TAKEDA PHARMACEUTICALS

PROTOCOL

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

A Study of 3 Doses of TAK-831 as an Adjunctive Treatment for Negative Symptoms of Schizophrenia

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd
40 Landsdowne Street
Cambridge MA 02139
USA

Study Number: TAK-831-2002

IND Number: 135,176 **EudraCT Number:** 2017-003471-54

Compound: TAK-831

Date: 08 June 2020 **Amendment Number:** 04

Amendment History:

Date	Amendment Number	Amendment Type	Region
30 October 2017	Initial Protocol	Not applicable	Global
26 June 2018	Amendment 01	Substantial	Global
19 July 2018	Amendment 02	Substantial	Local (Czech Republic)
13 March 2019	Amendment 03	Substantial	Global
08 June 2020	Amendment 04	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda-sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America Contact	Europe Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc Fax: +1-224-554-1052 Email: PVSafetyAmericas@tpna.com	Pharmacovigilance Takeda Development Center Europe, Ltd Fax: +44-207-242-1820 Email: eupv@tgrd.com
Medical Monitor (medical advice on protocol and study drug)	[redacted] IQVIA US: [redacted] Mobile: [redacted] Email: [redacted]	[redacted] IQVIA Mobile: [redacted] Email: [redacted]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted] Takeda Development Center Americas, Inc Office: [redacted] Mobile: [redacted] Email: [redacted]	[redacted] Takeda Development Center Americas, Inc Office: [redacted] Mobile: [redacted] Email: [redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic signatures are provided on the last page of this document.

[redacted] Date [redacted] Date

[redacted] Date [redacted] Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment No. 04 Summary of Changes and Rationale

Rationale for Amendment No. 04

This section describes the changes in reference to the protocol incorporating Amendment No. 04. The primary reason for this amendment is to describe management of study procedures (eg, alternative strategies for collecting data, conducting study visits and distributing investigational product) during unexpected, unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) such as the coronavirus disease 2019 (COVID-19) pandemic.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

A history of TAK-831-2002 protocol amendments 01 through 03 is provided in Appendix E.

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
1. Updated medical monitor and responsible medical officer contact information and names and titles of approval signatories.	To update contact information for medical monitors, the responsible medical officer, and names and titles of signatories who will approve this protocol amendment.	Sections: 1.1 Contacts 1.2 Approval
2. Added guidance regarding rescreening of potential subjects who discontinued during screening or the single-blind run-in due to COVID-19 related factors.	To allow for rescreening of subjects who were discontinued during screening or single-blind run-in period due to COVID-19 outbreak related factors. Sponsor made decision to ask sites to discontinue subjects due to uncertainty related to impact of COVID 19 outbreak on human activities in communities and at study sites. Because these subjects may have been qualifiable for the study otherwise, sponsor agrees for these subjects to be rescreened.	Section 6.1 Study Design
3. Added COVID-19-related guidance to criteria for discontinuation or withdrawal of a subject.	To ensure that subject discontinuations due to COVID-19 related factors are documented in ways that best fit within the categories previously supplied.	Section 7.6 Criteria for Discontinuation or Withdrawal of a Subject (Reasons number 4 and 11)

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
4. Added guidance regarding supply of study drug to study subjects during unavoidable circumstances such as the COVID-19 pandemic.	To provide flexibility for sites to provide subjects with drug supply in situations where traveling to the site or presenting at the site may present a risk to health or well-being of subjects.	8.2 Study Drug Assignment and Dispensing Procedures
5. Added section with guidance on alternative approaches to executing study procedures and collecting study data due to COVID-19 or other unavoidable circumstances.	To eliminate apparent hazards to participants by providing flexibility in administration of study procedures during unavoidable circumstances such as the COVID-19 pandemic.	Sections: 9.1.1 Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 or Other Unavoidable Circumstances, 9.1.10 Efficacy Measurements
6. Corrected a typographical error in guidance for female subjects and women of childbearing potential for female subjects.	To correct a typographical error.	Section 9.1.17.3 Definitions and Procedures for Contraception and Pregnancy Avoidance
7. Added COVID-19-related guidance for informed consent procedures.	To ensure informed consent procedures are in accordance with all applicable laws and regulations.	Section 9.1.2 Informed Consent Procedure
8. Added COVID-19-related guidance for documentation of screen and randomization failure.	To ensure that reasons for screen failure or randomization failure due to COVID-19 related factors are documented.	Sections: 9.1.20 Documentation of Screen Failure 9.1.21 Documentation of Randomization Failure.
9. Added clarification to text regarding documentation of pretreatment events (PTE)/adverse events (AEs).	Original author of protocol inadvertently deleted the abbreviation PTE from this text which describes how PTE/AE data are to be collected in the database. This is a typographical error and does not indicate a change in process.	Section 10.2.1.2 PTE and AE Reporting

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
10. Added COVID-related terms to the table of Takeda Medically Significant AEs.	To comply with Takeda Global Patient Safety Evaluation guidance on the medically significant AE list.	Table 10.a Takeda Medically Significant AEs
11. Updated serious adverse event (SAE) reporting guidance.	Text was revised per a new Takeda process for SAE reporting that includes an acknowledgment of receipt for information sent via fax or email.	Section 10.2.2 Collection and Reporting of SAEs
12. Added guidance for analysis of data impacted by COVID-19.	To provide guidance regarding analysis of data impacted by COVID-19 in terms of completeness or collection modality.	Section 13.1.3 Efficacy Analysis
13. Added COVID-19-related guidance for protocol deviations.	To further clarify that on occasion unexpected circumstances such as COVID-19 pandemic will require a deviation from protocol-specified procedures and investigators should consult with sponsor regarding these kinds of protocol deviations.	Section 14.3 Protocol Deviations
14. Added guidance in case of a delay in delivery of screening laboratory test results due to unavoidable circumstances such as the COVID-19 pandemic	To allow flexibility during unavoidable circumstances such as the COVID-19 pandemic to extend the Visit 3 (randomization) window for a maximum of 7 days in case of a delay in delivery of screening laboratory test results needed to determine subject eligibility.	Appendix A Schedule of Study Procedures, footnote b
15. Extended visit window for final visit (Day 84/End of Treatment [ET]).	To allow flexibility during unavoidable circumstances such as the COVID-19 pandemic for subjects to return to site for final visit assessments which are critical for the primary endpoint and key secondary endpoint analyses.	Appendix A Schedule of Study Procedures, Visit Window

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
16. Added clarification to footnote b in Schedule of Study Procedures regarding conduct of final visit (Day 84/ET) in unavoidable circumstances such as the COVID-19 pandemic.	To emphasize the importance of performing the final visit (Day 84/ET) in person and the need to contact the sponsor or designee to discuss individual subject circumstances if it may not be feasible due to unavoidable circumstances such as the COVID-19 pandemic.	Appendix A Schedule of Study Procedures, footnote b
17. Added footnote describing conduct of study visits during unavoidable circumstances such as the COVID-19 pandemic.	To eliminate apparent hazards to participants by providing flexibility in administration of study procedures during unavoidable circumstances such as the COVID-19 pandemic.	Appendix A Schedule of Study Procedures

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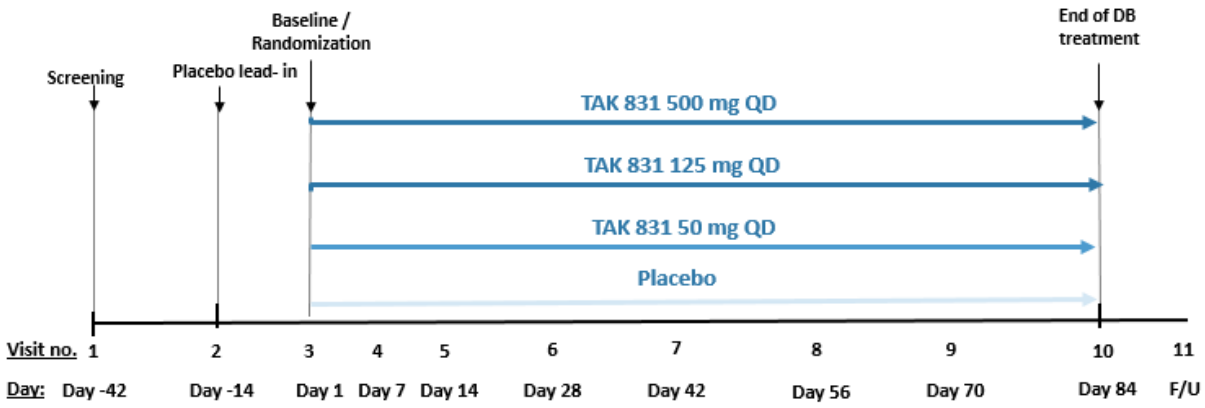
2.0 STUDY SUMMARY

<table>
<tr><td>Name of Sponsor:
Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd
40 Landsdowne Street
Cambridge MA 02139
USA</td><td colspan="2">Compound:
TAK-831</td></tr>
<tr><td>Title of Protocol: 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</td><td>IND No.:
135,176</td><td>EudraCT No.:
2017-003471-54</td></tr>
<tr><td>Study Number: TAK-831-2002</td><td colspan="2">Phase: 2</td></tr>
<tr><td colspan="3">Study Design:
This is a randomized, double-blind, parallel, placebo-controlled, phase 2 study to evaluate the efficacy, safety, tolerability, and pharmacokinetics (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 up to 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, and undergo other screening assessments. Subjects must be currently receiving stable treatment on 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. 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 Brief Negative Symptom Scale (BNSS) total score (12-item, excluding item number 4) ≥28 and limited Positive and Negative Syndrome Scale (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. Confirmation that the subject meets these and other selected entry criteria will be provided by an external subject eligibility assessment vendor based on review of data from the screening visit.
The 2-week single-blind placebo run-in period will be used to evaluate compliance with study drug intake and stability of the BNSS assessment. At baseline (predose Day 1), subjects who continue to meet all eligibility criteria, including placebo run-in drug compliance requirements, will be randomized to 12 weeks of double-blind oral treatment with TAK-831 (T2 tablet formulation) or matching placebo.</td></tr>
</table>

Schematic of Study Design



Primary Objective:

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).

Secondary Objectives:

- To determine whether add-on TAK-831 is superior to placebo on the 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 PANSS total score and additional subscales and factors.
- To assess the safety and tolerability of TAK-831.
- To assess the PK of TAK-831.

Subject Population: Male or female subjects, between 18 and 60 years of age, inclusive, with a diagnosis of schizophrenia with persistent negative symptoms of schizophrenia.

Number of Subjects:	**Number of Sites:**
Approximate number of subjects per treatment group: TAK-831 50 mg QD: 52 TAK-831 125 mg QD: 52 TAK-831 500 mg QD: 52 Placebo QD: 78 Estimated total: 234 randomized	Approximately 48 sites in North America and Europe

Dose Levels:	**Route of Administration:**
TAK-831 50 mg QD TAK-831 125 mg QD TAK-831 500 mg QD Placebo QD	Oral
Duration of Treatment:	**Period of Evaluation:**
12 weeks	Approximately 20 weeks from screening visit to final visit (4 weeks of screening, a 14-day single-blind placebo run-in period, 12 weeks of double-blind treatment, and 10 to 14 days of follow-up).

Main Criteria for Inclusion:

- The subject has a current diagnosis of schizophrenia as defined by the MINI 7.0.2 for Psychotic Disorders for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the general psychiatric evaluation.
- The subject's initial diagnosis must be ≥1 year from screening.
- The subject is male or female and aged 18 to 60 years, inclusive.
- The subject is receiving primary background antipsychotic therapy (other than clozapine) at a total daily dose between 2 mg and 6 mg of risperidone equivalents (as outlined in an Antipsychotic Reference document). Concomitant treatment with a subtherapeutic dose of a second antipsychotic may be permitted with sponsor or designee approval if used to treat specific symptoms such as insomnia, but not if it is used for refractory positive psychosis symptoms.
- The subject is treated with a stable regimen of psychotropic medications with no clinically meaningful change (no increase in dose, ≤25% decrease in dose for tolerability) in the 2 months prior to the screening visit and no dose adjustment is anticipated throughout study participation up to the Day 84/early termination visit.
- The subject has a BNSS total score (12-item, excluding number 4) ≥28; stable single-blind placebo run-in and baseline BNSS total (12-item, excluding number 4) scores (≤20% change from the screening score).
- The subject has no more than moderate-severe (≤5) rating on PANSS positive symptom items P1, P3, P4, P5, P6, or unusual thought content (G9), with a maximum of 2 of these items rated "5"; no more than moderate (≤4) rating on conceptual disorganization (P2).
- There is evidence that the subject has stable symptomatology ≥3 months prior to the screening visit (eg, no hospitalizations for schizophrenia, no emergency room admission due to symptoms of schizophrenia, no increase in level of psychiatric care due to worsening of symptoms of schizophrenia).
- The subject must have an adult informant who will be able to provide input for completing the study rating scales including the PANSS and SCoRS (eg, family member, social worker, caseworker, residential facility staff, or nurse who spends ≥4 hours/week with the subject) considered reliable by the investigator.

Main Criteria for Exclusion:

- The subject has a lifetime diagnosis of schizoaffective disorder; a lifetime diagnosis of bipolar disorder; or a lifetime diagnosis of obsessive compulsive disorder based on the MINI combined with the general psychiatric evaluation. As an exception, subjects with a historical prior lifetime diagnosis of schizoaffective disorder may be enrolled in the study with sponsor or designee approval provided that the principal investigator can attest that the subject's overall history and current clinical presentation and history is most consistent with schizophrenia, not schizoaffective disorder.
- The subject has a recent (within the last 6 months) occurrence of panic disorder, depressive episode, or other comorbid psychiatric conditions currently requiring clinical attention based on the MINI for DSM-5 and the general psychiatric evaluation.
- The subject has a diagnosis of substance use disorder (with the exception of nicotine dependence) within the preceding 6 months based on the MINI for DSM-5 and the general psychiatric evaluation.
- The subject is participating in a formal structured nonpharmacological therapeutic treatment program (cognitive

remediation, cognitive-behavioral therapy, intensive symptom/vocational rehabilitation) for <3 months prior to randomization. In addition, initiation of such nonpharmacological treatment programs is not permitted during study participation through the Day 84 visit.
- The subject exhibits more than a minimal level of antipsychotic-induced parkinsonism symptoms, as documented by a score on the modified Simpson Angus Scale (SAS) (excluding item number 10, Akathisia) >6.
- The subject has evidence of depression as measured by a Calgary Depression Scale Score (CDSS) >9.
- The subject's diagnosis of schizophrenia occurred prior to 12 years of age.
- The subject has a history of developmental intellectual disability or mental retardation.
- Antipsychotic plasma levels for the subject's primary background antipsychotic are below the minimum acceptable concentration criteria per the Antipsychotic Reference document at the screening or placebo run-in visits. This criterion is not applicable to subjects on a primary background antipsychotic for which a clinical assay is unavailable (ie, not listed in the Antipsychotic Reference document).
- The subject is taking concomitant treatment that can impact cognition as determined by the principal investigator in consultation with the sponsor or designee.

Main Randomization Criteria:

The subject must continue to meet all of the inclusion criteria and none of the exclusion criteria at the time of the baseline visit (Day 1; Visit 3). The subject has completed the single-blind placebo run-in period and has met the study drug compliance criteria (75% to 125%) as assessed using the digital compliance technology.

Main Criteria for Evaluation and Analyses:

Baseline is defined as the assessment prior to dosing on Day 1.

Primary Endpoint:

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

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.

