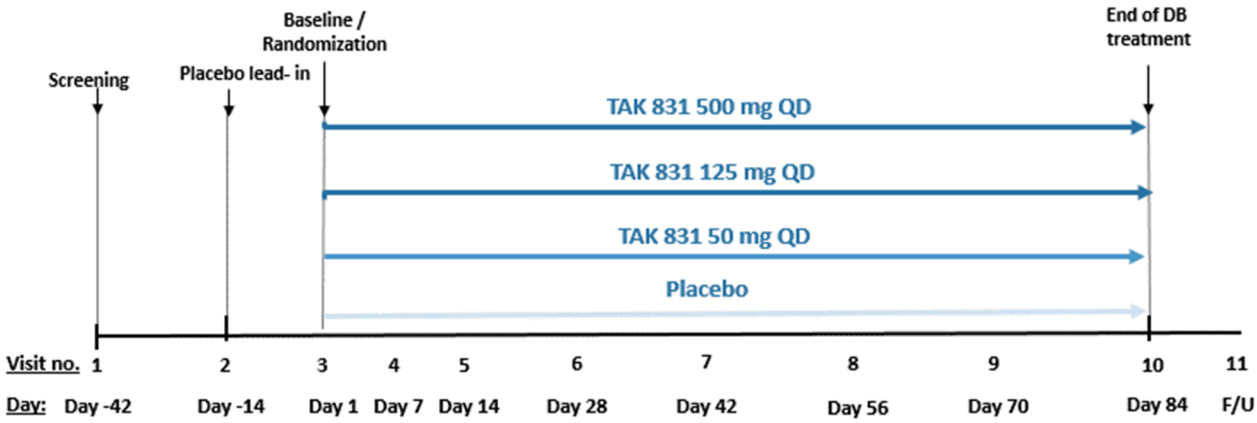
An interim analysis for futility may be performed during the study, allowing for early study termination if the probability of success on the primary endpoint fails to meet a prespecified criterion. The specifics of this analysis will be included in an interim analysis plan that will be finalized before interim unblinding.

The end of the study is defined as the date the last subject completes the Safety Follow-up Visit (Visit 11).

Permuted block randomization will be used. The randomization will be stratified by age at Screening (<35 and ≥35 years of age). The allocation ratio will be 2:2:2:3 to the 3 TAK-831 arms and placebo arm respectively.

A schematic of the study design is included as Figure 4.a.

Figure 4.a Schematic of Study Design



5.0 ANALYSIS ENDPOINTS

Baseline is defined as the assessment prior to dosing on Day 1 for all assessments other than the [redacted] where Baseline is defined as the Day -14 assessment.

5.1.1 Primary Endpoint

- Change from Baseline on the PANSS NSFS at Day 84.

5.1.2 Secondary Endpoints

- Change from Baseline on the PANSS NSFS at Days 28 and 56.
- Change from Baseline on the BNSS at Day 84.
- Change from Baseline on the BACS composite score at Day 84.
- Change from Baseline on the CGI-SCH-S score at Day 84.
- CGI-SCH-I score at Day 84.
- Change from Baseline on the SCoRS at Day 84.
- Change from Baseline on the PANSS total score and additional subscales and factors at Day 84.
- TAK-831 plasma concentrations.

5.1.3 Safety Endpoints

- Percentage of subjects who experience at least 1 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 electrocardiogram (ECG) parameters at least once postdose.
- Percentage of subjects with treatment-emergent suicidal ideation or suicidal behavior as measured using the C-SSRS.

5.1.4 [redacted]

[redacted]

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Assuming that the effect size is at least 0.4 for the as 125 mg QD and 500 mg QD doses and that at least 85% of the 234 subjects complete the Day 84 assessment, the study has at least 82% power for at least 1 dose to be statistically significant at the 0.10 level with correction for multiple doses.

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.

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

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 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.

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.

7.2 Study Definitions

7.2.1 Definition of Study Days

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

7.2.2 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.

7.2.3 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 the double-blind study medication. 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 of study medication, 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 of double-blind study medication 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 of double-blind study medication or the stop date is prior to the first dose of study medication, then January 1st will be used for 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 of double-blind study medication and the stop date is not prior to the date of first dose, then the date of first dose will be used for start date.

