TAKEDA PHARMACEUTICALS

PROTOCOL

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

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

Study Number: TAK-831-2001

Compound: TAK-831

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1.0 STUDY SUMMARY

Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge MA 02139 USA	**Compound:** TAK-831
Study Number: TAK-831-2001	**Phase:** 2
Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate Pharmacodynamic Effects, Safety, Tolerability, and Pharmacokinetics of Multiple Oral Doses of TAK-831 in Adult Subjects With Schizophrenia	
Study Design: This study is a randomized, double-blind, placebo-controlled, 2-period crossover phase 2 study to evaluate the pharmacodynamic (PD) effects, safety, tolerability and pharmacokinetics (PK) of multiple daily oral doses of TAK-831 in adult patients with schizophrenia. Effects of up to 2 dose levels of TAK-831 or placebo will be assessed. Each treatment will be administered daily for a period of 8 consecutive days, separated by a 14- to 21-day washout. The planned dose levels of TAK-831 to be evaluated will be 500 and 50 mg. The study will consist of 2 treatment periods, and visits to the clinic at the following times: (1) Screening Period (Days -30 to -3) covering full medical, neurological, and psychiatric examinations; (2) Treatment Visits and inpatient stays: On Day -2 of Periods 1 and 2, subjects will be admitted to the clinic for 2-night stays; on Day -2, subjects will undergo baseline clinical assessment procedures and cognitive battery assessment. On Day -1, subjects will receive the baseline EEG and EBC assessments. In Period 1, those who continue to meet all eligibility criteria will be randomized via an interactive response technology (IRT) system to 1 of 2 treatment sequences. On Day 1, subjects will undergo predose blood PK/PD samples, first dosing, and postdose blood draws, after which they will be discharged from the clinic to continue dosing at their residence. Subjects will receive double-blind treatment from Days 1 through 8 (inclusive) with completion of efficacy and PK/PD-related assessments on Days 7 and 8 of each treatment period; and (3), a washout period between Treatment Periods 1 and 2 lasting between 14 to 21 days. Subjects will be adults between ages 18 and 60, with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia who are receiving stable antipsychotic therapy (no increase or decrease >25% in dose in the preceding 2 months), and stable negative symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS) during Screening and Baseline (no fluctuations in PANSS negative symptom factor score [NSFS] >25%). PANSS total score will not exceed 90 points and the NSFS will be at least 15. Subjects with extrapyramidal signs or depressive symptoms will be excluded. Additional screening assessments include physical and neurological examinations, clinical laboratory and electrocardiogram (ECG) measures, a toxicological screen, Screening for suicidality and depression using the Columbia Suicide Severity Rating Scale (C-SSRS) and the Calgary Depression Scale Score (CDSS), respectively, assessment of extrapyramidal symptoms will be performed with the Simpson Angus Scale (SAS), and the presence of dyskinesias will be assessed with the Abnormal Involuntary Movement Scale (AIMS). Clinical laboratory testing, PK and D- and L-serine sample collection will be performed as per the schedule of events. If caregiver accompaniment is required, an adult caregiver will be permitted to attend clinical assessment visits with the study participant. After completion of the initial treatment period, subjects will participate in a washout period lasting between 14 to 21 days. After the second treatment period, a final follow-up safety assessment visit will be conducted approximately 10 to 14 days after the last administration of study drug. During the double-blind treatment periods, subjects will arrive at the clinic on Day 7 of each Treatment Period, as required (see schedule of events for details), to receive study drug and/or undergo specified study procedures. Study drug for Days 2 to 6 may be dispensed to the participant to take at their place of residence, or may be dispensed at the clinic through a qualified member of the research team. A process for ensuring adherence to study drug intake at the	

subject's place of residence, such as supervision by study staff, a caregiver or a mobile device application to remotely monitor study drug adherence will be implemented.

A previous version of this protocol was started at a different site and stopped after 1 subject completed all study procedures. The data from that subject, including safety endpoints, will be analyzed separately from those obtained in the subjects enrolled in this study.

Primary Objectives:

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

Secondary Objectives:

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

Subject Population: Adults between ages 18 and 60, inclusive, with a DSM-5 diagnosis of schizophrenia who are receiving stable antipsychotic therapy.

Number of Subjects:	**Number of Sites:**
32	up to 2
Dose Levels: TAK-831 500 mg and matching placebo once daily (QD) for 8 days TAK-831 50 mg and matching placebo QD for 8 days	**Route of Administration:** Oral
Duration of Treatment: Eight days in each period.	**Period of Evaluation:** Total approximately up to 81 days (Screening: 30 days, Treatment Period 1: 8 days, Washout 14 to 21 days, Treatment Period 2: 8 days, Follow-up: 10 to 14 days)

Main Criteria for Inclusion:

In order to be eligible for study participation, subjects must be:

- Provide written informed consent or from a legally acceptable representative.
- Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and prior to administration of the initial dose of study drug/invasive procedure.
- Between 18 and 60 years old, inclusive.
- Body weight >45 kg; body mass index (BMI) between 18.5 to 40 kg/m^2.
- With stable schizophrenia.
- Receiving stable antipsychotic medication at doses not to exceed risperidone 6 mg or its equivalent.
- Known to be stable with no clinically meaningful change in psychotropic medications for the preceding 2 months

prior to Baseline.