Safety Endpoints:

- Percentage of subjects who experience at least 1 treatment-emergent adverse event.
- 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 parameters at least once postdose.
- Percentage of subjects with treatment-emergent suicidal ideation or suicidal behavior as measured using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Statistical Considerations:

Primary Efficacy Analysis

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. Additional analyses to address sensitivity to missing data will be specified in the statistical analysis plan.

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 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.

Secondary Efficacy Analyses

Other change from baseline endpoints will be analyzed in the same manner as the primary endpoint, but without control for multiple doses. 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.

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.

Sample Size Justification:

Assuming that the effect size is at least 0.4 for the 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.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor (or designee) will perform all study-related activities with the exception of those identified in the Clinical Study Supplier template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research, as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and, by doing so, agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
anti-HCV	antibody to hepatitis C virus
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_t	area under the plasma concentration-time curve from time 0 to time t
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
$AUEC_{24}$	area under the effect curve from time 0 to 24 hours
BACS	Brief Assessment of Cognition in Schizophrenia
BMI	body mass index
BNSS	Brief Negative Symptom Scale
CDSS	Calgary Depression Scale Score
CFR	Code of Federal Regulations
CGI-SCH	Clinical Global Impression-Schizophrenia
CGI-SCH-I	Clinical Global Impression-Schizophrenia-Improvement
CGI-SCH-S	Clinical Global Impression-Schizophrenia-Severity
CIAS	cognitive impairment associated with schizophrenia
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DAO	D-amino acid oxidase
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EDC	electronic data capture
EIIB	eosinophilic intranuclear inclusion body
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GluRδ2	δ2 glutamate receptor
GPS	Global Positioning System

HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HPLC	high-performance liquid chromatography
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IQ-PANSS	Informant Questionnaire for the Positive and Negative Syndrome Scale
IRB	institutional review board
IRT	interactive response technology
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
MCP-Mod	Multiple Comparison Procedure Modeling
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
MRD	multiple-rising dose
[redacted]	[redacted]
NMDA	N-methyl-D-aspartate
PANSS	Positive and Negative Syndrome Scale
PANSS NSFS	Positive and Negative Syndrome Scale Negative Symptom Factor Score
PD	pharmacodynamic(s)
PET	positron emission tomography
[redacted]	[redacted]
PK	pharmacokinetic(s)
PT	preferred term
PTE	pretreatment event
QD	once daily
QHS	once daily at bedtime
QTcF	QT interval with Fridericia correction method
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SCoRS	Schizophrenia Cognition Rating Scale
SOC	system organ class
SOP	standard operating procedure
SRD	single-rising dose

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UGT	uridine 5′-diphospho-glucuronosyltransferase
ULN	upper limit of normal

3.4 Corporate Identification

TDC	Takeda Development Center
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Study Drug

TAK-831 is a highly selective and potent inhibitor of D-amino acid oxidase (DAO), a peroxisomal enzyme active toward neutral D-amino acids, being developed by Takeda. DAO is involved in D-serine metabolism in the brain and has been connected to the regulation of glutamatergic neurotransmission [1]. D-serine is generated from its stereoisomer, L-serine, by serine racemase in the brain, and is a potent *N*-methyl-D-aspartate (NMDA)–type glutamate receptor co-agonist and an agonist for the δ2 glutamate receptor (GluRδ2), which has been implicated in synaptic plasticity and long-term depression [2]. The presence of DAO has been identified in the cerebellum, brain stem, and other brain regions relevant to the pathophysiology of schizophrenia, and numerous studies have verified that endogenous and exogenous D-serine potentiate NMDA receptor function in these regions [1,3,4]. TAK-831 inhibition of DAO in the liver, kidney, and cerebellum leads to higher D-serine levels in the plasma and cerebellum in animal models. As such, TAK-831 has the potential to increase NMDA-dependent glutamatergic signaling via its impacts on D-serine–modulated neuronal activity.

4.1.2 Schizophrenia

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. The onset of the disease is usually in late adolescence or early adulthood. Schizophrenia affects up to 1% of the population and increases to 10% in individuals having a first-degree relative suffering from the disorder (40% to 65% for identical twins) [5-7]. Symptoms of schizophrenia can be subdivided into 3 broad classes: positive, negative, and cognitive symptoms [8]. Positive symptoms include hallucinations, delusions, and disordered thought and speech, and can be summarized as psychosis. Negative symptoms include reduced emotion, reduced ability to experience pleasure (anhedonia), lack of motivation, and reduced social interaction. Finally, cognitive symptoms include poor information processing, impaired ability to focus on objectives, and abnormalities of working memory and learning [8]. Deficits in glutamatergic transmission are hypothesized to play an important role in the pathophysiology of the disorder, particularly in relation to the genesis of cognitive impairment and negative symptoms, including anhedonia [9].

While currently available antipsychotics are broadly effective for the treatment of positive symptoms, the treatment of persistent negative symptoms and cognitive deficits of schizophrenia remains a major unmet medical need. These symptom domains are associated with poor functional outcomes to a greater degree than positive symptoms with currently available treatments [10,11], and there are no approved therapies. Thus, addressing these symptoms remains an important area of focus for the development of novel therapeutics.

Inhibition of DAO is a promising target for the treatment of schizophrenia. Hypofunction of NMDA receptors is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain [12]. Changes in the

D-serine levels or D-serine to total serine ratios have been reported in the plasma of patients with schizophrenia both naive to and undergoing drug treatment [13-16]. In addition, serine racemase (the D-serine generating enzyme) and the NMDA NR2A subunit are among the risk genes identified from the recent large-scale genome-wide association studies analysis, indicating the biological relevance to schizophrenia of the genetic pathway in which DAO is a component [17].

DAO is involved in D-serine metabolism in the brain and has been connected to the regulation of glutamatergic neurotransmission [1]. Inhibition of DAO elevates endogenous D-serine in the cerebellum, increasing Purkinje cell long-term depression via activation of GluRδ2 and/or NMDA receptors with subsequent α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor internalization [2].

Adding to the above evidence of a potential role of DAO in the pathophysiology of schizophrenia, a weak inhibitor of DAO, sodium benzoate, demonstrated efficacy in positive, negative, and cognitive symptoms in a proof-of-concept study in subjects with schizophrenia [18].

4.1.3 Clinical Background

The safety evaluations performed in the TAK-831 early clinical development program (Studies TAK-831-1001 and TAK-831-1003) allowed for the initial characterization and quantification of the safety profile of TAK-831 in healthy subjects. The first-in-human study TAK-831-1001 was designed to assess the pharmacokinetics (PK) of an oral suspension of TAK-831 and plasma D-serine levels after single-rising dose (SRD) and multiple-rising dose (MRD) administration of TAK-831, as well as the relative bioavailability and effect of food on the PK of the T1 tablet formulation of TAK-831. Study TAK-831-1003 was designed to evaluate DAO target engagement in the brain, as measured by positron emission tomography (PET), as well as assess plasma D-serine levels, TAK-831 plasma concentrations, and the safety of TAK-831.

TAK-831 has been administered to a total of 103 healthy subjects in these 2 studies; 74 subjects received single doses ranging from 10 to 750 mg and 29 subjects received multiple doses ranging from 30 to 400 mg once daily (QD) for up to 13 days. TAK-831 was safe and well tolerated at the doses studied in healthy subjects. Headache was the most common treatment-emergent adverse event (TEAE) potentially related to study drug. Headaches were mild to moderate in intensity and generally self-limiting. The rate of postural dizziness in TAK-831–treated subjects did not markedly differ from that observed in placebo-treated subjects. No concerning trends in clinical laboratory, electrocardiogram (ECG), or vital sign data were observed. Additional detail on the safety and tolerability data from these studies may be found in the current TAK-831 Investigator's Brochure.

After both single and multiple dosing with TAK-831 (Study TAK-831-1001), increases in the mean area under the effect curve from time 0 to 24 hours ($AUEC_{24}$) of D-serine were dose dependent; changes in D-serine were noticeably higher after multiple QD doses of TAK-831 400 mg than after multiple QD doses of TAK-831 30, 100, and 200 mg. Single oral doses of

TAK-831 temporally increased D-serine plasma concentrations in the PET study (TAK-831-1003); the results were similar to those obtained in Study TAK-831-1001.

Since these studies were conducted, dosing in a single-dose PK and food-effect bioavailability study with the T2 tablet formulation of TAK-831 has been completed (Study TAK-831-1004). Also, a study examining additional escalating multiple (QD) doses of TAK-831 higher than those achieved in Study TAK-831-1001 was initiated and is ongoing (Study TAK-831-1005).

Study TAK-831-1004 is a phase 1, randomized, open-label, single-dose, 2-period crossover study designed to characterize the PK and effect of food on the bioavailability of TAK-831 400 mg (administered as 4 × 100 mg oral T2 tablets) in 15 healthy adult subjects. In this study, only a single TEAE of mild upper respiratory tract infection was reported, considered by the investigator to be unrelated to study drug. One subject met the criteria for orthostatic hypotension at a single time point without an accompanying report of a dizziness TEAE. No concerning trends in clinical laboratory, ECG, or vital sign data were observed. When the TAK-831 T2 tablet formulation was coadministered with a nutritional drink (Ensure Plus), mean maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}) values were increased by 35% and 21%, respectively. Treatment with a single oral dose of TAK-831 400 mg T2 formulation temporally increased D-serine plasma concentrations, similar to the results obtained in Study TAK-831-1001. The magnitude and kinetics of the change in D-serine plasma concentrations were similar when the drug was administered in either water or nutritional drink.

Study TAK-831-1005 is an ongoing, investigator- and subject-blinded, sponsor-unblinded, placebo-controlled study designed to continue evaluation of the safety, tolerability, PK, and pharmacodynamics (PD) of escalating multiple (QD) doses of TAK-831 in healthy subjects at doses higher than those achieved in Study TAK-831-1001. The following data from this study are preliminary, being based on blinded AE data reported by the investigator and blinded safety endpoint data. Although not expected, these data are subject to change upon finalization following study monitoring, source data verification, and discrepancy query management before database lock. As of the cut-off date of 18 September 2017, 2 cohorts of 8 subjects each (6 TAK-831:2 placebo) have completed dosing with TAK-831 600 mg QD (T2 tablets), TAK-831 800 mg QD (oral suspension) or placebo, administered first as a single dose and then QD for up to 14 days. In addition to standard safety assessments, subjects underwent catheterized cerebrospinal fluid (CSF) collection for a 24-hour period starting before dosing on Day 1 of single-dose treatment and on Day 14 of multiple-dose treatment. Nausea and postlumbar puncture syndrome were the most commonly reported TEAEs; nausea in the absence of postlumbar puncture syndrome was reported by 1 subject in each cohort. All episodes of nausea were mild in intensity and self-limiting. Two subjects in each cohort met the criteria for orthostatic hypotension on at least 1 assessment; none of these findings were associated with a TEAE of dizziness. No concerning trends in clinical laboratory, ECG, or vital sign data were observed for these cohorts.

Following QD dosing, mean plasma exposures of TAK-831 were higher (C_{max}: 1.3-fold and area under the plasma concentration-time curve [AUC]: 1.8-fold) when dosed as an oral suspension

than as T2 tablets. Geometric mean C_{max} values were 1466 and 1976 ng/mL with 600 mg QD (T2 tablets) and 800 mg QD (oral suspension), respectively. Mean steady-state exposures (area under the plasma concentration-time curve from time 0 to time t [AUC_t]) over the 24-hour dosing interval were 4993 and 8853 h*ng/mL for the 600 and 800 mg QD doses, respectively. The mean 24-hour PK profile of TAK-831 in CSF was parallel to that in plasma, and observed TAK-831 CSF concentrations were well in agreement with the TAK-831 unbound fraction in plasma. After both single and multiple dosing with TAK-831 600 mg (T2 tablets) and 800 mg (oral suspension), the mean $AUEC_{24}$ of D-serine in CSF increased notably compared with placebo; changes in CSF D-serine concentrations were noticeably higher after multiple (QD) doses than after a single dose of TAK-831. The magnitude of the increase in $AUEC_{24}$ of CSF D-serine was similar for both the 600 mg (T2 tablets) and 800 mg (oral suspension) doses, suggesting that the maximal PD effect in the CSF was achieved at drug exposures attained with both doses.

Overall, the emerging safety data from Studies TAK-831-1004 and TAK-831-1005 are consistent with the safety data collected in prior clinical studies and do not alter the risk profile of TAK-831.

4.2 Rationale for the Proposed Study

TAK-831 is a highly selective and potent inhibitor of DAO, a peroxisomal enzyme active toward neutral D-amino acids. TAK-831 was shown to increase D-serine levels in the cerebellum of normal mice and rats, and it also demonstrated a positive effect on social interaction and cognition at a broad range of repeated doses in rodent behavioral models. As noted above, TAK-831 has been also demonstrated to increase D-serine levels in human CSF. TAK-831 is under development for the treatment of the negative symptoms of schizophrenia, cognitive impairment associated with schizophrenia (CIAS), and cerebellar ataxia. The current phase 2 study is being conducted to assess the efficacy and safety of adjunctive administration of TAK-831 in the treatment of negative symptoms and cognition in symptomatically stable outpatients with chronic schizophrenia on stable antipsychotic and other psychotropic medications.

4.3 Benefit/Risk Profile

The current study is designed to evaluate the efficacy, safety, PD, and PK of 3 dose levels of TAK-831 oral T2 tablets in the adjunctive treatment of adult subjects with schizophrenia for up to 84 days. The proposed doses of TAK-831 have been selected based on the available PK, brain target occupancy (PET), CSF D-serine, and safety data for TAK-831 in healthy subjects (see Section 6.2.2). The safety data from healthy subjects cannot be directly generalized to subjects with schizophrenia. However, no safety signal has manifested that would prevent additional studies in healthy subjects or subjects with schizophrenia. A placebo-controlled study is standard in the evaluation of novel therapeutics for neuropsychiatric disorders; as TAK-831 is being administered as an add-on to standard therapy in stable subjects in this study, the risk of subjects experiencing an exacerbation of their underlying condition is minimized.

The risk mitigation measures that will be implemented in the current study are described below. These measures are based on what is known about the mechanism of action of TAK-831, the available nonclinical data, the available phase 1 clinical data, and general considerations in the development of new chemical entities for central nervous system disorders. Procedures may be added during the study if necessary based on evaluation of any additional clinical or nonclinical safety data.

- The exposures associated with the TAK-831 dosing regimens selected for this study have been evaluated in prior studies in healthy subjects and have not resulted in a safety signal that would prevent additional studies.
- Acute hypersensitivity/anaphylactic reactions to new chemical entities are always a possible risk in any clinical study. Appropriate procedures should be used to manage such possible risks.
- Subjects with a risk of suicide according to the investigator's clinical judgment (or as assessed by the Columbia-Suicide Severity Rating Scale [C-SSRS]), or who have made a suicide attempt in the previous 12 months, will be excluded from this study. The C-SSRS will be administered at prescribed intervals to monitor emergent suicidality. Subjects should be monitored for any signs of suicidal ideation or behaviors, and appropriate psychiatric interventions or other precautions should be instituted, if warranted.
- Eosinophilic intranuclear inclusion bodies (EIIBs) were observed in the proximal tubule epithelium of the kidneys at doses of ≥10 mg/kg/day in rats. The EIIBs were not accompanied by apparent necrosis, inflammation, or impaired renal function and were not considered adverse. Similar findings have been reported in the literature and are considered to be species-specific to the rat [19]. Elevated creatinine levels were not reported in the TAK-831 clinical studies summarized above; creatinine will continue to be measured in the clinical studies.
- Postural hypotension and dizziness were observed in prior TAK-831 studies in healthy subjects. However, the incidence of dizziness in subjects treated with TAK-831 and placebo was similar. Subjects will be informed of these findings and possible ways to mitigate this risk, and orthostatic vital sign assessments will be monitored periodically at study visits.
- Study procedure–specific risks include issues relating to blood collection for safety assessment/PK monitoring (venipuncture may cause discomfort at the site of puncture; bruising and swelling; and rarely, infection or faintness from the procedure), and the placement of ECG pads, which may cause some local redness and/or erythema/itching. The PD assessments planned for the study, aside from those requiring a blood draw, are noninvasive and are associated with minimal risk.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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).