7.2.4 Conventions for Missing Concomitant Medication Dates

Missing concomitant medication dates will not be imputed. Also see Section 7.7.

7.2.5 Pooling of Sites

The study team has reviewed the data in blinded fashion and decided to group sites into the following two groups: European sites and Non-European sites.

7.2.6 Protocol Deviations

Significant protocol deviations will be summarized, and all protocol deviations will be listed. A sperate listing will be created for protocol deviations due to COVID-19.

Important Protocol Deviations (IPD) are those, which have the potential to influence the outcome of the primary analysis and therefore, will be used to define the Per Protocol Set. Along with other protocol deviations, the IPD will include subjects that had < 75% compliance between visits for more than one occasion during the study, as assessed via the digital compliance technology. Those noncompliant subjects will be listed.

Additional important protocol deviations may also be identified prior to unblinding. If so, the additional important protocol deviations will be finalized and documented prior to database lock and used for deleting subjects from FAS set to define the Per Protocol Set. Important protocol deviations will also be summarized in a table by treatment groups and overall, and presented in the CSR. Also, important protocol deviations will be marked in the protocol deviation listing.

7.3 Analysis Sets

The Full Analysis Set (FAS) will include all subjects who were randomized and received at least 1 dose of the study drug during the Double-Blind Treatment Period. In FAS summaries, subjects will be analyzed by the treatment to which they were randomized.

The Per Protocol Set (PPS) will include all subjects in the FAS excluding those who had important protocol deviations.

The Safety Analysis Set will include all randomized subjects who received at least 1 dose of double-blind study drug. In safety summaries, subjects will be analyzed according to the treatment they received.

The PK Analysis Set will include all randomized subjects who received at least 1 dose of double-blind study drug and who have any available TAK-831 plasma concentration data.

The PD Analysis Set will consist of all subjects who received at least 1 dose of study drug and have at least 1 postdose PD (plasma D-serine and L-serine) measurement.

7.4 Disposition of Subjects

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

Summaries will be presented by treatment arm, TAK-831 overall and overall.

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 treatment.
- Subjects who prematurely discontinued study.

Primary reasons for discontinuation of study treatment or study will be entered on the electronic case report form (eCRF), will be tabulated. Reasons for premature discontinuation of study an and/or study treatment include death, adverse event, protocol deviation, lost to follow-up, withdrawal by subject, study termination by sponsor, pregnancy, lack of efficacy, noncompliance with study drug during the double-blind period, significant risk of suicide, 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. Subjects who enter the Single-Blind Run-in Period but are not randomized, e.g., due to noncompliance with single-blind treatment, will be included as screen failures.

7.5 Demographic and Other Baseline Characteristics

Demographics and other Baseline characteristics including age, gender, race, body mass index, and medical history will be listed and summarized by treatment group and overall based on the FAS. Number of subjects by country and age category will be summarized.

Baseline values for efficacy assessments will also be summarized by treatment group and overall based on the FAS.

7.6 Medical History and Concurrent Medical Conditions

Medical and psychiatric history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the condition/disease under study that stopped at or prior to informed consent, specifically psychiatric history, including number of previous hospitalizations (lifetime and in past year), duration of each hospitalization (in the past year), and age of initial diagnosis of schizophrenia. Ongoing medical or psychiatric conditions are considered concurrent medical conditions.

Medical history and concurrent medical conditions will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA, version 19.0) and will be summarized by treatment group and overall using System Organ Class (SOC) and MedDRA preferred term. The table will include number and percentages of subjects and will be sorted in alphabetical order by system organ class and preferred term. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms. Summaries will be based on the safety analysis set.

All medical history and concurrent medical condition data will be presented in listings.

7.7 Medication History and Concomitant Medications

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent.

Concomitant medication is any drug given in addition to the study drug. If it is not possible to determine algorithmically from the reported data whether a medication was concomitant, it will be assumed to be concomitant.