- Have a PANSS Negative Symptom Factor Score (NSFS) ≥15; stable screening and baseline PANSS NSFS scores (≤25% change).
- Have a PANSS total score ≤90; stable screening and baseline PANSS total score (<20% change).
- Willing and able to comply with all study procedures and restrictions.
- A female participant is eligible to participate if she is of:
  - Nonchildbearing potential.
  - Childbearing potential and agrees to use 2 forms of contraception methods.
  - Women of childbearing potential must have a negative pregnancy test at Screening and at Baseline.
- A male subject who is nonsterilized and sexually active with a female partner of childbearing potential must agree to use adequate contraception from signing of informed consent throughout the duration of the study and for 95 days after last dose.
- Able to swallow study drug in tablet form.
- Should a subject require a caregiver to accompany him/her during the study, the caregiver should be available for the full duration of the study.

Main Criteria for Exclusion:

The subject must be excluded from participating in the study if the subject:

- Ongoing disability, medical, neurological, or psychiatric history, cognitive impairment or conditions that, in the opinion of the investigator, are of a nature or severity that may interfere with study conduct or clinical assessments.
- The subject has a recent (within the last 6 months) diagnosis of panic disorder, depressive episode, or other comorbid psychiatric conditions requiring clinical attention based on the DSM-5 and the general psychiatric evaluation.
- Substance abuse or dependence (with the exception of nicotine dependence) within the preceding 6 months based on the DSM-5 and the general psychiatric evaluation.
- Positive drug screen for disallowed substances at Screening or Baseline.
- Evidence of extrapyramidal adverse events as measured by a SAS score >6 at Screening or Baseline.
- Evidence of depression as measured by a CDSS score >11 at Screening. Subjects with a CDSS score of 9 to 11 must be discussed with the sponsor and will also be excluded if the item scores are determined to reflect the presence of depression rather than schizophrenia negative symptoms.
- Evidence of suicidality as measured by a C-SSRS score >3 at Screening or Baseline.
- Hearing deficits preventing participation in event related potential testing.
- History of brain trauma associated with loss of consciousness for >15 minutes.
- Female subjects who are lactating or pregnant (positive pre-randomization serum pregnancy test) or plan to become pregnant during the study.
- Received treatment with other experimental therapies within the preceding 30 days or <5 half-lives prior to the first dose.
- Unwilling or unable to comply with the requirements of the protocol Subject has a known hypersensitivity to any component of the formulation of TAK-831
- Subjects known to be positive for hepatitis B surface antigen (HBsAg)-positive, or known or suspected active hepatitis C infection.
- Use of disallowed concomitant medications.

Main Criteria for Evaluation and Analyses:

All analyses are for comparison between TAK-831 and placebo.

The primary endpoints of the study are:

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

The secondary endpoints will be assessed through evaluation of the following parameters:

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

Statistical Considerations:

The 2-period crossover design for this study will allow for each subject to provide data on each of the 2 active doses as well as placebo. The crossover analysis of this design will take into account the within-subject correlation. While some subjects may drop from the study before completing all periods, all available data will be used for analyses.

The expected effect size, defined as the ratio between the mean difference between treatment and placebo divided by the standard deviation of this difference, is 0.6 for the primary endpoint. This effect size is a conservative estimate based on data from a previous report, which showed an effect size of 0.74 on the EBC test at 24 hours after initiation of treatment with secretin.

A frequentist analysis will be done for the full data set, using simulations to adjust for effect of the interim analysis on the type 1 error. The results of the primary endpoint will be considered statistically significant at either of the 2 doses (as applicable) if the one-sided $p < 0.05$, without adjustment for multiplicity (ie, the type 1 error rate will be separately controlled for each dose).

In addition, the primary endpoint will be analyzed using a Bayesian normal linear model with treatment sequence, period, and treatment as fixed effects and subject within sequence as a repeated factor. The dependent variable is the change in response from the period baseline assessment to the final treatment day for each period. The response data will be logit transformed before the change is calculated. The Bayesian model will be used to estimate the posterior distribution of the treatment effect from each dose (as applicable).

Interim Analysis:

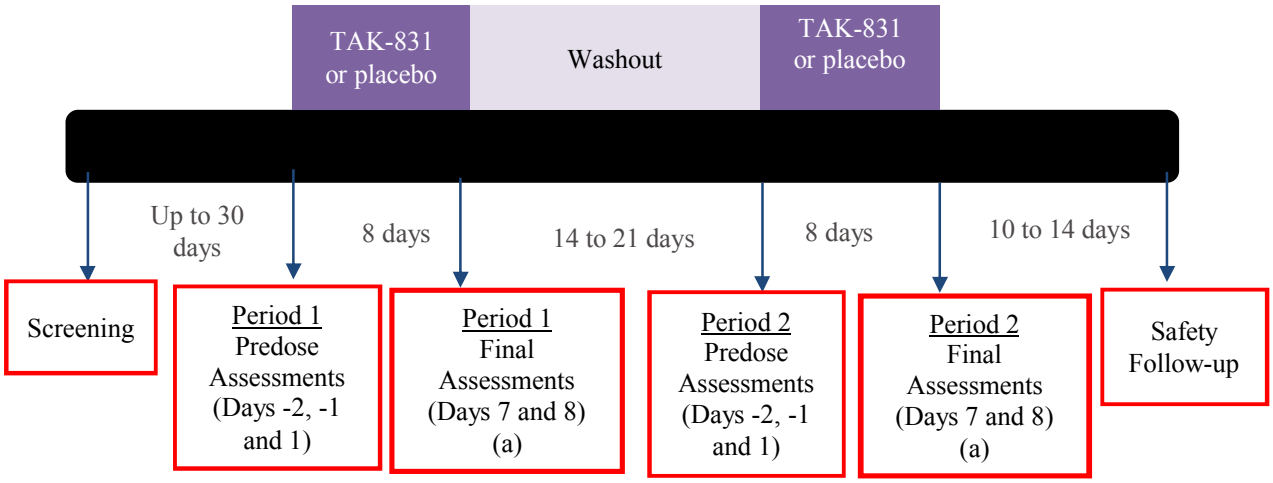
A small group from the sponsor will remain unblinded to treatment assignment during the study for the purpose of conducting interim analyses of PD effects. In order to minimize any potential unblinding of investigators, these staff will not interact with the investigators or their staff.

A planned unblinded interim analysis of the primary endpoint will be conducted when approximately 14 patients have completed the evaluation for the primary endpoint. The site will be allowed to continue enrollment to the high/placebo comparison, with the goal that approximately 16 patients will be randomized by the time the interim analysis is complete. (The additional approximately 2 subjects will be included in the final analysis but not the interim.) The purpose of the interim PD analysis will be to determine whether to continue enrolling subjects to the high-dose/placebo comparison, switch enrollment to the low-dose/placebo comparison, or discontinue enrollment. The decision rule will be specified in an interim analysis plan before the data are unblinded for the interim analysis. In addition, a decision to switch to the low dose may be made based on safety or tolerability of the high dose.

Sample Size Justification:

Up to 32 subjects will be enrolled into this 2-period crossover study. Initially 16 subjects will be randomized to one of the 2 sequences comparing the high dose to placebo: high-placebo or placebo-high. Based on the results of an interim analysis, an additional 16 subjects may be randomized to one of the 2 sequences comparing the low dose to placebo: low-placebo or placebo-low. This design and choice of sample sizes has been selected to be sensitive to a plausible and biologically meaningful range of effect sizes.

2.0 STUDY SCHEMATIC



(a) Assessments on Days 7 and 8 may be performed 1 day before or after, (ie, Day 6 or 8 for Day 7 and Day 7 or 9 for Day 8).

2.1 Protocol Amendment No. 06 Summary of Changes

Rationale for Amendment No. 06

This document describes the changes in reference to the protocol incorporating Amendment No. 06.

The primary reason for this amendment is to modify inclusion criterion 3 to revise the maximum subject age from 50 to 60 years of age, to allow for increasing patient recruitment.

For specific description of text changes and where the changes are located, see Appendix E.

Changes in Amendment No. 06

1. Updated entry criteria.

3.0 SCHEDULE OF STUDY PROCEDURES

	Screening	Periods 1 and 2 (a)										Safety Follow-Up (b)	Early Termination Visit
		Pretreatment Day		Treatment Day (c)									
Study Day	Days -30 to -3	-2	-1	1	2	3	4	5	6	7	8	Post-Treatment 2 Day 20±2	
Administrative Procedures													
Confinement		X	X							X			
Informed consent	X												
Inclusion/exclusion criteria (d)	X	X	X	X									
Demographics/ medical history	X												
Medication history	X												
Concurrent medical conditions	X												
Clinical Procedures/Assessments													
Full physical examination	X	X								X			X
Psychiatric examination	X												
Height	X												
Weight, and BMI	X												
Vital signs (oral [floor of the mouth]/ tympanic temperature) (e)	X	X	X	X						X	X	X	X
Concomitant medications (e)	X	X	X	X						X	X	X	X
ECG	X	X								X			X
C-SSRS	X	X								X		X	X
CDSS	X												
SAS	X												
AIMS	X												
PANSS	X	X								X			
EBC test (f)			X								X (f)		
ERPs (f, g)			X								X (f)		
Resting state EEG (f)			X								X (f)		
BACS cognitive battery (f)		X								X (f)			
Dispense study medication (h)				X									
Study drug dosing (c) (h)				X	X	X	X	X	X	X	X		
AE assessment (e)	X	X	X	X						X	X	X	X
Laboratory Procedures													
Clinical laboratory tests (hematology, serum chemistry, urinalysis) (i)	X	X									X		X
Hepatitis panel (HBsAg and Anti-HCV)	X												
FSH	X												
Pregnancy test (hCG) (i) (j)	X	X								X		X	X
Drug screen (i)	X	X								X			X

	Screening	Periods 1 and 2 (a)										Safety Follow-Up (b)	Early Termination Visit
		Pretreatment Day		Treatment Day (c)									
Study Day	Days -30 to -3	-2	-1	1	2	3	4	5	6	7	8	Post-Treatment 2 Day 20±2	
[redacted]													
PK Evaluations													
PK blood collection (m)				X						X	X		X
PD/Biomarker Evaluations													
Blood collection (D- and L-serine) (n)				X						X	X		X