5.1.2 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 PK of TAK-831.

5.1.3 [redacted]

[redacted]

- [redacted]

5.2 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.

5.2.1 Primary Endpoint

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

5.2.2 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.

5.2.3 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 ECG parameters at least once postdose.
- Percentage of subjects with treatment-emergent suicidal ideation or suicidal behavior as measured using the C-SSRS.

5.2.4 [redacted]

[redacted]

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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 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 Section 9.1.12, 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, as outlined in Appendix A. 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 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 rescheduled.

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 4 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 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. This study also includes [redacted] These assessments will be included in a subset of study sites and subjects.

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. Subjects who were in screening or the single-blind run-in period at the time that COVID-19 related factors resulted in discontinuation may also be rescreened with approval.

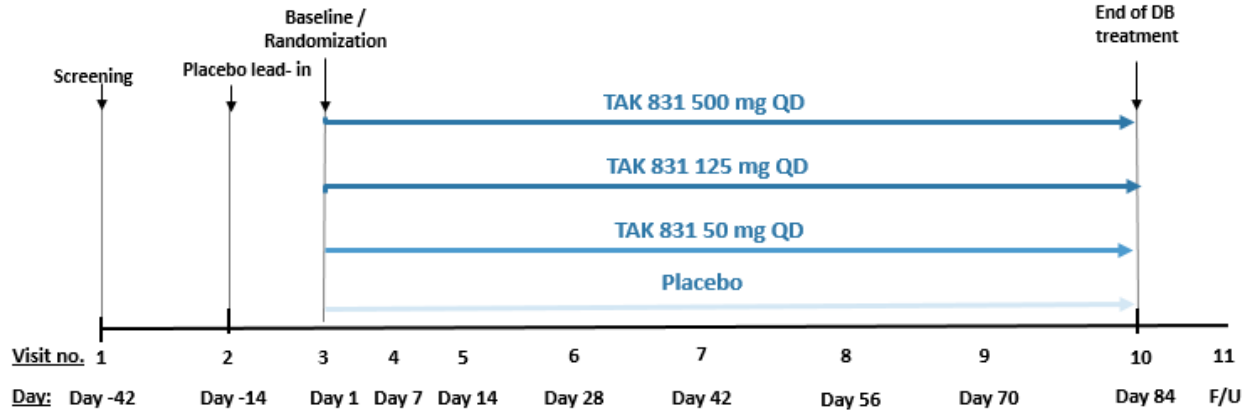
In the event that a subject prematurely discontinues the study, an early termination visit must be conducted, at which time all the assessments scheduled for the final visit will be performed.

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).

A schematic of the study design is included as Figure 6.a. A schedule of study procedures is provided in Appendix A.

Figure 6.a Schematic of Study Design



DB: double-blind; F/U: follow-up; QD: once daily.

Sites should see subjects at the study site to conduct the study procedures. In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Procedures (Appendix A), contingency measures may be implemented. Restrictions of human activities or institution activities placed by hospitals, local, state and national governments may prevent conduct of study procedures according to the Schedule of Procedures. Alternative approaches to study procedures and data collection for the current study are described in Section 9.1.1.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

A multicenter, double-blind, placebo-controlled, parallel design is the standard approach for assessing clinical efficacy in neuropsychiatric disorders. To evaluate efficacy in treating negative and cognitive symptoms, subjects who have stable psychiatric symptomatology and psychotropic medications are chosen to control for potential confounding effects of fluctuating psychosis or other symptoms independent of the investigational treatment. The presence of other disorders or AEs that can mimic negative symptoms or impact treatment response is also excluded to minimize any potential negative impact on efficacy detection. Hence, subjects who participate in the study will be receiving stable antipsychotic and other psychotropic medication therapy, and subjects will be excluded if presenting with clinically relevant symptoms of depression, excessive positive symptoms, specific comorbid disorders, or extrapyramidal side effects.

6.2.2 Dose

The effects of 3 dose levels of TAK-831 or placebo will be evaluated in the current study. The proposed doses of TAK-831 (50, 125, and 500 mg QD) have been selected based on the SRD/MRD PK data (Studies TAK-831-1001 and TAK-831-1005), food-effect PK data (Study TAK-831-1004), brain target occupancy (PET) data (Study TAK-831-1003), CSF D-serine data (Study TAK-831-1005), and safety data from all clinical studies after oral administration of TAK-831 in healthy subjects. D-serine levels in CSF and plasma after administration of TAK-831 600 mg QD (oral T2 tablets) and 800 mg QD (oral suspension) increased similarly, suggesting that 600 mg QD produced levels of D-serine approaching maximal DAO inhibition in the brain. The planned 500 mg QD dose is expected to result in CSF D-serine level increases near the plateau that are maintained over 24 hours with QD dosing. Preliminary PK/PD modeling analyses showed that the high-dose regimen (500 mg QD) resulted in steady-state exposures associated with mean peak target occupancy near the maximum (>90%) and provided mean target occupancy ≥50% over 16 hours, whereas the low-dose regimen (50 mg QD) produced daily exposures associated with a peak target occupancy of ≥50% of all subjects. The middle dose (125 mg QD) produced daily exposures associated with a peak target occupancy between 50% and the maximum. All 3 doses selected for the current study are predicted to demonstrate PD effects based on nonclinical efficacy models. The planned dose regimens are expected to deliver mean exposures within the range previously studied in Studies TAK-831-1001 and TAK-831-1005 that were found to be well tolerated in healthy subjects.

6.2.3 Endpoints

6.2.3.1 Efficacy Endpoints

Established, validated efficacy measures will be utilized to assess relevant schizophrenia symptom domains (negative, positive, general symptoms, global improvement, cognitive impairment, functional capacity, and quality of life).

6.2.3.1.1 PANSS

The PANSS is a reliable, validated comprehensive evaluation scale of the severity of various symptoms of schizophrenia and is commonly employed in clinical studies involving antipsychotics [20,21]. The subscales of the PANSS and the 5-factor model of the PANSS are commonly employed to explore different symptom domains of schizophrenia [22]. Change from baseline in the PANSS NSFS is the primary endpoint of the current study. In addition, the secondary endpoints will include the PANSS total score and additional subscales and factors.

6.2.3.1.2 Clinical Global Impression-Schizophrenia

The Clinical Global Impression-Schizophrenia (CGI-SCH) scale [23] is an adapted version of the CGI scale [24] that is designed to assess global severity of illness and change in schizophrenia patients over time. The assessment consists of 2 subscales, the CGI-SCH-S and the CGI-SCH-I, which assess severity and improvement of illness, respectively. The CGI-S and CGI-I are validated measures that have been shown to corroborate efficacy, as measured by the PANSS [21,24,25]. The CGI-I score and change from baseline in CGI-S score are included as secondary endpoints in the current study.

6.2.3.1.3 BNSS

The BNSS is a 13-item instrument designed for use in clinical trials and other studies that measures 5 domains of negative symptoms: blunted affect, alogia, asociality, anhedonia, and avolition [26]. Examination of the correlations between other instruments supports the discriminant validity (ie, low correlations with other instruments measuring positive symptoms) and convergent validity (ie, high correlations with other instruments measuring negative symptoms). The BNSS has been demonstrated to have a 2-factor structure similar to other negative symptom scales, consisting of a diminished expressivity subscale and a motivation and pleasure subscale [27]. This feature will support examination of effects on these clinically important subsyndromes of negative symptoms. Change from baseline in BNSS total score is included as a secondary endpoint in the current study.

6.2.3.1.4 BACS

Cognitive symptoms of schizophrenia will be assessed as a secondary endpoint using the BACS, which is a reliable and sensitive measure of cognitive function in schizophrenia [28]. The BACS assesses 6 domains of cognitive function found to be consistently impaired in schizophrenia: verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency. The BACS is specifically designed to measure treatment-related improvements in cognition and includes alternate forms. The BACS has high test-retest reliability and is sensitive to cognitive dysfunction in schizophrenia. The selection of the BACS was informed by the results of a schizophrenia clinical trial with a weak DAO inhibitor, sodium benzoate [18], which demonstrated beneficial effects on similar cognitive tasks.

6.2.3.1.5 SCoRS

The SCoRS is an interview-based measure of cognitive functioning that was developed to specifically assess aspects of cognitive functioning found in each of the 7 cognitive domains assessed by the MATRICS primary outcome measure for clinical trials of new medications to improve cognition in schizophrenia [29]. The psychometrics and performance of the SCoRS were evaluated with a number of other cognition-focused functional endpoints and found to have good test-retest reliability and the highest feasibility of the interview-based assessments [30]. The SCoRS has also been found acceptable as a functional coprimary measure in a phase 3 program by regulators for approval of an indication for cognition in schizophrenia [31].

6.2.3.2 Safety Endpoints

The secondary endpoint of safety will be evaluated by TEAE assessment, clinical laboratory tests, physical examinations, ECGs, vital signs, and suicidality assessment with C-SSRS.

The C-SSRS is a well-established 3-part scale that measures suicidal ideation (eg, subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actual, interrupted, and aborted attempts at suicide) [32].

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by the investigational site during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to the first dose of study drug in the single-blind placebo run-in period.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has a current diagnosis of schizophrenia as defined by the MINI 7.0.2 for Psychotic Disorders for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the general psychiatric evaluation.
4. The subject is male or female and aged 18 to 60 years, inclusive.
5. The subject weighs at least 45 kg and has a body mass index (BMI) between 18 to 40.5 kg/m^2, inclusive.
6. The subject's initial diagnosis must be ≥1 year from screening.
7. A female subject is eligible to participate if she is of (a) nonchildbearing potential or (b) childbearing potential and, if sexually active with a nonsterilized* male partner, agrees to use an acceptable effective method of contraception* from signing of informed consent throughout the duration of the study and for 35 days after the last dose. Female subjects of childbearing potential must also have a negative pregnancy test at the screening, single-blind placebo run-in, and baseline visits. Male subjects are not required to use barrier contraception in this study.

   *Definitions of acceptable effective methods of contraception are defined in Section 9.1.17, and reporting responsibilities are defined in Section 9.1.18.

8. The subject is receiving primary background antipsychotic therapy (other than clozapine) at a total daily dose between 2 mg and 6 mg of risperidone equivalents (as outlined in an Antipsychotic Reference document supplied to the sites). Concomitant treatment with a subtherapeutic dose of a second antipsychotic may be permitted with sponsor or designee approval if used to treat specific symptoms, such as insomnia (for example, quetiapine 100 mg or its equivalent once daily at bedtime) or anxiety (for example, quetiapine 25-50 mg or its equivalent as needed for anxiety), but not if it is used for refractory positive psychosis symptoms. Under this exception, the total daily dose of the second antipsychotic will not have to be included in the calculation of the 6 mg/day risperidone-equivalent limit. Recognizing that some prescribers use higher doses of quetiapine as a hypnotic, subjects taking up to 200 mg quetiapine or its equivalent as a hypnotic may be enrolled after

discussion with and approval from the sponsor or designee. Under this circumstance, the dosage above 100 mg quetiapine equivalent must be included in the calculation of the 6 mg/day risperidone-equivalent limit.

9. The subject is treated with a stable regimen of psychotropic medications with no clinically meaningful change (no increase in dose, ≤25% decrease in dose for tolerability) in the prescribed dose for 2 months before the screening visit, and no dose adjustment is anticipated throughout study participation up to the Day 84/early termination visit. As an exception, prohibited medications that are used as hypnotics or anxiolytics may be replaced with permitted medications as medically appropriate with approval from the sponsor or designee. Recognizing that physicians outside of the study may be managing the subject's background antipsychotic and other psychotropic medications, changes in background medication dosing that exceed this limit during the conduct of the study should be discussed with the sponsor or designee to determine subject disposition (based on consideration of safety and the study scientific objectives).
10. The subject has a BNSS total score (12-item, excluding number 4) ≥28; stable single-blind placebo run-in and baseline BNSS total (12-item, excluding number 4) scores (≤20% change from the screening score).
11. The subject has no more than moderate-severe (≤5) rating on PANSS positive symptom items P1, P3, P4, P5, P6, or unusual thought content (G9), with a maximum of 2 of these items rated "5"; no more than moderate (≤4) rating on conceptual disorganization (P2).
12. There is evidence that the subject has stable symptomatology ≥3 months prior to the screening visit (eg, no hospitalizations for schizophrenia, no emergency room admission due to symptoms of schizophrenia, no increase in level of psychiatric care due to worsening of symptoms of schizophrenia).
13. The subject must have an adult informant who will be able to provide input for completing study rating scales, including the PANSS and SCoRS (for example, a family member, social worker, caseworker, residential facility staff, or nurse) who spends ≥4 hours/week with the subject and is considered reliable by the investigator. The informant must be able and willing to provide written informed consent and to participate in at least 1 in-person interview (during the screening period in the clinic, at Visit 2, or via site staff conducting informed consent at the informant's location), then be able to provide continuing input by attending each clinical assessment visit or via participating in a telephone interview for other study visits that include the PANSS or SCoRS endpoints. Informant participation at the screening visit is preferred, if possible. 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.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. A female subject who is lactating or pregnant (positive prerandomization serum pregnancy test) or plans to become pregnant during the study.
2. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the study results.
3. The subject has a lifetime diagnosis of schizoaffective disorder; a lifetime diagnosis of bipolar disorder; or a lifetime diagnosis of obsessive compulsive disorder based on the MINI combined with the general psychiatric evaluation. As an exception, subjects with a historical prior lifetime diagnosis of schizoaffective disorder may be enrolled in the study with sponsor or designee approval provided that the principal investigator can attest that the subject's overall history and current clinical presentation and history is most consistent with schizophrenia, not schizoaffective disorder.
4. The subject has a recent (within the last 6 months) occurrence of panic disorder, depressive episode, or other comorbid psychiatric conditions currently requiring clinical attention based on the MINI for DSM-5 and the general psychiatric evaluation.
5. The subject has a diagnosis of substance use disorder (with the exception of nicotine dependence) within the preceding 6 months based on the MINI for DSM-5 and the general psychiatric evaluation.
6. The subject has any other medical or psychiatric condition or cognitive impairment that, in the opinion of the investigator, may interfere with study conduct or clinical assessments.
7. The subject is participating in a formal structured nonpharmacological psychosocial therapeutic treatment program (cognitive remediation, cognitive-behavioral therapy, intensive symptom/vocational rehabilitation) for a duration of <3 months before randomization. In addition, initiation of such nonpharmacological treatment programs is not permitted during study participation through the Day 84 visit. Recognizing that physicians outside of the study may be managing the subject's psychosocial treatment, changes to this type of treatment during the conduct of the study should be discussed with the sponsor (or designee) to determine subject disposition.
8. The subject has a positive drug screen for disallowed substances, including amphetamines, barbiturates, cocaine, marijuana, methadone, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), phencyclidine, or nonprescribed benzodiazepines or opiates.

   Note: Subjects testing positive for marijuana at screening may be eligible for participation in the study provided that the principal investigator's clinical assessment indicates that the subject is not a regular user of marijuana, and after discussion with and approval from the sponsor or designee. Under this circumstance, a local urine dipstick drug screen must be

performed at the placebo run-in and Day 1 visits and verified to be negative prior to conducting any other study procedures at these visits. If the subject is confirmed to be eligible for randomization at the Day 1 visit, the central laboratory urine drug screen will be performed at all study visits to confirm that the subject is complying with restrictions on substances of abuse. Any positive urine drug screens during conduct of the study must be discussed with the sponsor or designee to determine the subject's disposition.