Medication history and concomitant medications will be coded using the latest version of the World Health Organization (WHO, Version 01March2015) Drug Dictionary and summarized by giving the number and percentage of subjects by preferred term within each therapeutic class, with therapeutic class and medications in each class sorted in alphabetical order. The total number of subjects with medications in each selected therapeutic class will also be presented. If a subject reports taking 2 drugs belonging to the same class, he/she will only be counted once within that class. Summaries of medication history and concomitant medication will be based on the safety analysis set.

All prior and concomitant medications data will be presented in listings.

7.8 Study Drug Exposure and Compliance

Duration of exposure to double-blind study medication is defined as (date of last dose – date of first dose +1). It will be summarized as a continuous variable.

Study medication data will be collected by the study digital compliance technology and also by the number of tablets returned. The primary method of assessing compliance will be the digital technology.

The percentage of study drug compliance will be defined in two ways:

1) Using the digital compliance technology, as {(number of tablets recorded as taken) / [5*(date of last dose – date of first dose +1)]}x 100%,
2) Using number of returned tablets, {(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 (<75%, 75 to 125%, and >125%) 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).

7.9 Efficacy Analysis

The analyses and summaries for efficacy will be based on the FAS, unless otherwise noted.

7.9.1 Primary Efficacy Endpoint(s)

The primary endpoint is the change from Baseline on the PANSS NSFS at Day 84. The details of PANSS NSFS calculation can be found in Section 7.9.4.

The primary endpoint will be analyzed by comparing TAK-831 and placebo over all assessed time points using estimates from a mixed model for repeated measures (MMRM) with Baseline value as a covariate; pooled site, visit, treatment, and categorical age (randomization factor) as fixed factors; and treatment-by-visit and Baseline-by-visit interactions. 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 treatment is allowed to vary freely and an unstructured covariance matrix is assumed. If the model does not converge, other covariance structures (unstructured, compound symmetry, 2-Toeplitz, etc) will be considered.

Multiplicity will be controlled across dose-arms by first testing the 125 mg QD and 500 mg QD dose-arms in parallel using Holm's method to control the overall type I error rate at the 0.10 level (one-sided), then testing the 50 mg QD dose-arm at the 0.10 level if at least 1 of other doses is found to be statistically superior to placebo.

In order to provide additional insight about dose-response, the primary endpoint may be analyzed using a Multiple Comparison Procedure-Modeling (MCP-Mod) approach (Pinheiro et al, 2014).

For MCP-Mod approach, DoseFinding package in R statistical analysis software will be used. R has been validated by the contract research organization for this study. The following set of models will be fit to detect a dose response: linear, E_{max}, quadratic, and exponential. The stratification factor of age (<35 and ≥35 years) will be included in the models. Each of the dose-response shapes in these models will be evaluated using optimal contrasts and applying MCP-Mod techniques to preserve the family-wise error rate (FWER) with the overall 1-sided significance level of 0.10. The effective dose(s) will be determined within this framework. The stratification factor of age may be omitted if the dose response for the stratified models cannot be reliably estimated.

The following supplementary analyses will also be conducted for the primary endpoint:

1) A method for missing value imputation based on pattern mixture models (PMM) using standard SAS STAT procedures. It is assumed that after discontinuation from the study, subjects receiving a TAK-831 dose will exhibit the same future evolution of the disease as subjects on the placebo treatment. The missing PANSS NSFS scores in the TAK-831 dose arm will be imputed using placebo-based pattern mixture models. This method uses sequential regression and multiple imputation methodology to impute missing values for visits after a subject's discontinuation from the study in the placebo arm. Then based on the available data from placebo subjects, the missing values from active treatment arm will be imputed using pattern mixture models until missing values at all visits are imputed.
2) The primary endpoint also be analyzed using analysis of covariance (ANCOVA), with pooled center, stratification factor, and treatment as fixed factors, and PANSS NSFS Baseline score as a covariate. ANCOVA based on the multiply-imputed data will be performed.

As a supportive analysis, the primary endpoint will be analyzed using MMRM in the same manner as described in section 7.9.1, but based on the PPS.

7.9.2 Secondary Efficacy Endpoint(s)

Other continuous change from Baseline endpoints will be analyzed using MMRM in the same manner as the primary endpoint (as described in section 7.9.1), but without control for multiple doses.