AE=adverse event, BMI-body mass index, ERP=event-related field, FSH=follicle-stimulating hormone, HBcAg=hepatitis B core antigen, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, PANSS=Positive and Negative Syndrome Scale.
(a) A washout interval of 14 to 21 days will separate the last dose of study drug in Period 1 and the first dose in Period 2.
(b) A follow-up safety visit will be conducted 10 to 14 Days post-treatment Period 2.
(c) Assessments on Days 7 and 8 may be performed 1 day before or after (ie, Day 6 or 8 for Day 7 and Day 7 or 9 for Day 8). If the Day 8 assessments are conducted on Day 9, study drug dosing duration will be extended for 1 additional day as well.
(d) Inclusion/exclusion criteria will be assessed only in Period 1.
(e) Vital signs, concomitant medications and AE assessment on Days 2 to 6 to be performed only on subjects who attend the clinic site for any reason. Vital signs will be conducted for safety only and will not be entered into the database for these visits.
(f) Day 8 EBC, ERP, and EEG assessments are to be performed at approximately (± 1 hour) the same time as on Day -1, and the Day 7 BACS cognitive battery assessments are to be performed at approximately (± 1 hour) the same time of day as on Day -2.
(g) Procedures to be conducted only in subjects who receive at least 1 dose of study medication and are assessed within 36 hours of the last dose.
(h) Study drug intake on Days 2 to 6 may be supervised by a caregiver or family member, conducted at the investigator site or supervised by a qualified designee.
(i) These tests can be repeated at any time at investigator discretion.
(j) Serum Beta hCG at Screening and at the Final Visit, at other visits urine Beta hCG determination on women of childbearing potential only.
[redacted]
(m) Blood samples (approximately 4 mL) will be collected from each subject for the determination of plasma concentrations of TAK-831 at the following time points: Day 1 (predose and at 0.25 to 2 hours and 3 to 6 hours postdose), Day 7 (predose and at 0.25 to 2 hours and 3 to 6 hours postdose), and Day 8 (predose). One additional blood sample will be collected for subjects at the Early Termination Visit, if applicable. The sampling schedule may change based on emerging data but will not exceed the number of planned samples.
(n) Blood sample (6 mL) will be collected for analysis of plasma concentrations of D- and L-serine immediately following PK blood collections on Day 1 (predose and 3 to 6 hours postdose), Day 7 (predose and 3 to 6 hours postdose), and Day 8 (predose). Time of sample collection, time since last dose administered and time of last meal should be recorded for each sample collection. Samples may be analyzed for other amino acids, but total blood volume collected will not change.

4.0 INTRODUCTION

4.1 Background

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, it 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) [1-3]. Symptoms of schizophrenia can be subdivided into 3 broad classes: positive, negative, and cognitive symptoms [4]. 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 [4]. 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, negative symptoms, and anhedonia [5].

While currently available antipsychotics are broadly effective for the treatment of positive symptoms, the treatment of negative symptoms and cognitive deficits of schizophrenia remains a major unmet medical need. These are the most disabling aspects of schizophrenia, for which there are no approved therapies.

Inhibition of D-amino acid oxidase (DAO) is a promising target for the treatment of schizophrenia. Hypofunction of *N*-methyl-D-aspartate (NMDA) receptors is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain [6]. 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 and under drug treatment [7-10]. 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 sits [11].

DAO is involved in D-serine metabolism in the brain and has been associated with the regulation of glutamatergic neurotransmission [12]. Inhibition of DAO elevates endogenous D-serine in the cerebellum, increasing Purkinje cell long term depression via activation of glutamate receptor (GluR)δ2 and/or NMDA receptors with subsequent α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor internalization [13].

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 [14].

While current medications mitigate positive symptoms of schizophrenia, persistent negative symptoms and cognitive impairment represent areas of unmet medical need. Moreover, cognitive impairment and negative symptoms are associated with functional outcomes to a greater degree than positive symptoms and remain an area of focus for the development of novel therapeutics.

4.2 Clinical Background

Two phase 1 clinical studies have been conducted in healthy subjects: a first-in-human study to determine the pharmacokinetic (PK) profiles of TAK-831 oral suspension after single-rising dose (SRD) and multiple-rising dose (MRD) administration, as well as the relative bioavailability and effect of food on the PK of the T1 tablet formulation of TAK-831 (TAK-831-1001); and a study to demonstrate DAO target engagement in the brain as measured by positron emission tomography (PET) (TAK-831-1003). Plasma D-serine levels, TAK-831 plasma concentrations and safety were also evaluated. Since these studies were conducted, a single dose PK and food-effect bioavailability study with the T2 tablet formulation (TAK-831-1004) has completed active dosing, and a study examining additional escalating multiple doses of TAK-831 higher than those achieved in the TAK-831-1001 study was initiated and is ongoing (TAK-831-1005).

TAK-831 was safe and well tolerated in 103 healthy subjects in doses administered in studies TAK-831-1001 and TAK-831-1003. Headache was the most common treatment-emergent adverse event. 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 the rate observed in placebo-treated subjects. There were no concerning trends in laboratory, ECG, or vital sign data.