9. The subject exhibits more than a minimal level of antipsychotic-induced parkinsonism symptoms, as documented by a score on the modified SAS (excluding item number 10, Akathisia) >6.
10. The subject has evidence of depression as measured by a Calgary Depression Scale Score (CDSS) >9.
11. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year prior to screening. Subjects who have positive answers on item number 4 or 5 on the C-SSRS (based on the past year) prior to randomization are excluded.
12. The subject has a history of brain trauma associated with loss of consciousness for >15 minutes.
13. The subject's diagnosis of schizophrenia occurred prior to 12 years of age.
14. The subject has received electroconvulsive therapy within 6 months (180 days) before screening.
15. The subject has a history of developmental intellectual disability or mental retardation.
16. Antipsychotic plasma levels for the subject's primary background antipsychotic are below the minimum acceptable concentration criteria per the Antipsychotic Reference document at the screening or placebo run-in visits. This criterion is not applicable to subjects on a primary background antipsychotic for which a clinical assay is unavailable (ie, per the Antipsychotic Reference document). Screening antipsychotic plasma levels that do not meet the criteria listed in the Antipsychotic Reference document should be repeated as soon as possible if, in the judgment of the investigator, the subject may actually be adherent to their medication regimen. Please see Section 9.1.16.1 and the Antipsychotic Reference document for specific procedures to follow and for determination of subject eligibility in this circumstance.
17. The subject is treatment resistant. Treatment resistance is defined as prior nonresponse of positive symptoms of schizophrenia to 2 courses of treatment with antipsychotics of different chemical classes for at least 4 weeks, each at doses considered to be effective.
18. Use of disallowed concomitant medications as documented in Section 7.4 that cannot be discontinued during the screening period (as medically appropriate). Note that disallowed psychotropic medications may not be discontinued during screening because of the psychotropic medication stability requirements for the study. Subjects taking disallowed psychotropic medications should not be considered for participation in the study (except those explicitly addressed in Sections 7.4 and 8.1.1).

19. The subjects is taking concomitant treatment that can impact cognition as determined by the principal investigator in consultation with the sponsor or designee, including (but not limited to) the following: anticholinergics (exception: up to 2 mg benztropine/day or equivalent for treatment of extrapyramidal motor symptoms with sponsor or designee approval; must not be taken within 8 hours of any cognition assessment), stimulants, tricyclic antidepressants, anticonvulsants (exception for pregabalin and gabapentin), and lithium.
20. The subject has received TAK-831 in a previous clinical study; or has previously or is currently participating in this study; has received treatment with other experimental therapies within the preceding 60 days or <5 half-lives prior to randomization, whichever is longer; has participated in 2 or more clinical studies within 12 months prior to screening; or has participated in a clinical study for a psychiatric condition that is exclusionary per this protocol.
21. The subject is known by history or subject reporting to be currently infected or to have been infected with human immunodeficiency virus (HIV).
22. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or to the practice pills (ie, small candies) used during the compliance monitoring device training.
23. The subject has a history of cancer. As an exception, subjects may be enrolled if they have a history of treated basal cell carcinoma, stage I squamous cell skin cancer, or in situ cervical cancer that has been in remission for ≥5 years prior to first dose of study drug.
24. Subjects with evidence or history of current clinically significant cardiovascular disease, including uncontrolled hypertension (supine diastolic blood pressure >95 mm Hg and/or supine systolic blood pressure >160 mm Hg, with or without treatment), symptomatic ischemic heart disease, uncompensated heart failure or recent (past 12 months) acute myocardial infarction or bypass surgery. Controlled essential hypertension and nonclinically significant sinus bradycardia and sinus tachycardia will not be considered significant medical illnesses and would not exclude a subject from the study.
25. The subject has a QT interval with Fridericia correction method (QTcF) >450 msec (males) or >470 msec (females), confirmed with 1 repeat testing, at screening or Day 1, or the subject has long QT syndrome or is under the treatment with Class 1A (eg, quinidine, procainamide) or Class 3 (eg, amiodarone, sotalol) antiarrhythmic drugs.
26. The subject has type 1 diabetes that requires insulin for their treatment; has type 2 diabetes that is poorly controlled; has had changes to their diabetic treatment regimen within 30 days before screening; or has had hospitalizations for diabetes and/or diabetes-related conditions in the past 6 months before screening. As an exception, subjects who have consistently demonstrated the ability to adhere to their insulin and dietary regimens for an extended period of time in addition to demonstrating stable control of type 2 diabetes mellitus for an extended period of time may be considered for enrollment after discussion with the sponsor or designee.

27. The subject has 1 or more laboratory values outside the normal range that are considered by the investigator to be clinically significant at the screening visit.
28. The subject has any of the following at the screening visit: a serum creatinine value >1.5 × upper limit of normal (ULN); a serum total bilirubin value >1.5 × ULN; a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 × ULN. As an exception, subjects with Gilbert syndrome may be considered for enrollment after discussion with the sponsor or designee if the direct bilirubin is within the normal range. Subjects with a positive hepatitis B surface antigen (HBsAg) test result, or known or suspected active hepatitis C infection are also excluded.
29. The subject does not have a stable residence or is homeless.

7.3 Randomization Criteria

1. The subject must continue to meet all of the inclusion criteria and none of the exclusion criteria at the time of the baseline visit (Day 1; Visit 3).
2. The subject has completed the single-blind placebo run-in period and has met the study drug compliance criteria (75% to 125%) as assessed using the digital compliance technology. As an exception, subjects who are in a residential setting that incorporates directly observed medication administration who meet this criterion (but not via the digital compliance technology) may be eligible for randomization with site documentation and approval of the sponsor or designee.

NOTE: Before enrollment into the single-blind run-in period, the site must confirm that approval has been received from the study sponsor or designee, and from the central eligibility vendor. The sponsor or designee approval will also serve as approval of subject randomization provided that the subject meets the specified randomization criteria at the baseline visit.

7.4 Excluded/Allowed Medications, Procedures, and Treatments

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Subjects who require treatment with one or more of the specified medications should be excluded or discontinued (as appropriate) from the study. If a subject is prescribed treatment with a prohibited medication during the conduct of the study, the investigator should contact the sponsor or designee to review the relevant clinical information and medication treatment to determine subject disposition.

Excluded agents (prescription or nonprescription) or dietary products are listed in Table 7.a. Items with an 'X' indicate restrictions on either chronic or episodic use. Drug classes without an 'X' in these columns indicate no restrictions. This table encompasses the most commonly used medications; however, it is not a comprehensive list. Additional detailed guidance on

excluded/allowed medications may be provided in separate reference documentation provided to study sites.

Table 7.a Excluded Medications and Dietary Products

Drug Class	Disallowed (X) During the Study (sections without [X] indicate no restriction unless noted in Comments)		
	Chronic Use	**Episodic Use**	**Comments or Exceptions**
Any investigational drug	X	X	<60 days before screening or 5 half-lives – whichever is longer
Narcotic analgesics	X		Episodic use permitted if prescribed, must not be taken within 8 hours. of any study efficacy assessment.
Anorexiants (eg, phentermine, benzphetamine, phendimetrazine, methamphetamine, amphetamine, stimulants, sibutramine, Belviq (lorcaserin), Qsymia (phentermine/topiramate)	X	X	Must be discontinued for ≥30 days prior to screening
Antiarrhythmics of 1C class, quinidine	X	X	
Antibiotics	X		
Anticholinergics	X	X	Exception: The maximum permitted dose of chronic anticholinergic treatment is 2 mg/day benztropine or equivalent; episodic use of anticholinergics must adhere to requirements outlined in Section 8.1.1.3.
Antithrombic agents and anticoagulants (excluding warfarin, which is excluded)		X	
Antidepressants (excluding tricyclic antidepressants, MAOIs, and reversible Inhibitors of MAO [RIMAs])		X	Tricyclic antidepressants, MAOIs, and RIMAs are excluded, and subjects taking them should not be considered for participation in the study, as their discontinuation could lead to symptom instability. Chronic treatment with SSRIs, SNRIs, and other antidepressants not listed above is permitted if they are prescribed at a stable dose for ≥2 months before screening and throughout study treatment.
Antihistamines	X	X	Except nonsedating antihistamines including loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine, or country-specific equivalent. Note that antihistamines used for anticholinergic properties are addressed separately in the relevant section above.
Antihypertensives			Clonidine NOT allowed.
Antipsoriatic agents	X	X	Topical agents are allowed.

Table 7.a Excluded Medications and Dietary Products

Drug Class		Disallowed (X) During the Study (sections without [X] indicate no restriction unless noted in Comments)		
		Chronic Use	Episodic Use	Comments or Exceptions
Antipsychotics			X	Clozapine is excluded; all other treatments must adhere to requirements outlined in the study entry criteria and Section 8.1.1.2. Subjects being treated with low-dose clozapine (up to 100 mg/day) for anxiety or insomnia before screening may be switched to a permitted medication during screening, as clinically appropriate, with sponsor or designee approval. Episodic use: As an exception, occasional use of an additional episodic dose of the background antipsychotic may be permitted with sponsor or designee approval (see Section 8.1.1.3).
Herbal remedies, which are psychoactive (eg, St John's wort, kava, valerian, ginkgo biloba, melatonin)		X	X	Must be discontinued ≥7 days prior to Visit 2.
Sedative hypnotics				Barbiturates are excluded. Chronic treatment with BZs is allowed up to 3 mg/day lorazepam or equivalent (BZ equivalence standards will be provided in a site reference document). Episodic use of BZs must adhere to requirements outlined in Section 8.1.1.3. Note that hypnotics are excluded from the 2-month stability requirement for other psychotropic medications.
Insulin		X	X	As an exception, subjects with type 2 diabetes treated with insulin who have consistently demonstrated the ability to adhere to their insulin and dietary regimens for an extended period of time in addition to demonstrating stable control of type 2 diabetes mellitus for an extended period of time may be considered for enrollment after discussion with the sponsor/designee.
Lithium		X	X	
Steroids:	Systemic oral or injectable	X	X	As an exception, treatment with local steroid injections for orthopedic conditions may be permitted with sponsor or designee approval.
	Topical			
	Inhalant			
Stimulants		X	X	Must be discontinued for ≥30 days prior to screening.

BZ: benzodiazepine; MAOI: monoamine oxidase inhibitor; RIMA: reversible inhibitor of monoamine oxidase type A, SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.

7.5 Diet, Fluid, and Activity Control

Study subjects will be instructed to take their study drug with water or milk. Subjects should avoid drinking juices 1 hour before and 1 hour after taking study drug.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.20.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   - Liver Function Test (LFT) Abnormalities:

     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status), if any of the following circumstances occur at any time during study drug treatment:

     – ALT or AST >8 × ULN, or

     – ALT or AST >5 × ULN and persists for >2 weeks, or

     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5.

2. Important protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the study site and multiple attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Withdrawal by subject. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category). If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for subject withdrawal in the eCRF.

5. Study termination. The sponsor, IRB/IEC, or regulatory agency terminates the study.

6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.18.

7. Unsatisfactory therapeutic response. The investigator has determined that the subject is not benefitting from study treatment and continued participation would pose an unacceptable risk to the subject.

8. Noncompliance with study drug during the double-blind treatment period. Noncompliance with study drug includes subjects who are <75% compliant between visits, as assessed via the digital compliance technology. As an exception, this criterion may be assessed via site-recorded compliance documentation for subjects who are in a residential setting that incorporates directly observed medication administration with approval of the sponsor or designee, as described for the placebo run-in period in Section 7.3. If these criteria for noncompliance are met on more than 1 occasion during the study, the subject will be considered significantly out of compliance and the site investigator will need to discuss the subject's continuation in the study with the sponsor or designee. Based upon the assessment of the investigator and sponsor or designee, an out-of-compliance subject may be withdrawn from the study.

9. Throughout the study, signs of suicidal risk will be assessed by C-SSRS and the investigator's clinical judgment. If the subject has a significant risk of suicide according to the investigator's clinical judgment, the subject will be withdrawn from the study.

10. Symptomatic deterioration: Any subject from the study who experiences a clinically significant psychotic episode, relapse in positive symptoms, or overall worsening of illness that poses an unacceptable risk to the subject based on the judgment of the investigator should be discontinued from study participation, and the event documented as an AE.

11. Other: The reason for discontinuation should be entered into the eCRF including unavoidable circumstances such as the COVID-19 pandemic.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study Drug (TAK-831 and Matching Placebo Tablets)

TAK-831 will be supplied as matching tablet dosage forms in 10, 25, and 100 mg and placebo. Each TAK-831 tablet strength and the placebo tablets will be bottled in a 60-count round high-density polyethylene bottle with a child-resistant cap.

8.1.1.2 Companion Medication

Subjects must be on a stable ongoing oral or depot maintenance antipsychotic (other than clozapine) monotherapy regimen and on stable ongoing treatment with any nonprohibited concomitant psychotropic medications for ≥2 months prior to the single-blind placebo run-in visit and throughout the double-blind treatment period. Subjects must be treated with a primary background antipsychotic at a total daily dose between 2 mg and 6 mg of risperidone equivalents. A reference document listing the dose equivalency of currently marketed antipsychotics will be provided to study investigators. Subjects may also be treated with other nonprohibited psychotropic medications including antidepressants, anxiolytics, and hypnotics with a stable treatment regimen for ≥2 months prior to the single-blind placebo run-in visit and throughout study participation up to the Day 84/early termination visit.

All efforts should be made to maintain background nonprohibited psychotropic medications at consistent doses throughout the double-blind treatment period. Allowable exceptions to this rule include the following:

1. Primary background antipsychotic medication: Minor adjustments (no increase, ≤25% decrease) to manage drug-specific tolerability issues with sponsor or designee approval if required to support the subject's continued participation in the study. Recognizing that physicians outside of the study may be managing the subject's background antipsychotic and other psychotropic medications, changes in background medication dosing that exceed this limit should be discussed with the sponsor or designee to determine subject disposition. The evaluation will include assessment of whether the change in dosing poses a risk to clinical stability of the subject's condition as well as the potential for impact on subject safety or the scientific objectives of the study.
2. Other background psychotropic medications: Minor adjustments (≤25% increase or decrease) with sponsor or designee approval if required to support the subject's continued participation in the study. Recognizing that physicians outside of the study may be managing the subject's background antipsychotic and other psychotropic medications, changes in background medication dosing that exceed this limit should be discussed with the sponsor or designee to determine subject disposition. The evaluation will include assessment of whether the change in dosing poses a risk to clinical stability of the subject's condition as well as the potential for impact on subject safety or the scientific objectives of the study.

3. 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 it is used for refractory psychotic symptoms. Under this exception, if the total nightly dose of the second antipsychotic is ≤100 mg of quetiapine or its equivalent, the total daily dose of the second antipsychotic will not have to be included in calculation of the 6 mg/day risperidone-equivalent limit. If a subject is taking up to 200 mg quetiapine or its equivalent as a hypnotic (the maximum allowed under this exception), the dosage above 100 mg quetiapine equivalent must be included in the calculation of the 6 mg/day risperidone-equivalent limit.
4. Prohibited medications that are used as hypnotics or anxiolytics may be substituted with nonbenzodiazepine hypnotics (eg, zolpidem up to 10 mg/day, zaleplon up to 20 mg/day, eszopiclone up to 3 mg/day, or zopiclone 7.5 mg/day) within their respective recommended dose ranges.

8.1.1.3 Rescue Medication

The guidelines below refer to use of medications that are not part of the subject's routine ongoing background psychotropic companion medication regimen.