The change from Baseline on the BNSS total (12-item, excluding item 4) will be analyzed using MMRM in the same manner as the primary endpoint, but without control of multiple doses. The same analysis will be repeated on the change of Baseline on the BNSS total (13-item).

The change from Baseline on the CGI-SCH-S at Day 84, and the CGI-SCH-I score at Day 84 will be analyzed using a Cochran-Mantel-Haenszel test. This analysis will be stratified by age and performed using observed cases only.

7.9.3 [redacted]

[redacted]

7.9.4 Analysis of PANSS Subscales and factors using the Marder Five-factor Model

The PANSS consists of 30 items across 3 subscales: positive symptoms (items P1-P7), negative symptoms (items N1-N7), and general psychopathology (items G1-G16). In addition, 5 factors are calculated by the Marder five-factor model [2]. The five factors are: (1) negative symptoms,

(2) positive symptoms, (3) disorganized thought, (4) uncontrolled hostility/excitement and (5) anxiety/depression. The items included in each factor are listed in Appendix E.

PANSS subscales/ factors will be calculated by summing the individual items within each subscale/factor. For example, PANSS NSFS will be calculated by summing the individual items within the negative symptoms factor.

The PANSS total score will be calculating by summing the 30 individual items. If individual items are missing, the following rule will be used: PANSS total = sum of (non-missing items) × 30] / (# non-missing items)], rounded to the nearest integer. If more than 5 of the items are missing, the PANSS total will be set to missing.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

Plasma concentrations of TAK-831 will be listed for each subject and summarized by each time point for each dose 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 (D- or L-serine plasma levels and/or selected measures of efficacy) 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. Additional details will be specified in a separate analysis plan.

7.10.2 Pharmacodynamic Analysis

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 using descriptive statistics. In addition, mixed effects regression models will be fitted to the change from Baseline in these concentrations. Pairwise comparisons between the test regimens (TAK-831 doses and placebo) will be made and the CIs for the difference in the LS means will be constructed for selected time points.

7.11 Other Outcomes

The analysis of the [redacted] will be described in a separate analysis plan.

7.12 Safety Analysis

7.12.1 Adverse Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with

study participation. Placebo administered during the Single-Blind Placebo Run-in Period is not considered study drug for the purpose of this definition or for defining an AE.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. In the protocol, this is also referred to as a treatment-emergent adverse event.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. To be included in summary tables, they must occur with 30 days (onset date – last date of dose + 1 ≤30) after the last dose of study drug or early termination.

AEs are recorded in the eCRF as being related or not related to study drug and/or study procedure. AEs that are recorded as related to study drug and/or study procedure will be summarized separately. AEs will also be presented by intensity/severity (mild, moderate, and severe). Serious AEs, AEs leading to study drug discontinuation, and AEs leading to death will also be summarized using SOC and PT.

When calculating the frequency and percentage of subjects who reported AEs, a subject will be counted only once for each SOC or PT when multiple AEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple AEs coded to the same SOC or PT, the AE with maximum intensity or strongest relationship will be included in the summary.

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
- Treatment-Emergent Adverse Events by Preferred Term
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- 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
- Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

- Drug-Related Treatment-Emergent Adverse Events by Preferred Term
- Most Frequent (> 5% in Any Treatment Arm) Non-Serious 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

In addition, subject mappings for the AEs by SOC and PT will be generated. For this study, Treatment-Emergent Adverse Event (TEAE) is synonymous with AE.

Data listings will be provided for PTEs, AEs, AEs leading to study drug discontinuation, liver function abnormalities, SAEs, and AEs that resulted in death. AEs happened after 3 days post the last dose of the study drug will be listed as well.

7.12.2 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 9.1.10 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 in both SI units and conventional (CV) units. For test results not in SI units, the conversion to SI units will be done in the derived Study Data Tabulation Model (SDTM) and Analysis Data Model (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. 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. Study baseline 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. 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 clinical safety laboratory data will be provided in Appendix 16.2 and will be presented in both SI and CV units. 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 group, study visit, and sample collection date.

7.12.3 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. Only observations within 3 days of the study drug will be included in the tables.

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. 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.