After both single and multiple dosing with TAK-831 (Study TAK-831-1001), increases in the area under the effect curve from time 0 to 24 hours of D-serine were dose-dependent; changes in D-serine were noticeably higher after multiple daily doses of TAK-831 400 mg than after multiple daily doses of TAK-831 30, 100, and 200 mg. Single oral doses of TAK-831 temporally increased plasma concentrations of D-serine in the PET study (TAK-831-1003); the results are similar to those obtained from Study TAK-831-1001.

TAK-831-1004 was a phase 1, randomized, open-label, single-dose, 2-period crossover study designed to characterize the PK of a single dose of 400 mg of TAK-831 and assess the effect of food on the bioavailability of TAK-831 400 mg when administered as four 100 mg oral tablets of the T2 formulation in 15 healthy adult subjects. In the TAK-831-1004 study, there was only a single AE of mild upper respiratory tract infection, judged to be unrelated to study treatment. One subject met criteria for orthostatic hypotension at a single time point without an accompanying report of a dizziness AE. There were no concerning trends in laboratory, ECG, or vital sign data. Treatment with a single oral dose of 400 mg of TAK-831 T2 formulation temporally increased plasma concentration of D-serine, similar to the results obtained in the Study TAK-831-1001. The magnitude and kinetics of the change in plasma D-serine were similar when the drug was administered in either water or nutritional drink. TAK-831 given as a T2 tablet coadministered with the nutritional drink increased mean C_{max} and AUC_{∞} values by 35% and 21%, respectively.

TAK-831-1005 is an ongoing investigator and subject blinded, sponsor unblinded, placebo-controlled clinical study progressively assessing independent cohorts of healthy subjects to continue evaluation of the safety, tolerability, PK, and pharmacodynamics (PD) of escalating multiple doses of TAK-831 at doses higher than those achieved in the TAK-831-1001 study. The following study information is preliminary and is based on blinded adverse event data reported by the investigator and blinded safety endpoint data in study TAK-831-1005. Although not expected, these data are subject to change upon finalization following study monitoring, source data

verification, and discrepancy query management prior to database lock. At this time, four cohorts with 8 subjects each (6 TAK-831 and 2 placebo) have completed treatment at dose levels of 100 mg QD (T2 tablet formulation), 600 mg QD (T2 tablet formulation), 800 mg QD (oral suspension), or 1200 mg (oral suspension) administered first as a single dose, and then administered for up to 14 days of multiple dosing. In addition to standard safety assessments, subjects in three of these cohorts underwent catheterized CSF collection for a 24 hour period starting prior to dosing on Day 1 single dose treatment and on Day 14 of multiple dose treatment. Nausea and post-lumbar puncture syndrome were the most common treatment-emergent AEs; nausea in the absence of post-lumbar puncture syndrome was reported by one subject in each cohort. All episodes of nausea were mild in intensity and self-limiting. Two subjects in each of the two first cohorts met categorical criteria for orthostatic hypotension on at least one assessment; none of these findings were associated with an AE of dizziness. There were no concerning trends in laboratory, ECG, or vital sign data collected in these cohorts.

After both single and multiple dosing with TAK-831, there was a notable increase in the area under the effect curve from time 0 to 24 hours of CSF D-serine for both the 600 mg T2 and 800 mg oral suspension treatment groups when compared to placebo; changes in CSF D-serine were noticeably higher after multiple doses of TAK-831 than after administration of a single dose of TAK-831. The magnitude of the increase in the area under the effect curve for CSF D-serine was similar for both the 600 mg T2 and 800 mg oral suspension, suggesting that the maximal PD effect in the CSF was achieved at drug exposures attained with the 600 mg T2 dose and 800 mg suspension. Following once-daily dosing, mean plasma exposures of TAK-831 were higher (C_{max}: 1.3-fold and 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 tablet formulation) and 800 mg QD (oral suspension), respectively. Mean steady-state exposures (AUC_t) over the 24-hour dosing interval were on average 4993 and 8853 ng.hr/mL for the respective 600 and 800 mg QD dosing cohorts. The mean 24-hour TAK-831 PK profile in CSF was parallel to that of plasma and observed TAK-831 CSF concentrations were well in agreement with the TAK-831 unbound fraction in plasma.

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

The safety data from healthy subjects cannot be directly generalized for patients with schizophrenia. However, no safety signal has manifested that would prevent additional studies in healthy subjects or in subjects with schizophrenia.

4.3 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 rats and it also demonstrated a positive effect on cognition and social interaction in rodent cognition and behavioral models. TAK-831 is under development for the treatment of cerebellar ataxia, and cognitive impairment associated with schizophrenia (CIAS), and negative symptoms

of schizophrenia. The proposed study is aimed at providing evidence of pharmacodynamic (PD) effects of TAK-831 treatment on brain function in subjects with schizophrenia.

A cross-over design was chosen for this study to minimize the potential impact of inter-subject variability on the ability to detect a treatment effect of TAK-831. As each subject serves as his/her own comparator, cross-over designs tend to have greater power to detect treatment effects compared to parallel designs. A placebo control is standard in the evaluation of novel therapeutics for neuropsychiatric disorders; as this study is an add-on to standard therapy in stable subjects the risk of subjects experiencing an exacerbation of their underlying condition is minimized. Preclinical data indicates that PD effects of TAK-831 may be apparent with single doses, supporting the short treatment duration period.