1. Treatment of insomnia as needed with benzodiazepine and nonbenzodiazepine hypnotics (eg, zolpidem up to 10 mg/day, zaleplon up to 20 mg/day, eszopiclone up to 3 mg/day, or zopiclone 7.5 mg/day) is permitted within their respective recommended dose ranges.
2. Treatment of anxiety or agitation as needed with up to 2 mg/day lorazepam (or the equivalent dose of another benzodiazepine) is permitted up to 3 times per week but cannot be taken within 8 hours of the administration of study assessments.
3. Treatment of extrapyramidal motor symptoms as needed with up to 2 mg/day benztropine (or the equivalent dose of another anticholinergic) is permitted up to 2 times per week but cannot be taken within 8 hours of the administration of study assessments.
4. The occasional use of an additional dose of the background antipsychotic medication, as occurs during standard of care treatment, may be permitted with sponsor or designee approval.

8.1.1.4 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

- TAK-831 10 mg T2 tablets.
- TAK-831 25 mg T2 tablets.
- TAK-831 100 mg T2 tablets.
- Matching placebo tablets.

8.1.2 Storage

Please refer to clinical labels for local storage conditions.

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

For the single-blind placebo run-in period, the first dose of study drug (placebo) will be administered to subjects by the investigator or investigator's designee in the clinic on Day -14 (Visit 2) as subjects are familiarized with the compliance monitoring technology. Subjects will be instructed to take study drug orally each morning during the remainder of this period.

For the double-blind treatment period, the first dose of study drug (TAK-831 or placebo) will be administered to subjects by the investigator or investigator's designee in the clinic on Day 1 (Visit 3) after completion the Day 1 study procedures. Subjects will also take study drug at the clinic on the morning of Day 28 (Visit 6). For all other dosing days during this period, subjects will be instructed to take study drug orally each morning. Note: While morning dosing is the preferred approach for subjects in this study, exceptions may be granted with sponsor/designee approval based on individual subject contingencies and will not be considered protocol deviations.

Subjects should be advised to be consistent in the study drug dosing time throughout the duration of the study.

The dose and tablet count that will be provided to each treatment group are described in Table 8.a.

Table 8.a Dose and Regimen

Treatment Group	Dosage	Treatment Description
Placebo Run-in Period	Placebo QD	5 oral placebo tablets
A	Placebo QD	5 oral placebo tablets
B	TAK-831 50 mg QD	5 oral TAK-831 10 mg T2 tablets
C	TAK-831 125 mg QD	5 oral TAK-831 25 mg T2 tablets
D	TAK-831 500 mg QD	5 oral TAK-831 100 mg T2 tablets

QD: once daily.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRFs according to Section 10.0.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, supportive measures should be employed as dictated by the subject's clinical status and additional clinical monitoring should be initiated.

8.2 Study Drug Assignment and Dispensing Procedures

At screening, the investigator or designee will access the IRT to obtain the subject identification (ID) number (subject number). The investigator or designee will utilize the IRT to initiate the Placebo Run-in treatment on Day -14 and to randomize the subject to study drug treatment on Day 1. During these contacts, the investigator or designee will provide the necessary subject identifying information, including the subject ID number assigned at screening. The medication ID number of the study drug to be dispensed will then be provided by the IRT. If sponsor-supplied drug (TAK-831 or placebo) is lost or damaged, the site can request a replacement from the IRT. (Refer to IRT manual provided separately).

At subsequent drug-dispensing visits, the investigator or designee will again access IRT to request additional study drug for the subject. The medication ID number of the study drug to be dispensed will be provided by the IRT.

On occasion, in unavoidable circumstances such as the COVID-19 pandemic that may impact the ability to conduct on-site visits, in order to reduce the risk of spreading infection and protect the safety of subjects, study drug can be shipped directly from study sites to subjects' residences using the process known as Direct to Patient shipment. Additional drug supply may also be provided to subjects (either at an in-person visit or delivered to subject's residence) to cover extended periods between on-site visits. Any additional resupply must be reviewed and approved in advance by the sponsor or designee.

8.3 Randomization Code Creation and Storage

All randomization information will be stored in a secured area, accessible only by authorized personnel.

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.

8.4 Study Drug Blind Maintenance

The study drug blind will be maintained using the IRT. The investigator must not disclose the details of study drug (ie, placebo run-in) to subjects until the study has been completed.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the sponsor or designee should be contacted before the study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be obtained by the investigator or emergency personnel, by accessing the IRT.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded during the double-blind treatment period, study drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee. or before destruction at the site according to the site's internal standard operating procedure (SOP).

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the study drug is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to the following:

- Continuously monitoring expiration dates if provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed with, at a minimum, the medication ID and lot number for each dose.
- Verifying that all containers used are documented accurately on the log.

- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Current inventory of all study drug will be recorded in the IRT. The following information will be recorded at a minimum:

- Protocol number.
- Subject ID number.
- Name of investigator, site number.
- Description of sponsor-supplied drugs.
- Date and amount dispensed.
- Date and amount returned.
- Name of the person making each IRT transaction.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

In the event of expiry date extension of supplies already at the study site, supplies may be relabeled with the new expiry date at that site. In such cases, Takeda or designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the relabeling procedure at the sites.

At appropriate intervals before site closure, a representative from the sponsor or designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or designee for destruction. The investigator will retain a copy of the documentation regarding clinical study material accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures to be performed and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 or Other Unavoidable Circumstances

In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Procedures (Appendix A), contingency measures may be implemented. In acknowledgement of study site, hospital, local, state and national restrictions established in response to circumstances like COVID-19, the following measures are being taken for the current study:

- For subjects impacted while in the double-blind period, all attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:
  - Sites must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection due to COVID-19 or other unavoidable circumstances.
  - Sites may seek approval from the sponsor or designee to continue subjects in the study despite departures from the Schedule of Procedures. The principal investigator is expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.
  - Other than the final visit, alternative methods for conducting subject visits (eg, video conferencing, telephone visits, or in-home study visits conducted by study site personnel or designated clinical personnel, contingent upon local regulations) may be used per approval by the sponsor or designee:
    - Under these circumstances, collection of certain study assessments may be omitted and visit windows may be extended.
    - When approval is given for a subject to miss an in-person study visit, a study site physician will speak directly with the subject by telephone or other medium (e.g. a computer-based video communication) during each visit window to assess subject safety and overall clinical status.
    - The study site physician or other qualified site personnel should conduct the following assessments within specified-visit window timeframes: AE assessments, documentation of concomitant medication, administration of C-SSRS, and an assessment of clinical symptoms.
    - Other study assessments may be collected using an alternative method as feasible, and may involve audio or video recording where allowed by local regulation. In some cases, audio and/or video recording of subject interviews may not be

possible and thus will deviate from the planned rater monitoring plan. This will be documented in the study records.

- In some instances sites may need to split visits or sites may only be able to perform a few procedures on site and some procedures may need to be performed remotely. Sites should inform sponsor or designee when this occurs.
- Sites may seek approval to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window or within the visit window granted by the sponsor or designee will be considered missing data and such departures will be recorded in the study records.
- There will be no interval longer than 8 weeks between visits at which clinical laboratory tests are performed and vital signs are measured. Should this 8 week interval be reached for a particular subject, the site should reach out to the sponsor or designee to discuss withdrawal of the subject.

– Study site personnel may dispense additional investigational medicinal product to subjects at a visit to allow for potentially longer intervals between visits than originally planned per protocol, or investigational medicinal product may be supplied to subjects via delivery by site personnel or by courier.

– The final visit should be performed in person. When it is not possible for the subject to come to the study site and the protocol specified visit window cannot be extended further, the preferred alternative for the final visit is for qualified study site personnel or designated clinical personnel to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at a subject's residence should comply with applicable local regulations. If neither option is available with sponsor or designee approval, sites may conduct final visit procedures remotely as is feasible.

All subject discontinuations and alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Procedures) due to the COVID-19 pandemic must be documented in the study records as related to COVID-19. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan (SAP).

9.1.2 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

[redacted]

The provision of informed consent to participate in remote study visits due to COVID-19 will be provided separately. A separate informed consent in regions where remote data verification is permitted per local regulations will also be obtained before implementation.

The Subject Database Authorization will be a component of the overall study informed consent (see Section 9.1.3) in some countries where this process is permitted by local regulations and ethics standards.

A unique subject ID number will be assigned to each subject at the time that informed consent is obtained/explained; this subject ID number will be used throughout the study.

In addition, as a requirement for entry into this study, subjects are required to have an informant. Informants will be required to sign a separate Designated Study Partner consent form.

When subjects have completed screening assessments prior to the study under a generic screening consent form, the data from this screening can be used in this study for those subjects who were subsequently enrolled, as long as the screening procedures were performed within the protocol-defined screening window.

9.1.3 Clinical Trial Subject Database Authorization

Clinical trial subject registries seek to reduce subjects from enrolling into multiple clinical trials by identifying potential duplicates before enrollment. This study will utilize 1 or more subject registry databases in some countries where they are available. At the time of providing the informed consent for the study, the investigator or designee will explain to the subject the IRB-approved Subject Database Authorization and witness the signature.

During screening, site staff who have received training and login information to access the registry will enter the subject ID number and authorized subject identifiers on the registry website. An immediate report detailing matches is generated and should be printed for source documentation. The report will specify either (1) no potential matches found, (2) a potential match was found with a subject participating in another study within 30 days, and/or (3) the subject potentially matches with a subject who has prescreened/screened at another site.

9.1.4 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity (United States sites only), race as described by the subject, education, work status, tobacco use, reproductive status, alcohol consumption, and caffeine consumption of the subject at screening.

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 date of initial diagnosis of schizophrenia. Ongoing medical or psychiatric conditions are considered concurrent medical conditions (see Section 9.1.9).

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.

9.1.5 Physical Examination Procedure

A baseline physical examination (defined as the last 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.

All subsequent physical examinations should assess clinically significant changes from baseline.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. All clinically significant findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF as described in Section 10.0 or Section 9.1.9.

9.1.6 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms with 1 decimal place. For assessment of entry criteria at screening, BMI should be derived as follows:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818\ kg/m^2$.

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2. If BMI is used as a study entry criterion, this determination must be made after rounding.

9.1.7 Vital Sign Procedure

Vital signs will include body temperature, blood pressure (systolic and diastolic), and pulse (bpm). Supine blood pressure, and pulse will be collected at a subset of study visits as outlined in the Schedule of Study Procedures (Appendix A). All other vital signs assessments will be collected in a sitting position.

Body temperature will be measured with an oral (temperature taken at floor of the mouth), tympanic, or infra-axillary thermometer. The same method (eg, oral, tympanic, or infra-axillary) must be used for all subsequent measurements for each individual subject and should be the same for all subjects.

Subjects should rest in the specified position for at least 5 minutes prior to blood pressure and pulse measurements. The same method (eg, same size cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects. It is also recommended that the same arm be used for all blood pressure measurements for each individual subject.

Pulse should be recorded separately and should not be derived from the ECG.

9.1.8 Documentation of Concomitant Medication

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. This includes the subject's background antipsychotic medication (which will be recorded on a specific antipsychotic medication eCRF) as well as the other stable background medications in the subject's treatment regimen. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medications including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.9 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening and single-blind placebo run-in visits, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.10 Efficacy Measurements

All assessments will be performed per the Schedule of Study Procedures (Appendix A). Clinical interviews will be video recorded for the MINI, PANSS, and BNSS and may be recorded for other measures at the discretion of the sponsor. The purpose of these recordings is to assess subject eligibility during the screening period and to provide feedback on interview technique and accuracy of ratings to raters throughout the study for endpoint quality assurance. To accommodate local cultural considerations in the schizophrenia population with regard to video recording versus audio recording, individual subject exceptions for video recording (record audio only instead) may be considered for sites that have already demonstrated high-quality subject interviews and ratings. Exceptions to proceed with only an audio recording will be made only after assessment of these factors, discussion of the subject and clinical contingencies between the investigator and the sponsor or designee, and receipt of documented approval from the sponsor or designee.

Note: in unavoidable circumstances such as the COVID-19 pandemic, it may be necessary to administer clinical interviews and assessments using alternative approaches (please refer to Section 9.1.1). In some cases, audio/or video recording of subject interviews may not be possible This will be documented in the study records.

9.1.10.1 MINI

The MINI is a short structured diagnostic interview developed jointly by psychiatrists and clinicians in the United States and Europe for DSM-5 and International Classification of Diseases 10th Revision psychiatric disorders. With an administration time of approximately 15 minutes, the MINI was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies. Validation and reliability studies have been performed comparing the MINI to the Structured Clinical Interview for DSM-IV, Patient Edition and the Composite International Diagnostic Interview. The results of these studies showed that the MINI has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7±11.6 minutes, median 15 minutes) than the above-referenced instruments [33-35].

The assessment of the criterion for schizophrenia will be standardized using the MINI Version 7.0.2 for DSM-5. The MINI will also be used to evaluate the presence of comorbid psychiatric disorders in order to assess the appropriateness of the subject for inclusion. Administration of the MINI will be video recorded (for exceptions, see Section 9.1.10) to facilitate review by third party independent expert clinicians.

9.1.10.2 PANSS

The PANSS is a reliable, validated comprehensive evaluation scale of the severity of various symptoms of schizophrenia and is commonly employed in clinical studies involving antipsychotics [20,21]. The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) must be used to support the rating of each item and in accordance with guidelines provided by the sponsor (or designee). The Informant Questionnaire for the Positive and Negative Syndrome Scale (IQ-PANSS) must be used to collect information from the informant.

For all study visits, including the screening visit, administration of the PANSS will be recorded to facilitate review by third party independent expert clinicians (see Section 9.1.22.5) and may be used for exploratory analyses. Relevant data from each recorded PANSS administration, including scores on each of the 30 PANSS Items, CGI scores for the visit, and supporting information (including corroborating informant data for the past week) may be submitted along with the recording file to third party clinicians. Additional instructions will be provided during rater training and documented in the rater training manual.

The PANSS total score is derived from the summation of each item. The total time to administer the PANSS is approximately 45 minutes. PANSS raters will be required to have suitable experience and training (as deemed by the sponsor or designee) to be eligible to rate subjects within the study.

9.1.10.3 CGI-SCH Scale

The CGI-SCH scale is an adapted version of the CGI scale that is designed to assess global illness status in patients with schizophrenia [23]. The assessment consist of 2 subscales, the CGI-

SCH-S and the CGI-SCH-I, which assess global severity of illness and change in the clinical condition over time, respectively, on a 7-point scale.

9.1.10.4 BACS

The BACS is a cognition assessment battery that assesses 6 domains of cognitive function found to be consistently impaired in schizophrenia: verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency [28]. It takes approximately 30 minutes to complete and is devised for easy administration and scoring by nonpsychologists. It is specifically designed to measure treatment-related improvements in cognition and includes alternate forms.

9.1.10.5 BNSS

The BNSS is a13-item instrument designed for use in clinical trials and other studies that measures 5 domains of negative symptoms: blunted affect, alogia, asociality, anhedonia, and avolition [26]. Examination of the correlations between other instruments supports the discriminant validity (ie, low correlations with other instruments measuring positive symptoms) and convergent validity (ie, high correlations with other instruments measuring negative symptoms). Similar to the procedures for the PANSS assessment noted in Section 9.1.10.2, administration of the BNSS will be video recorded (for exceptions, see Section 9.1.10) for all study visits including the screening visit to facilitate review by third party independent expert clinicians.