Orthostatic hypotension, identified by the criteria defined in Appendix C, will be calculated at every time point where standing and supine measurements are available using the formula: standing vital measurement – supine vital measurement. The mapping of the subjects who meet the criteria for orthostatic hypotension will be listed by study visit as a table. All orthostatic hypotension observations, including ones at unscheduled visits, will be included in the subject mappings.

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 group, study visit, and sample collection date.

7.12.4 12-Lead ECGs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters, including heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (Fredericia's and Bazett's corrections), will be presented for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Only the scheduled measurements will be included in the summary. Only observations within 3 days of the study drug will be included in the tables. No inferential statistics will be presented.

ECG MAVs, identified by the criteria defined in Appendix D, will be tabulated. If a subject has a MAV for a particular 12-lead ECG 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 12-lead ECG measurement will be summarized. 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.

Overall ECG interpretation category (normal, abnormal not clinically significant, abnormal clinically significant) is collected by eCRF at baseline and at each scheduled post-baseline visit. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations with missing, if applicable, and total categories by regimen.

Listings of all 12-lead ECG data will be provided in Appendix 16.2. MAVs will be flagged in the listings. The listing will include site number, subject identifier, age, gender, treatment group, study visit, and sample collection date.

7.12.5 Other Observations Related to Safety

The modified Simpson Angus Scale and C-SSRS will be summarized at all time points for each treatment group and TAK-831 total and overall total using descriptive statistics.

7.13 Interim Analysis

An interim analysis for futility may be performed during the study, allowing for early study termination if the probability of success on the primary endpoint fails to meet a pre-specified criterion. The specifics of this analysis will be included in an interim analysis plan that will be finalized before interim unblinding.

7.14 Changes in the Statistical Analysis Plan

Considering the potential impact of noncompliant subjects, a supportive analysis on the primary endpoint based on PPS described in section 7.9.1 is added.

Section 7.2.5 is updated to provide details on site pooling method.

A separate listing for protocol deviations due to COVID-19 is added.

In section 7.9.2, clarification is added to describe the analyses on BNSS total (12-item, excluding item 4) and BNSS total (13-item).

Typographical errors are corrected.

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 Identification of Markedly Abnormal Orthostatic Changes

Parameter	Criteria
Orthostatic Hypotension	(Orthostatic Systolic Blood Pressure < -20 mm Hg OR Orthostatic Diastolic Blood Pressure < -10 mm Hg) AND Heart Rate Increase > 20 beats/min

Note: Orthostatic measurement = standing vital measurement – supine vital measurement.

Appendix D 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

Appendix E PANSS Items Included in Each Factor using the Marder Five-Factor Model

Factor	Item (Item Number)
1. Negative symptoms	Blunted affect (N1)
	Emotional withdrawal (N2)
	Poor rapport (N3)
	Passive/apathetic social withdrawal (N4)
	Lack of spontaneity and flow of conversation (N6)
	Motor retardation (G7)
	Active social avoidance (G16)
2. Positive symptoms	Delusions (P1)
	Hallucinatory behavior (P3)
	Grandiosity (P5)
	Suspiciousness/persecution (P6)
	Stereotyped thinking (N7)
	Somatic concern (G1)
	Unusual thought content (G9)
	Lack of judgement and insight (G12)
3. Disorganized thought	Conceptual disorganization (P2)
	Difficulty in abstract thinking (N5)
	Mannerisms and posturing (G5)
	Disorientation (G10)
	Poor attention (G11)
	Disturbance of volition (G13)
	Preoccupation (G15)
4. Uncontrolled hostility/ excitement	Excitement (P4)
	Hostility (P7)
	Uncooperativeness (G8)
	Poor impulse control (G14)
5. Anxiety/depression	Anxiety (G2)
	Guiltfeelings (G3)
	Tension (G4)
	Depression (G6)

8.0 REFERENCES

1. Pinheiro, J., Bornkamp, B., Glimm, E. and Bretz, F. (2014), Model‐based dose finding under model uncertainty using general parametric models. Statist. Med., 33: 1646-1661. doi:10.1002/sim.6052
2. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58(12):538-46.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	[redacted]	03-Feb-2021 02:01 UTC