4.4 Benefit/Risk Profile

There is no benefit to subjects in this clinical study.

The following risk mitigation measures will be implemented in this study with TAK-831. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, and the 2 phase 1 studies conducted to date, and general considerations in the development of new chemical entities. Procedures may be added during the study if necessary based on evaluation of any additional clinical or nonclinical safety data.

- The dosing and duration of TAK-831 proposed for this study has been used 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 [15]), or who have made a suicide attempt in the previous 12 months, will be excluded from this study. The Columbia-Suicide Severity Rating Scale (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.
- Emesis and diarrhea were reported in laboratory animals exposed to TAK-831 and in clinical studies in healthy subjects. Nausea has been observed in clinical studies in subjects taking TAK-831, but there has been no consistent relationship observed between frequency or severity of nausea and dose of TAK-831, and all reports of nausea at the highest dose examined in the TAK-831-1005 study were mild in severity. Subjects will be informed of these findings and instructed to contact the investigator for guidance in the management of these symptoms and possible ways to mitigate them.
- Postural hypotension and dizziness were observed in prior studies in healthy subjects. However, the incidence of dizziness in subjects treated with TAK-831 and placebo was similar. In addition, some healthy subjects who received TAK-831 met vital signs criteria

consistent with orthostatic hypotension without accompanying clinical symptoms, although a number of these observations were considered not related to TAK-831. Subjects will be informed of these findings and instructed to contact the investigator for guidance in the management of these symptoms and possible ways to mitigate them.

- 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 [16]. There have been no findings of elevations in creatinine in clinical studies with TAK-831 summarized above; creatinine will continue to be measured in the clinical studies.
- Study procedure–specific risks include issues relating to blood collection for safety assessment/ pharmacokinetic (PK) monitoring (venipuncture may cause bruising), and the placement of electrocardiogram (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 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Trial Objectives

5.1.1 Trial Primary Objective

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

5.1.2 Trial Secondary Objectives

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

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

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

5.2.2 Secondary Endpoints

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

[redacted]

5.2.4 Safety Endpoints

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

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

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

Approximately 32 adult male and female subjects between ages 18 and 60, inclusive, with a current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia who are receiving stable antipsychotic therapy (no increase, no decrease >25% in dose in the preceding 2 months) will be randomized in to the study. Subjects will have a PANSS NSFS of at least 15 with no fluctuation between Screening and Baseline >25%. PANSS total score will not exceed 90 points with no fluctuations between Screening and Baseline >25%. Subjects with extrapyramidal signs or symptoms or depressive symptoms will be excluded.

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

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

Effects of up to 2 dose levels of TAK-831 or placebo will be assessed. Each treatment will be administered daily for a period of 8 consecutive days, separated by a 14- to 21-day washout (see Section 2.0 Study Schematic).

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

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

The study schedule is detailed in Table 6.a.

Table 6.a Part 1: Study Schedule

Screening Period	Pretreatment	Dose Administration Period 1 (a)	Washout (b, c)	Dose Administration Period 2 (a)	Follow-Up (c)
Day -30 to -3	Period 1 Days -2, -1, 1	Days 1 to 8	Days 9 to 22	Days 1 to 8	Period 2 Day 20±2

(a) Subjects will be admitted to the clinic on the afternoon of Day -2 of each period for pretreatment assessments. On Day -2, they will receive clinical assessments and cognitive testing, and on Day -1 they will receive EBC and EEG/ERP assessments. On Day 1, they will receive the first dose of study medication and predose and postdose PK assessments. Study drug for Days 3 to 6 may be dispensed to the participant to take at their place of residence or may be dispensed at the clinic through a qualified member of the research team. On Day 7 in the morning, subjects will be admitted to the clinic for a 1 night stay. On Days 7 and 8, they will receive drug and specified study procedures.
(b) Washout duration may range from 14 to 21 days based on emerging data.
(c) A follow-up safety visit will be performed 10 to 14 days after the last dose in Period 2. Subjects may be brought back to the study clinic for re-evaluation at any time during the study per investigator's discretion.

Study participants will receive daily study drug dosing until Day 8 of each period. Clinical assessments, laboratory tests and ECG will be repeated after dosing on Days 7 and 8 as per the schedule of events. Upon completion of the first dosing period, subjects will enter a washout period lasting between 14 to 21 days and will then return to the study site to undergo Day -2 procedures for the next dosing period.

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

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

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

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

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

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale of Study Design and Regimen

The cross-over design was chosen to minimize potential confounding from inter-subject variability of baseline characteristics and PD measures, as each subject will serve as their own

control. PD measures were selected based on their potential as translational measures from preclinical TAK-831 efficacy models, due to their linkage to NMDA receptor or cerebellar function, or their association with relevant aspects of schizophrenia pathophysiology. The selection of neurocognitive measures was informed by the results of a schizophrenia clinical study with a weak DAO inhibitor, sodium benzoate [14]. A small Takeda team will remain unblinded for the purposes of conducting interim analyses. Limited treatment duration is needed for a cross-over design and is consistent with PD effects observed in nonclinical studies with single doses or multiple doses up to 14 days.