9.1.10.6 SCoRS

The SCoRS is an interview-based measure of cognitive functioning that was developed to specifically assess aspects of cognitive functioning found in each of the 7 cognitive domains assessed by the MATRICS primary outcome measure for clinical trials of new medications to improve cognition in schizophrenia [29]. The scale is intended to incorporate information obtained from an informant who bases his/her responses on interaction with and knowledge of the patient. The SCoRS includes 20 items focusing on cognitive impairment and the degree to which it affects day-to-day functioning, as well as a global functioning scale; at follow-up visits there is also a global scale reflecting change from the beginning of the subject's treatment rated by the administrator, the informant, and the subject.

9.1.10.7 CDSS

The CDSS was developed to assess symptoms of major depressive disorder in patients with schizophrenia, and specifically designed to assess comorbid depressive symptoms [36]. The CDSS consists of 9 items: depressed mood, hopelessness, self-deprecation, guilty ideas of reference, pathological guilt, depression worse in the morning, early wakening, suicide, and observed depression. The items on the CDSS are all typical depressive symptoms and do not appear to overlap with the negative symptoms of schizophrenia. The tool is administered via an interview with the subject.

9.1.10.8 [redacted]

[redacted]

9.1.10.9 [redacted]

[redacted]

9.1.10.10 [redacted]

[redacted]

[redacted]

9.1.10.10.1 Optional Smartphone Passive Data Collection

Data will be collected with an application on a smartphone that will be periodically sent to a secure database. After completing informed consent, an application will be installed in a provided smartphone or the subject's smartphone. The application will collect data from the smartphone from Day -14 through Day 84/early termination. These data will be collected during the typical use of the smartphone and do not require any additional action on the subject's part. The subject can at any time choose to discontinue participating in the passive data collection assessments; in this case, the application will be deactivated or uninstalled. The data captured by the application will be transmitted over a secure channel to a secure data storage site. All data captured by the application will be encrypted and stored encrypted at rest. The data collected

from the smartphone will include the number and time of certain activities during phone use such as texts, emails, and phone calls (but not any content from these activities); keyboard input activities and gestures (without collecting the specific keyboard characters); location information (from the Global Positioning System [GPS]); and movement and orientation (position) of the smartphone. No absolute GPS data will be captured; GPS data will be measured relative to a random location, masking the user's true location. These data will be used to develop a digital phenotype of subjects with schizophrenia and will be analyzed for any correlations with clinical endpoints. The data collection application does not collect information on who or what phone numbers are called, nor similar information from received calls. The data collection application does not capture the content of text messages that are sent or received. No personally identifiable information is captured, and all other data is encrypted on the smartphone before transmission to the secure database.

9.1.10.10.2 Optional Smartphone Visual/Audio/Electronic Clinical Assessments and Patient-Reported Outcome Assessments

These assessments will combine active and passive data collection via the smartphone that is used for study drug compliance monitoring. Active data collection assessments will include (1) standard schizophrenia symptom assessments and self-report questionnaires administered at regular intervals during the study, and (2) presentation of images from a standard set developed to elicit moderate emotional responses of positive valence (eg, duckling) or negative valence (eg, trash) and asking the subject to describe the image in a few sentences. The subject's facial expression, head posture, and properties of speech are analyzed after each image presentation. Passive data collection will be conducted during use of the device's compliance monitoring function and will include (1) analyzing the subject's facial expressions, head movements, and gestures, and (2) passive collection of smartphone use and movement/location data, as described above.

9.1.11 Additional Safety Assessments

9.1.11.1 Modified SAS

The SAS is a clinician-administered rating scale that has been widely used to assess antipsychotic-induced parkinsonism in clinical practice and research settings [42]. The present study uses a modified 10-item version of the SAS (for the screening and Day 1 assessment of eligibility) in which "Leg Pendulousness" and "Head Dropping" items included in the original version have been replaced with "Head Rotation" and "Akathisia," which has been used frequently in schizophrenia clinical trials [43]. Each item is rated using a 5-point scale (0-4); the modified SAS scores can range from 0 to 40.

9.1.11.2 C-SSRS

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical study of centrally-acting drugs [32]. The C-SSRS is composed of 3 questions addressing suicidal

behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via an interview with the subject.

Two versions of the C-SSRS will be used in this study: the Screening/Baseline C-SSRS Lifetime (assessing lifetime and the past year separately) and the Since-Last-Visit C-SSRS.

9.1.12 Order of Psychiatric/Neurological Rating Scales/Assessments

At screening, it is recommended to administer the BNSS first, followed by the C-SSRS. These assessments should precede all other psychiatric and neurological assessments at screening. After these assessments, the PANSS and then the MINI should be administered. At all other visits, the PANSS should take precedence over all other psychiatric assessments, and the BNSS should be administered after the PANSS. Thereafter, the order of assessments is not defined, except for the requirement that the CGI-SCH-I and CGI-SCH-S are completed after completion of all other psychiatric assessments (with an exception for the BACS, which does not contribute to the CGI assessments). Efforts should be made to perform the BACS cognition testing at approximately the same time of day throughout the study (postbaseline assessments must be administered ±2 hours from the time of baseline assessment administration).

9.1.13 PK Measurements

9.1.13.1 PK Sample Collection

Serial blood samples (one 4 mL sample per scheduled time point) for measurement of TAK-831 plasma concentrations will be collected into chilled Vacutainers containing the anticoagulant dipotassium ethylenediaminetetraacetic acid (K_2EDTA), according to the Schedule of Study Procedures (Appendix A).

The actual date and time of each PK blood sample collection, time since last dose was administered, and time since last meal will be recorded on the source document and eCRF.

Instructions for sample collection, processing, and shipment are provided in the laboratory manual.

9.1.13.2 Bioanalytical Methods

Plasma concentrations of TAK-831 will be measured by a validated high-performance liquid chromatography (HPLC) with tandem mass spectrometry method.

9.1.13.3 Population PK

PK will be assessed via population PK analysis (see Section 13.1.4).

9.1.14 [redacted]

[redacted]

[redacted]

9.1.14.1 [redacted]

[redacted]

9.1.14.2 [redacted]

[redacted]

9.1.14.3 [redacted]

[redacted]

9.1.15 [redacted]

[redacted]

[redacted]

9.1.15.1 [redacted]

[redacted]

9.1.16 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 39 mL (Visit 3), and the approximate total volume of blood for the study is 182 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a Approximate Blood Volume

Sample	Volume per Sample (mL)	Number of Samples Per Subject									Total Volume (mL)
		Screening (Days -28 to -15)	Placebo Run-in (Day -14)	Baseline (Predose Day 1)	Day 28	Day 42	Day 56	Day 70	Day 84/ET	Safety Follow-up (Days 94 to 98)	
		(Visit 1)	(Visit 2)	(Visit 3)	(Visit 6)	(Visit 7)	(Visit 8)	(Visit 9)	(Visit 10)	(Visit 11)	
HBsAg, anti-HCV	4	1									4
Hb1Ac	2	1									2
Serum chemistry [a]	6	1		1	1		1		1	1 [b]	36
Hematology	2	1		1	1		1		1	1 [c]	12
Antipsychotic medications [e]	4	1	1			1			1		16
[redacted]											
PK (TAK-831)	4			1	2	1	1		1		24
PD (D- and L-serine)	6		1	1	2	1	1		1		42
[redacted]											
Total											**182**

Anti-HCV: antibody to hepatitis C virus; HBsAg: hepatitis B surface antigen; Hb1Ac: glycosylated hemoglobin; ET: early termination; PD: pharmacodynamics; [redacted]: [redacted]; PK: pharmacokinetics.

[a] Includes serum pregnancy test at the screening and safety follow-up visits and follicle-stimulating hormone (FSH) test at screening.

[b] Serum chemistry tests will be performed at this visit only if clinically significant test results were reported at Day 84/ET. However, a serum pregnancy test must be performed for women of childbearing potential at this visit (blood sample volume will be reduced to 2 mL if other serum chemistry tests are not required).

[c] Hematology will be performed at this visit only if clinically significant test results were reported at Day 84/ET.

[redacted]

[e] Levels may be retested at investigator's request.

The tests that will be performed for each clinical laboratory sample are listed in Table 9.b.

Table 9.b Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Hematocrit	Sodium	Specific gravity
Hemoglobin	Potassium	pH
RBC	Bicarbonate	Glucose
Mean cell volume	Chloride	Protein
Mean cell hemoglobin	Calcium	Occult blood
Mean cell hemoglobin concentration	Magnesium	Microscopic battery (WBC,
WBC with differential % and absolute	Phosphorus	RBC, epithelial cells, casts)
(neutrophils, lymphocytes, monocytes,	Glucose	
eosinophils, basophils)	Blood urea nitrogen	
Platelets	Uric acid	
	Total cholesterol	
	Triglycerides	
	High-density lipoprotein cholesterol	
	Low-density lipoprotein cholesterol	
	Total protein	
	Albumin	
	Total bilirubin	
	Direct bilirubin	
	Alkaline phosphatase	
	ALT	
	AST	
	GGT	
	Creatine kinase	
	Amylase	
	Prolactin	
	Lactate dehydrogenase	
	Creatinine	
	Thyroid-stimulating hormone	

Other	
Serum	**Urine**
HbA1c	Drug screen including: amphetamine, barbiturates, benzodiazepines,
HBsAg and anti-HCV	cocaine, marijuana, methadone, methamphetamine, MDMA, opiates
hCG (for pregnancy) [a]	(including oxycodone) and phencyclidine
FSH [b]	hCG (for pregnancy) [a]
Antipsychotic medications [c]	

ALT: alanine aminotransferase; anti-HCV: antibody to hepatitis C virus; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; GGT: γ-glutamyl transferase; HbA1c: glycosylated hemoglobin; HBsAg: hepatitis B surface antigen; MDMA: 3,4-methylenedioxymethamphetamine; hCG: human chorionic gonadotropin; RBC: red blood cells; WBC: white blood cells.

[a] Women of childbearing potential only. Serum hCG test to be performed at the screening and safety follow-up visits, and urine hCG test to be performed at all other scheduled time points. The hCG test can be repeated at any time at the investigator's discretion.

[b] Postmenopausal females only.

[c] For all antipsychotics for which an assay is available at the central laboratory.

The central laboratory will perform the hematology, serum chemistry, urinalysis, and other clinical laboratory tests. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3× ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.6 and Section 10.2.3 for the appropriate guidance on reporting abnormal LFTs.)

If ALT or AST remains elevated >3× ULN on these 2 consecutive occasions, the investigator must contact the sponsor or designee for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details, and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3).

9.1.16.1 Antipsychotic Plasma Levels

Experience with therapeutic blood monitoring of antipsychotic medications in clinical settings has demonstrated that a single antipsychotic plasma assessment may not be reliably representative of adherence to antipsychotic medications, so repeat testing may be warranted to confirm an initial finding of a lower than adequate plasma level.

Screening antipsychotic plasma levels that do not meet the criteria listed in the Antipsychotic Reference document should be repeated as soon as possible if, in the judgment of the investigator, the subject may actually be adherent to their medication regimen. Importantly, if the investigator's initial assessment results in a determination that the subject is most likely not being adherent with their antipsychotic medication regimen, the plasma level should not be repeated and the subject should be a screen failure.

If it is uncertain whether the subject is being adherent with treatment, it is recommended that antipsychotic plasma levels be urgently collected and sent to the central laboratory while the investigator collects additional information. If the investigator subsequently determines that the subject is not adherent to their medication regimen, the subject should be a screen failure.

It is important to note that Visit 2 should not be conducted before receipt of the antipsychotic plasma level indicating an acceptable value (in addition to the sponsor or designee and centralized eligibility vendor approvals). The Antipsychotic Reference document should be consulted for additional guidance in the management and interpretation of antipsychotic plasma level assays.

9.1.17 Contraception and Pregnancy Avoidance Procedure

9.1.17.1 Male Subjects and Their Female Partners

Male subjects are not required to use barrier contraception in this study.

9.1.17.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 35 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use an acceptable effective method of contraception (from the list below). In addition, they must be advised not to donate ova during this period.

9.1.17.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

*A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, <45 years of age) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

**Sterilized males should be at least 1 year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are as follows:
   - Nonhormonal Methods:
     - Intrauterine device.
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the study subject and that the vasectomized partner has received medical assessment of the surgical success).
     - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 35 days after last dose.
     - Cervical cap (PLUS spermicidal cream or jelly) PLUS male condom.
     - Diaphragm (PLUS spermicide cream or jelly) PLUS male condom.
   - Hormonal Methods:
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug

OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months.

- Oral.
- Intravaginal (eg, ring).
- Transdermal.

– Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter until she has been on contraceptive for 3 months.

- Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action, PLUS condom with or without spermicide.
- Oral.
- Injectable.
- Implantable.

2. Unacceptable methods of contraception are as follows:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
3. Subjects will be provided with information on acceptable effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova during the course of the study.
4. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential, and all female subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Assessment of subject compliance through questions such as the following:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?

iii. Are your menses late? (Even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes.")

iv. Is there a chance you could be pregnant?

5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses). At the single-blind placebo run-in visit (Day -14) and the baseline/randomization visit (Day 1), a negative urine hCG pregnancy test must be established prior to the subject receiving any dose of study drug.

9.1.18 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug (TAK-831 or placebo) should be immediately discontinued.

If the pregnancy occurs during administration of active study drug, eg, after Visit 3 (baseline/randomization visit) or within 95 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded study drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If a female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.19 ECG Procedure

A standard 12-lead ECG will be recorded. The following parameters will be recorded electronically by a central reader from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval and QTcF. The central reader will interpret the ECG using 1 of the following categories: within normal limits or abnormal. If interpreted as abnormal, the investigator will assess the findings as either abnormal clinically significant, or abnormal not clinically significant. The interpretation of the ECG will be recorded in the source documents and in the eCRF. ECG traces recorded on thermal paper will be photocopied to avoid degradation of the trace over time. Requirements for the ECG equipment and procedure for collecting and transferring information to the central reader will be provided in the study reference manual.

9.1.20 Documentation of Screen Failure

Investigators must account for all subjects who sign an informed consent. If the subject is found to be ineligible at the screening visit, the investigator should complete the eCRF. The IRT should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Important protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason including unavoidable circumstances such as the COVID-19 pandemic).

Subject ID numbers assigned to subjects who fail screening should not be reused.

9.1.21 Documentation of Randomization Failure

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the double-blind treatment period on Day 1. The IRT will be contacted for treatment assignment and this information should be captured on the appropriate eCRF. If the subject is found to be ineligible for randomization during the screening period, the investigator should record the primary reason for failure on the applicable eCRF and register the subject as a randomization failure in the IRT.

In addition, the primary reason for randomization failure will be recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Did not meet study drug compliance criteria.
- Important protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason including unavoidable circumstances such as the COVID-19 pandemic).

9.1.22 Rater Qualification and Certification Process

To ensure collection of quality data from scales administered by raters, raters assigned to this study will be required to fulfill qualification and/or training requirements. The process for qualifying and training raters will be described in manuals provided by rater training and assessment vendors. Furthermore, the study will include additional steps related to monitoring the quality of rater activity, which will be described in the manuals provided by these vendors.

All raters will be required to successfully fulfill the full scope of rater training requirements for any scale they will be administering prior to rating any subjects in this study. The sites will be responsible for ensuring that they have qualified raters who can conduct assessments in the study prior to enrollment of study subjects.

The training materials and requirements may be adjusted or modified as needed throughout the course of the study.

9.1.22.1 Rater Qualifications

Each site will be required to identify and provide skilled raters who meet appropriate prespecified qualifications. Takeda and/or designee will make the final decision regarding whether the site-assigned raters are acceptable to participate in the study.

9.1.22.2 Submission of Experience Details

Raters will be required to complete and submit experience details and curriculum vitae (if applicable) to the rater vendor in a timely manner. Once the rater's experience level is reviewed and deemed adequate, then study-assigned raters will be approved to participate in the rater certification process.