6.2.2 Rationale for Dose

Effects of 2 dose levels of TAK-831 or placebo will be evaluated. The proposed doses of TAK-831 (500 and 50 mg once daily [QD]) have been selected based on PK data from the single-rising (SRD)/multiple-rising dose (MRD) studies (TAK-831-1001 and TAK-831-1005), brain target occupancy data from the positron emission tomography (PET) study (TAK-831-1003), PK and food effect study (TAK-831-1004), CSF D-serine data from the TAK-831-1005 study, and safety data from all clinical studies after oral administration of TAK-831 in healthy subjects. D-serine levels at 600 mg QD using T2 tablet and 800 mg suspension produced a similar level of CSF and plasma D-serine, suggesting that 600 mg QD produced levels of D-serine approaching maximal DAO inhibition in the brain. The planned dose of 500 mg QD is expected to have D-serine increase near the plateau. Preliminary PK/PD modeling analyses also showed that the high dose regimen resulted in steady-state exposures associated with mean peak target occupancy of ≥90%, while the lower dose regimen produced daily exposures associated with mean peak target occupancy of ≥50%. Both doses are predicted to demonstrate D-serine (PD) effects based on preclinical efficacy models. These 2 dose levels may allow characterization of an exposure-response relationship with pharmacodynamic measures. The planned dose regimens are expected to deliver mean exposures within the range previously studied in study TAK-831-1001 and TAK-831-1005 that were found to be well tolerated.

6.2.3 Rationale for Endpoints

6.2.3.1 Primary Endpoint

EBC Test

Disrupted cerebellar function has been hypothesized to contribute to schizophrenia pathophysiology by way of disruption of cortico-cerebellar-thalamic-cortical circuits. Patients with cerebellar lesions may display non-motor deficits such as impaired attention, language and executive function. In schizophrenia, cerebellar abnormalities have been found including reduced volume of vermis, lobules and hemispheres, and reductions in size and density of Purkinje cells. In addition, cerebellar abnormalities are correlated with symptoms and clinical outcomes [17].

EBC is highly conserved among mammalian species and is a commonly used method to investigate cerebellar function [18,19]. In EBC, a conditioned stimulus (CS), a tone precedes but coterminates with an unconditioned stimulus (US), an airpuff to the eyelid. Learning is

demonstrated when an eyeblink (the conditioned response [CR]) occurs prior to the onset of the US. Multiple studies have evaluated EBC in schizophrenia with the majority indicating deficits relative to control subjects [19]. Neural circuits in the cerebellum, including cerebellar cortex and interpositus nucleus are essential to the development and manifestation of the CR. NMDA receptors, in particular the GluN2 subunit, appear to play a critical role for the development of EBC. In preclinical studies, TAK-831 1 mg/kg per oral administration improved the rate of acquisition of the conditioned response relative to untreated and vehicle treated control groups. Furthermore, it significantly compensated the deleterious effects of scopolamine (0.3 mg/kg, sc) administration on the generation of conditioned eyelid responses and completely reversed scopolamine induced deficits at 1 mg/kg.

As acquisition of delay EBC is impaired in schizophrenia and hypothesized to be linked to cerebellar-cortical circuit function, it may be subject to therapeutic intervention with TAK-831 [18]. Of note, the EBC test has been used previously for the evaluation of experimental therapeutics in schizophrenia [20].

6.2.3.2 Secondary Endpoints

ERPs

The ERPs to be measured (via scalp EEG) include the mismatch negativity potential during the oddball paradigm (MMN), and the ASSR task. These tests have been linked to NMDA receptor function [21-24] and have demonstrated differences between subjects with schizophrenia and control subjects.

MMN is an ERP evoked in response to unattended changes in background stimulation. MMN is believed to reflect an automatic process of detecting a mismatch between a deviant stimulus and a sensory-memory trace. Smaller amplitudes of MMN have been consistently identified in schizophrenia subjects, showing promise as a quantitative clinical biomarker of the disease [25]. MMN amplitude is significantly reduced by ketamine [21] and is associated with ketamine-induced psychotic experiences [22]. Hence, MMN may index NMDA function in humans. Moreover, MMN is associated with cognitive and psychosocial functioning in schizophrenia [26]. MMN has demonstrated stability in clinical populations with high test-retest reliability over 1 year [27,28]. Hence, MMN represents a potentially informative probe of sensory processes for use in experimental medicine studies of novel therapeutics. Its association with NMDA receptor function suggests that it may be sensitive to modulation with TAK-831.

The P300 wave is an ERP component that is elicited by the presentation of a novel, behaviorally relevant target stimulus embedded among irrelevant stimuli in a manner similar to MMN, but requiring active listening and responding from participants. Auditory stimuli are presented in an oddball paradigm consisting of 1 standard tone and 1 target tone. Subjects are instructed to push a button as quickly as possible when they hear the target tone, but not when they hear the standard tone. P300 reflects allocation of attention and activation of immediate memory. P300 amplitude indexes brain actions when the mental representation of the stimulus environment is updated, while P300 latency indexes stimulus classification speed unrelated to response selection

processes. The P300 paradigm can therefore be used to study drug effects on the speed and efficiency of effortful attentional processing and working memory performance.