9.1.22.3 Rater Training and Qualification Program

Formal rater training and qualification will be conducted at the Investigator's Meeting and via web portals. For those raters who need to be trained outside of the Investigator's Meeting, the training will be conducted via web portals and/or on-site or remote training. Specific elements of the rater training and qualification program will be described further in the rater training and assessment vendor manuals.

Raters who receive an unacceptable rating will be required to complete additional training in conjunction with the Takeda-designated rater training vendor.

9.1.22.4 Site Changes to Rater Personnel During the Study

If a site rater changes during the course of the study, the newly appointed rater must be approved by Takeda for participation and must complete all training and certification requirements satisfactorily before the rater can begin participation on any study-related activities.

9.1.22.5 Rater Monitoring

This study will use electronic clinical outcome assessments (eCOAs) to capture questionnaire data. The data will be transmitted electronically to a centralized database at the eCOA vendor.

Data may be reviewed by site staff via secure access. eCOA data will be collected using a device provided by the eCOA vendor. The device is designed for entry of data in a way that is compliant with regulations for electronic records.

Appropriateness of the MINI, PANSS, and BNSS assessment administration and the scoring of responses will be monitored through video recordings (for exceptions, see Section 9.1.10) and electronic workbooks at predefined intervals (see Sections 9.1.10.1, 9.1.10.2, and 9.1.10.5) located in the ratings vendor manual.

Additional scale data will be monitored for consistency and quality control throughout the study. Further instructional activities or advisement will occur and may be requested for certain sites, if necessary.

BACS and SCoRS ratings may be reviewed by the vendor providing these assessments at a frequency determined by the sponsor. Copies of BACS and SCoRS source documents will be reviewed by the vendor's data review specialists for errors in scoring and administration. Errors will be noted by reviewers, and feedback delivered to raters so that corrected scores can be entered into the study database.

9.2 Monitoring Subject Treatment Compliance

A digital compliance technology will be implemented in this study. Further details regarding this technology is provided in the study reference manual. Subjects also will be required to bring study drug packaging to each clinic visit, regardless of whether the study drug packaging is empty.

All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

Noncompliance with study drug includes subjects who are <75% compliant between visits (including noncompliance as assessed via the digital compliance technology). If these criteria for noncompliance are met on more than 1 occasion during the study, the subject will be considered significantly out of compliance and the site investigator will need to discuss the subject's continuation in the study with the sponsor (or designee). Based upon the assessment of the investigator and sponsor (or designee), an out-of-compliance subject may be withdrawn from the study. As an exception, subjects who are living in a residential setting that incorporates directly observed medication administration demonstrate ≥75% compliance (but not via the digital compliance technology) may be considered to be within these compliance requirements with study site documentation and approval of the sponsor or designee.

9.3 Schedule of Observations and Procedures

The Schedule of Study Procedures is provided in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Poststudy Care

Study drug will not be available upon completion of the subject's participation in the study. Since suitable subjects for this study will be symptomatically stable and on a stable antipsychotic treatment regimen, it is recognized that they will be under the care of the investigator or another treating physician before entry into the study and during study conduct. The subject should be returned to the care of a physician and standard therapies as required after study participation.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.15. The genetic material will be preserved and retained at the long-term storage biorepository for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

[redacted]. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study 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 this definition.

10.1.2 AEs

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.

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.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as a PTE or AE if the condition becomes more frequent, serious, or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE or AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after the first administration of study drug or any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs/serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AEs

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
COVID-19-related disease	Neuroleptic malignant syndrome/malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion/stillbirth and fetal death

AE: adverse event; COVID-19: coronavirus disease 2019; SAE: serious adverse event.
Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

AEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 AEs of Special Interest

No AEs of special interest have been identified for TAK-831.

10.1.6 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject. The event does not generally interfere with usual activities of daily living.

Moderate: An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.1.7 Assigning Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

10.1.11 Frequency

Episodic AEs/PTEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous or once.

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE, eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE/PTE.
- Recovering/resolving – the intensity is lowered by 1 or more stages; the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered double-blind study drug (Day 1; Visit 3) or until screen failure. For subjects who discontinue prior to double-blind study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered double-blind study drug (Day 1; Visit 3). Routine collection of AEs will continue until the Safety follow-up visit (between Days 94 and 98; Visit 11).

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a SAE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious AEs, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs/AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Pattern of AE (Frequency).
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not completed for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

- A short description of the event and the reason why the event is categorized as serious.
  - Subject ID number.
  - Investigator's name.
  - Name of the study drug(s).
  - Causality assessment.
- SAEs should be reported via the SAE eCRF page in electronic data capture ([EDC]/RAVE), which is the preferred method of reporting SAEs.
- If access to EDC/RAVE is not feasible within 24 hours of receiving the event, the paper SAE forms should be submitted via fax (please see fax numbers below).
  - In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.
- Email submission of SAE forms with a PDF attachment should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event.

  - In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

- If SAEs are reported via fax or by email, EDC/RAVE must be updated as soon as possible with the appropriate information.
- **Fax Numbers:**
  - United States and Canada: +1-224 554-1052
  - Rest of World: +1-224 554-1052
- **Email Addresses:**
  - United States and Canada: PVSafetyAmericas@tpna.com
  - Rest of World: eupv@tgrd.com.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3× ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an appropriate eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3× ULN and total bilirubin >2× ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the sponsor or designee for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up entry in the EDC by completing a SAE eCRF per Section 10.2.2 immediately or within 24 hours of receipt. Follow up SAE forms (if EDC is unavailable) or other written documentation must be faxed immediately or within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Data Monitoring Committee

This study does not include endpoints related to assessing mortality or major adverse health outcomes, and the study population is not at risk of serious safety events since subjects will be required to be symptomatically stable and maintained on their current standard of care treatments throughout the conduct of the study. In addition, as summarized in Section 4.1.3, TAK-831 has been well tolerated and safe across the full range of doses examined in clinical studies, and there have not been any safety findings that indicate the need for an independent Data Monitoring Committee (DMC).

However, in addition to the ongoing review of blinded safety data by the sponsor and designee during the conduct of this study, the sponsor will establish an internal DMC that is independent of the study and project teams to periodically review unblinded safety data during conduct of the study to complement the routine safety monitoring approach for drugs at this stage of development. If there is an interim analysis for futility, this committee will also be engaged to review the interim analysis results and make recommendations per the interim analysis plan. The functions and procedures of the committee will be outlined in a DMC Charter prior to the first DMC review meeting.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or designee will supply study sites with access to eCRFs. The sponsor or designee will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the data entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must e-sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or designee. The sponsor or designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), copies of all paper CRFs and query responses/electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities or from the sponsor or designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Council for Harmonisation (ICH) E6 (R2) Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 (R2) Section 4.9.5 states that the study records

should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

An SAP will be prepared and finalized prior to unblinding of treatment assignments to the study team. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of treatment assignments to the study team. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 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 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.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics including age, gender, race, BMI, and medical history will be listed and summarized by treatment group and overall based on the FAS.

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

13.1.3 Efficacy Analysis

13.1.3.1 Analysis of Primary Efficacy Endpoint

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.

Additional analyses to address sensitivity to missing data will be specified in the SAP.

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. Additional details of the MCP-Mod analysis will be specified in the SAP.

Before unblinding the data, the team will assess the degree of impact from COVID-19 on PANSS NSFS data completeness or collection modality. If the impact is deemed minimal, which is defined as less than 5% of the enrolled subjects having remote or missing final assessments due to COVID-19, then the original analysis plan will be followed. If there is more than a minimal impact, then a more thorough blinded review will be performed. After the blinded assessment, if substantial changes to the statistical analyses are needed to address the impact, the SAP will be amended before study unblinding. Minor changes may be documented in the clinical study report.

13.1.3.2 Analysis of Other Efficacy Endpoints

Other change from baseline endpoints will be analyzed in the same manner as the primary endpoint, but without control for multiple doses.

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.

For BNSS, BACS, CGI-SCH-I, CGI-SCH-S, SCoRS, PANSS total score and additional subscales and factors, the degree of impact from COVID-19 on completeness or collection modality will be assessed before unblinding the data. If the impact on an endpoint is deemed minimal, which is defined as less than 5% of the enrolled subjects having remote or missing final assessments due to COVID-19, then the original analysis plan will be followed. If there is more than a minimal impact, then a more thorough blinded review will be performed. After the blinded assessment, if substantial changes to the statistical analyses are needed to address the impact, the SAP will be amended before study unblinding. Minor changes may be documented in the clinical study report.

13.1.4 PK Analysis

PK samples will be collected for the purpose of assessing exposure and compliance with study drug treatment. Plasma concentrations of TAK-831 will be presented in the data listings.

Plasma concentrations of TAK-831 will be listed for each subject and summarized by each time point for each TAK-831 treatment group. Of note, the sparse PK sampling approach in this study will not support generation of typical PK parameters.

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. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses will be reported separately.

13.1.5 PD 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. Additional details and further analyses will be specified in the SAP (also see Section 13.1.4).

[redacted]

13.1.6 [redacted]

[redacted]

13.1.7 Safety Analysis

13.1.7.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. 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. TEAEs will be summarized by SOC and PT. The following summary tables will be generated: summary of TEAEs and drug-related TEAEs, relationship of TEAEs to study drug (related vs not related), severity of TEAEs, and related TEAEs. Data listings will be provided for all AEs, including TEAEs, TEAEs leading to study drug discontinuation, and SAEs.

13.1.7.2 Clinical Laboratory Evaluation

Individual results of clinical laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be summarized and provided in the data listings. baseline, postdose, and change from baseline to postdose laboratory data will be summarized. All clinical laboratory data will be provided in the data listings.

13.1.7.3 Vital Signs

Individual results of vital signs that meet Takeda's markedly abnormal criteria will be summarized and provided in the data listings. Baseline, postdose, and changes from baseline in vital sign measurements will be summarized. All vital sign data will be provided in the data listings.

13.1.7.4 ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet Takeda's markedly abnormal criteria will be summarized and provided in the data listings. 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.

13.1.7.5 C-SSRS

C-SSRS will be summarized at all time points for each treatment group using descriptive statistics.

13.2 Interim Analysis and Criteria for Early Termination

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.

13.3 Determination of Sample Size

Assuming that the effect size is at least 0.4 for the 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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Data Monitoring

A data monitoring plan will be developed to assess the cognition and functionality data in an ongoing manner over the course of the study to ensure validity and integrity of key study endpoint data.

14.3 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, such as the COVID-19 pandemic, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of an important protocol deviation, the site should notify the sponsor or designee (and IRB or IEC, as required). Important deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. Important protocol deviations will be reviewed at regular intervals by the sponsor and designee.

14.4 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where study drug is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom

Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study sites guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor or designee will ship drug/notify site once the sponsor or designee has confirmed the adequacy of site regulatory documentation.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's

medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

[redacted] Investigator will notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws, and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or designee.

16.0 REFERENCES

1. Verrall L, Burnet PW, Betts JF, Harrison PJ. The neurobiology of D-amino acid oxidase and its involvement in schizophrenia. Mol Psychiatry 2010;15(2):122-37.
2. Kakegawa W, Miyoshi Y, Hamase K, Matsuda S, Matsuda K, Kohda K, et al. D-serine regulates cerebellar LTD and motor coordination through the delta2 glutamate receptor. Nat Neurosci 2011;14(5):603-11.
3. Duffy S, Labrie V, Roder JC. D-serine augments NMDA-NR2B receptor-dependent hippocampal long-term depression and spatial reversal learning. Neuropsychopharmacology 2008;33(5):1004-18.
4. Balu DT, Takagi S, Puhl MD, Benneyworth MA, Coyle JT. D-serine and serine racemase are localized to neurons in the adult mouse and human forebrain. Cell Mol Neurobiol 2014;34(3):419-35.
5. Sham PC, Gottesman, II, MacLean CJ, Kendler KS. Schizophrenia: sex and familial morbidity. Psychiatry Res 1994;52(2):125-34.
6. Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999;56(2):162-8.
7. Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo UH, Bassett AS, Cornblatt BA, Kestenbaum CJ, et al. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch Gen Psychiatry 1995;52(10):857-65.
8. van Os J, Kapur S. Schizophrenia. Lancet 2009;374(9690):635-45.
9. Poels EM, Kegeles LS, Kantrowitz JT, Slifstein M, Javitt DC, Lieberman JA, et al. Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. Mol Psychiatry 2014;19(1):20-9.
10. Fervaha G, Foussias G, Agid O, Remington G. Motivational deficits in early schizophrenia: prevalent, persistent, and key determinants of functional outcome. Schizophr Res 2015;166(1-3):9-16.
11. Strassnig MT, Raykov T, O'Gorman C, Bowie CR, Sabbag S, Durand D, et al. Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity. Schizophr Res 2015;165(1):76-82.
12. Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 2003;169(3-4):215-33.
13. Calcia MA, Madeira C, Alheira FV, Silva TC, Tannos FM, Vargas-Lopes C, et al. Plasma levels of D-serine in Brazilian individuals with schizophrenia. Schizophr Res 2012;142(1-3):83-7.

14. Ohnuma T, Sakai Y, Maeshima H, Hatano T, Hanzawa R, Abe S, et al. Changes in plasma glycine, L-serine, and D-serine levels in patients with schizophrenia as their clinical symptoms improve: results from the Juntendo University Schizophrenia Projects (JUSP). Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):1905-12.
15. Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, et al. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the N-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch Gen Psychiatry 2003;60(6):572-6.
16. Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(5):767-9.
17. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511(7510):421-7.
18. Lane HY, Lin CH, Green MF, Hellemann G, Huang CC, Chen PW, et al. Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. JAMA Psychiatry 2013;70(12):1267-75.
19. Radi ZA, Stewart ZS, Grzemski FA, Bobrowski WF. Renal pathophysiologic role of cortical tubular inclusion bodies. Toxicol Pathol 2013;41(1):32-7.
20. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Treatment Recommendations for Patients With Schizophrenia. In: Practice Guideline for the Treatment of Patients With Schizophrenia. 2nd ed. Washington, DC: American Psychiatric Association; 2004; Part A, p. 3-35.
21. Note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia. European Medicines Agency, Committee for Medicinal Products for Human Use. Publication No. CPMP/EWP/5595/95.
22. 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.
23. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl 2003(416):16-23.
24. Guy W. Clinical Global Impression (CGI), ECDEU Version. In: ECDEU Assessment Manual for Psychopharmacology. Revised ed. Rockville, MD: U.S. Dept. of Health, Education, and Welfare; 1976; DHEW publication no. (ADM) 76-338, p. 218-22.
25. Mortimer AM. Symptom rating scales and outcome in schizophrenia. Br J Psychiatry Suppl 2007;50:s7-14.
26. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull 2011;37(2):300-5.

27. Strauss GP, Hong LE, Gold JM, Buchanan RW, McMahon RP, Keller WR, et al. Factor structure of the Brief Negative Symptom Scale. Schizophr Res 2012;142(1-3):96-8.

28. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 2004;68(2-3):283-97.

29. Keefe RS, Poe M, Walker TM, Kang JW, Harvey PD. The Schizophrenia Cognition Rating Scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. Am J Psychiatry 2006;163(3):426-32.

30. Green MF, Nuechterlein KH, Kern RS, Baade LE, Fenton WS, Gold JM, et al. Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS Psychometric and Standardization Study. Am J Psychiatry 2008;165(2):221-8.

31. Garay RP, Citrome L, Samalin L, Liu CC, Thomsen MS, Correll CU, et al. Therapeutic improvements expected in the near future for schizophrenia and schizoaffective disorder: an appraisal of phase III clinical trials of schizophrenia-targeted therapies as found in US and EU clinical trial registries. Expert Opin Pharmacother 2016;17(7):921-36.

32. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266-77.

33. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. European Psychiat 1997(12):224-31.

34. Sheehan DV, Lecrubier Y, Sheehan KH, Janavs J, Weiller E, Keskiner A, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry 1997;12:232-41.

35. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33;quiz 4-57.

36. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry Suppl 1993(22):39-44.

37. Bersani G, Paolemili M, Quartini A, Clemente R, Gherardelli S, Iannitelli A, et al. Neurological soft signs and cerebral measurements investigated by means of MRI in schizophrenic patients. Neurosci Lett 2007;413(1):82-7.

38. Ho BC, Mola C, Andreasen NC. Cerebellar dysfunction in neuroleptic naive schizophrenia patients: clinical, cognitive, and neuroanatomic correlates of cerebellar neurologic signs. Biol Psychiatry 2004;55(12):1146-53.

39. Emsley R, Chiliza B, Asmal L, Kilian S, Riaan Olivier M, Phahladira L, et al. Neurological soft signs in first-episode schizophrenia: State- and trait-related relationships to psychopathology, cognition and antipsychotic medication effects. Schizophr Res 2017.

40. Mulhern B, Mukuria C, Barkham M, Knapp M, Byford S, Soeteman D, et al. Using generic preference-based measures in mental health: psychometric validity of the EQ-5D and SF-6D. Br J Psychiatry 2014;205(3):236-43.

41. Isitt JJ, Nadipelli VR, Kouassi A, Fava M, Heidbreder C. Health-related quality of life in acute schizophrenia patients treated with RBP-7000 once monthly risperidone: An 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. Schizophr Res 2016;174(1-3):126-31.

42. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11-9.

43. Moore TJ, Furberg CD. The harms of antipsychotic drugs: Evidence from key studies. Drug Saf 2017;40(1):3-14.

Appendix A Schedule of Study Procedures

	Screening	Placebo Run-in	12-Week Double-Blind Treatment Period								Safety Follow-up
Study Day	**Days -42 to -15 [a]**	**Day -14**	**Day 1 [b]**	**Day 7 [q]**	**Day 14 [q]**	**Day 28 [q]**	**Day 42 [q]**	**Day 56 [q]**	**Day 70 [q]**	**Day 84/ ET [b, c]**	**Days 94-98 (10-14 days after last dose)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit Window (Days) [d]		**+7 [e]**	**±2**	**±2**	**±1**	**±2**	**±2**	**±2**	**±2**	**±5**	**±2**
Informed consent	X										
Clinical Trial Subject Database consent	X										
Informant informed consent [f]	X	X									
MINI	X										
Centralized subject eligibility assessment	X	X									
Inclusion/exclusion criteria	X	X	X								
Demographics, medical history, substance use	X										
Medication history	X										
Concurrent medical conditions	X										
Physical examination	X									X	
Vital signs [g]	X	X	X	X	X	X	X	X	X	X	X
Height, BMI, weight [h]	X									X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests [i]	X		X			X		X		X	
HBsAg, anti-HCV	X										
FSH	X										
HbA1c	X										
Pregnancy test (hCG) [j]	X	X	X			X		X		X	X
Urine drug screen [k]	X	X	X			X		X		X	
12-lead ECG	X		X							X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
CDSS	X										
Modified SAS	X										
PANSS	X	X	X			X		X		X	
BNSS	X	X	X			X		X		X	
CGI-SCH-I						X		X		X	
CGI-SCH-S	X	X	X			X		X		X	
[redacted]											
BACS [l]		X	X				X			X	

	Screening	Placebo Run-in	12-Week Double-Blind Treatment Period								Safety Follow-up
Study Day	**Days -42 to -15 [a]**	**Day -14**	**Day 1 [b]**	**Day 7 [q]**	**Day 14 [q]**	**Day 28 [q]**	**Day 42 [q]**	**Day 56 [q]**	**Day 70 [q]**	**Day 84/ ET [b, c]**	**Days 94-98 (10-14 days after last dose)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit Window (Days) [d]		**+7 [e]**	**±2**	**±2**	**±1**	**±2**	**±2**	**±2**	**±2**	**±5**	**±2**
SCoRS			X							X	
[redacted]											
Plasma sample for TAK-831 PK [n]			X			X	X	X		X	
Plasma sample for PD (D- and L-serine) [n]		X	X			X	X	X		X	
[redacted]											
Plasma sample for antipsychotic medications	X	X					X			X	
PTE/AE assessment	X	X	X	X	X	X	X	X	X	X	X
Call IRT for subject ID/medication ID		X	X	X	X	X	X	X	X	X	
Digital compliance technology training		X									
[redacted]											
Randomization			X								
Dispense study drug [p]		X	X	X	X	X	X	X	X		
Study drug return/accountability/compliance			X	X	X	X	X	X	X	X	
In-clinic study drug dosing		X	X			X					

AE: adverse event; anti-HCV: antibody to hepatitis C virus; BACS: Brief Assessment of Cognition in Schizophrenia; BMI: body mass index; BNSS: Brief Negative Symptom Scale; CDSS: Calgary Depression Scale Score; CGI-SCH-I: Clinical Global Impression-Schizophrenia-Improvement; CGI-SCH-S: Clinical Global Impression-Schizophrenia-Severity; COVID-19: coronavirus disease 2019; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; eCRF: electronic case report form; [redacted]; ET: early termination; FSH: follicle-stimulating hormone; HbA1c: glycosylated hemoglobin; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; ID: identification; IRT: interactive response technology; MINI: Mini International Neuropsychiatric Interview; [redacted]; PANSS: Positive and Negative Syndrome Scale; PD: pharmacodynamic(s); [redacted]; PK: pharmacokinetic(s); PTE: pretreatment event: QD: once daily; SAS: Simpson Angus S0ocale; SCoRS: Schizophrenia Cognition Rating Scale.

[a] Medical Evaluation Form must be reviewed by the sponsor or designee, and a third-party independent expert clinician review of selected assessments included in the study Entry Criteria must be completed, prior to subject entry into the placebo run-in period.

[b] Randomization is performed at Day 1 (Visit 3). If courier-related delays of laboratory test results occur (eg, due to COVID-19 related factors), Visit 3 may be delayed up to a maximum of 7 days after discussion with and approval from the sponsor or designee. For the screening and Day 1 visits, the study assessments may be conducted over 2 days that must be completed within a 5-day period or less. All Day 1 procedures must be completed and compared with the relevant study entry criteria prior to randomization. The first dose of study drug will be administered in the clinic at the end of the Day 1 visit (or as the last procedure if the Day 1 visit is split over 2 days). Subjects will then take study drug QD in the morning from Day 2 onward during the double-blind treatment period.
Study procedures for the Day 84/ET (Visit 10) may be conducted over 2 consecutive days for subject's comfort and assessment feasibility. The final visit (Day 84/ET) should be performed in person. Alternative methods for administering study assessments may be considered when it is not possible for the subject to come to the study site or for the site staff or designated clinical personnel to go to the subject's residence for the final visit (Day 84/ET) in cases where unavoidable circumstance such as the COVID-19 pandemic are prohibitive. Investigators should contact the sponsor or designee to discuss individual subject circumstances (Section 9.1.1).

[c] For subjects who prematurely discontinue the study, the PANSS, BNSS, BACS, SCoRS, CGI-SCH-I, CGI-SCH-S, and [redacted] assessments should be performed only in subjects who received at least 1 dose of study drug and are assessed within 1 week of the last dose of study drug; all other ET procedures should be performed for subjects who are assessed >1 week after the last dose of study drug.

[d] If the date of a subject visit does not conform to the study plan, the timing of the subsequent visits should be planned to maintain the visit schedule relative to randomization.

[e] In cases where antipsychotic serum levels are not available within the expected 7 days window, additional screening window may be granted in these cases with sponsor or designee approval.

[f] May be obtained at screening (Visit 1) or placebo run-in (Visit 2) or at the informant's location. The initial discussion with the informant may include an oral informed consent.

[g] Supine blood pressure and pulse will be measured at screening (Visit 1), Day 1 (Visit 3), Day 42 (Visit 7), and Day 84/ET (Visit 10); sitting blood pressure and pulse will be measured at all other scheduled time points.

[h] Height and BMI will be collected at screening (Visit 1) only.

[i] Hematology, serum chemistry, and urinalysis. Clinical laboratory blood samples will be collected after a 6-hour fast, with the exception of screening (Visit 1) when fasting is not required. Antipsychotic serum blood levels may be retested at investigator's request.

[j] Women of childbearing potential only. Serum hCG test will be performed at screening (Visit 1) and safety follow-up (Visit 11). Urine hCG tests will be performed at all other scheduled time points. The hCG test can be repeated at any time at the investigator's discretion.

[k] May be repeated at any time at the investigator's discretion.

[l] Efforts should be made to perform the BACS assessment at approximately the same time of day throughout the study (postbaseline assessments must be administered ±2 hours from the time of baseline assessment administration).

[redacted]

[n] On Day -14 (Visit 2), 1 PD sample will be collected. On Day 1 (Visit 3), 1 PK blood sample and 1 PD blood sample will be collected predose. On Day 28 (Visit 6), subjects will take study drug at the site after predose PK and PD blood samples have been collected, and repeat PK and PD blood samples will be collected at the end of the visit. On Day 42 (Visit 7), Day 56 (Visit 8), and Day 84/ET (Visit 10), 1 PK blood sample and 1 PD blood sample will be collected at each visit; the subject will take study drug at the usual time in the morning before each of these 3 visits. For Days 42 and 56, it is recommended that sites schedule the clinic visit at different times of the day: 1 visit in the morning and 1 visit in the afternoon. It is recommended that the Day 42 Visit be scheduled in the afternoon because the subject does not have to fast for safety laboratory assessments. The actual date and time of each PK blood sample collection, time since last dose was administered, and time since last meal will be recorded on the source document and eCRF.

[redacted]

[p] Study subjects will be instructed to take their study drug QD in the morning with water or milk; subjects should avoid drinking juices 1 hour before and 1 hour after taking study drug.

[q] All attempts should be made to perform the assessments with the subject present at the site. However, in certain unavoidable circumstances (such as the COVID-19 pandemic), alternative methods for conducting subject visits (eg, video conferencing, telephone visits, or in-home study visits conducted by site personnel contingent upon local regulations) may be used per approval by the sponsor or designee. It may be necessary to perform some of the visit procedures remotely or at subjects' residence contingent upon local regulations. Sites should contact the sponsor or designee (eg, contract research organization contact) to discuss individual subject and site circumstances. Approval may be granted for remote assessments, alternative methods to delivering investigational medicinal product or for study site personnel or designated clinical personnel to visit the subject at their residence. Additionally, approval may be granted to omit collection of certain study assessments and visit windows may be extended. There will be no interval longer than 8 weeks between visits at which clinical laboratory tests are performed and vital signs are measured. Should this 8 week interval be reached for a particular subject, the site should reach out to the sponsor or designee to discuss withdrawal of the subject (Section 9.1.1).

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities [by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
13. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the

subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. [redacted]
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use acceptable effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for 35 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during the study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information. Male subjects are not required to use barrier contraception in this study.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E History of Protocol Amendments 01 through 03

Amendment History:

Date	Amendment Number	Amendment Type	Region
30 October 2017	Initial Protocol	Not applicable	Global
26 June 2018	Amendment 01	Substantial	Global
19 July 2018	Amendment 02	Substantial	Local (Czech Republic)
13 March 2019	Amendment 03	Substantial	Global

Protocol Amendment No. 01 Summary of Changes and Rationale

This section describes the changes in reference to the protocol incorporating Amendment No. 01. The primary reason for this amendment was to revise elements of the study design.

In addition, inclusion/exclusion criteria, randomization criteria, excluded medications, criteria for discontinuation or withdrawal of a subject to include deterioration of the underlying illness, companion medications, monitoring of plasma levels of antipsychotic medication, contraception procedures, poststudy care, clarification of study procedures, and updating acceptable contraception options were revised for clarification or optimization of the prior protocol content. The number of subjects and statistical methods were revised for optimizing the study efficacy analysis based on re-evaluation of the relevant scientific contingencies.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Changes in Amendment No. 01

1. Revision of elements of study design.
2. Revision of exploratory objectives, safety endpoints, and exploratory endpoints.
3. Revision of inclusion/exclusion criteria.
4. Clarification on randomization criteria.
5. Revision of excluded medication and dietary products.
6. Revision of criteria for discontinuation or withdrawal of a subject.
7. Revision of storage conditions for drug supplies.
8. Monitoring of antipsychotic plasma levels.
9. Clarification on contraception and pregnancy avoidance procedure.
10. Clarification on poststudy care.
11. Revision of statistical methods.
12. Revision of benefit risk profile.

13. Updating treatment compliance.

Protocol Amendment No. 02 (Local Czech Republic)

The Czech Republic country-specific amendment was based on feedback from the Czech Republic regulatory authority in their review of the original protocol.

Protocol Amendment No. 03 Summary of Changes and Rationale

This section describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reason for this amendment was to revise the assessments to reduce subject and site burden, revise inclusion/exclusion criteria to provide appropriate flexibility to the subject and site, revise concomitant medication requirements, and to update recommendations for the management of pregnancy and lactation based on the relevant TAK-831 nonclinical studies. In addition, additional clarifications were provided in study design, inclusion/exclusion criteria, randomization criteria, excluded medications, criteria for discontinuation or withdrawal of a subject, video monitoring for assessments, monitoring of plasma levels of antipsychotic medication, and rater monitoring.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment No. 03

1. Updated medical monitor contact information.
2. Removed Q-LES-Q 18 assessment from the study.
3. Revised study design to increase the number of clinical sites, clarify management of run-in medication, clarify informed consent procedures for informants, and allow for flexibility in scheduling the Day 2 visit.
4. Revised inclusion and exclusion criteria based on updates made to excluded medications and new recommendations for the management of pregnancy and lactation; provided additional clarification of exclusionary characteristics for subjects with diabetes; added an exception for inclusion of subjects with Gilbert syndrome; and added criteria to exclude subjects who may be less likely to respond to treatment; additional changes were made for clarity and consistency.
5. Updated study drug compliance criteria and instructions for subject randomization approval.
6. Removed anticonvulsants and uridine 5′-diphospho-glucuronosyltransferase (UGT) enzyme inhibitors from excluded medications list and provided additional clarification on commonly prescribed concomitant medications permitted during the conduct of the study.
7. Revised study drug compliance threshold in criteria for discontinuation and added text for consistency with revisions to randomization criteria.
8. Clarified use of nonbenzodiazepine hypnotics.

9. Modified rescue medications to include benzodiazepine hypnotics when used within their recommended dose ranges.
10. Added text to allow for flexibility with morning dosing.
11. Corrected instructions for the destruction of sponsor-supplied drugs.
12. Added text to allow for infra-axillary temperature measurement.
13. Added text to allow for individual exceptions for video recording of clinical interviews.
14. Revised order of psychiatric/neurological scales/assessments.
15. [redacted]
16. Added text to clarify the management and interpretation of antipsychotic plasma level assays.
17. Updated contraceptive and pregnancy avoidance procedures.
18. Updated pregnancy procedures.
19. Revised SAE collection procedures to include instructions for electronic data capture.
20. Revised CDSS and modified SAS assessments in Schedule of Study Procedures.
21. Revised Schedule of Study Procedures footnotes for consistency and clarification.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]		08-Jun-2020 12:54 UTC
		08-Jun-2020 14:14 UTC
		08-Jun-2020 16:23 UTC
		08-Jun-2020 16:54 UTC