ASSRs are evoked oscillatory responses that are entrained to the frequency and phase of temporally modulated stimuli. Individuals with schizophrenia experience subjective sensory anomalies and objective deficits on assessment of sensory function. These deficits can be produced by abnormal signaling in the sensory pathways and sensory cortex or by later-stage disturbances in the cognitive processing of such inputs. SSRs can be used to assess the integrity of sensory pathways including cortical processing. Steady state response can be maximized when delivered as ASSR stimuli at ~40 Hz. Schizophrenia subjects have been shown to have deficits in ASSR power and phase locking of approximately 0.5 vs control subjects. ASSR has demonstrated adequate test-retest characteristics in healthy volunteers to both evoked power and intertrial phase coherence when measured using both a standard EEG array [29] or using magneto electroencephalography [30]. Therefore, ASSR appears to be a promising surrogate measure to evaluate NMDA function in humans.

Cognitive Battery

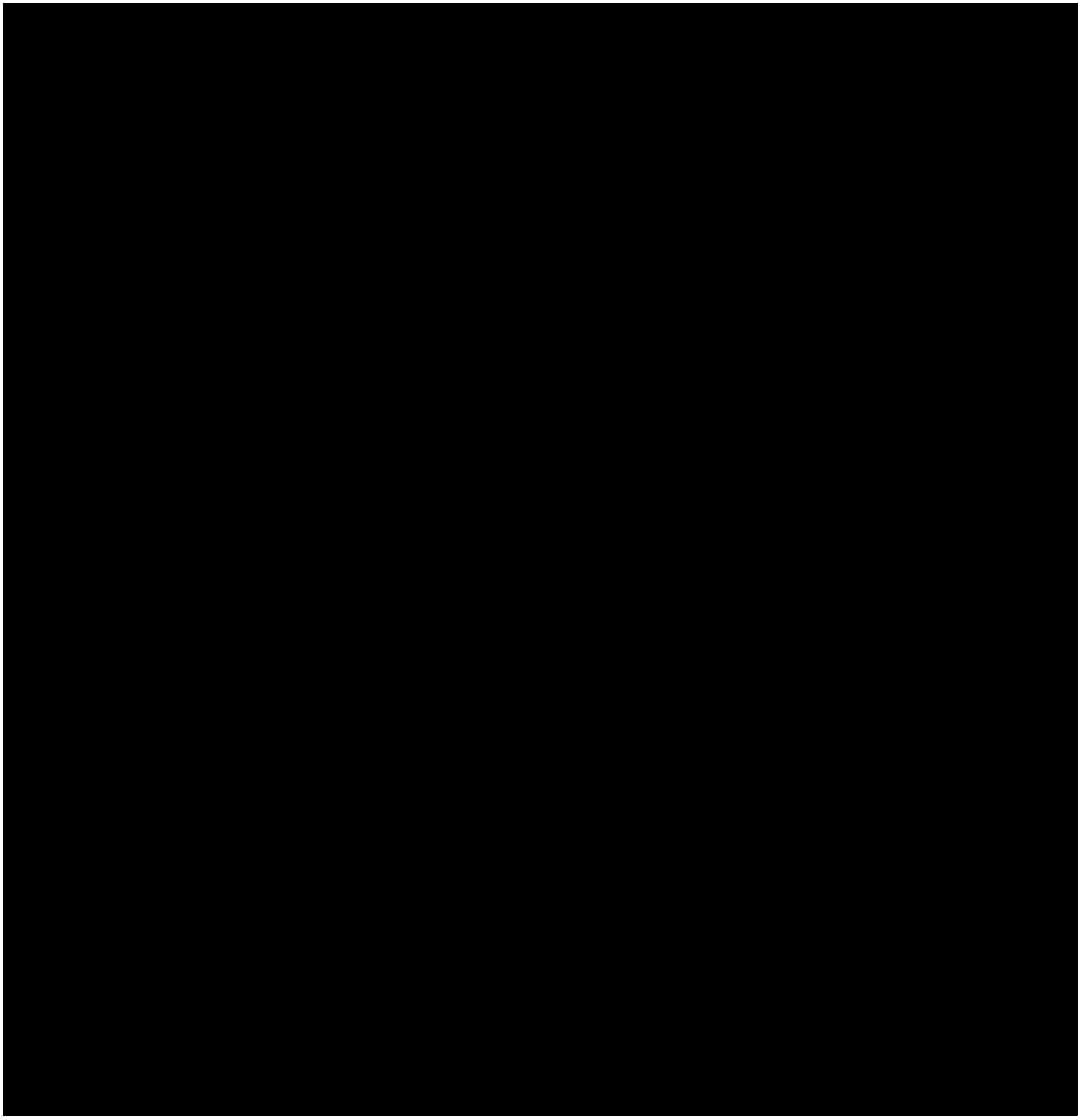
Cognitive deficits are a core, enduring aspect of schizophrenia. Cognitive deficits are more strongly associated with functional outcomes than psychotic symptoms, yet there are no therapies currently approved for their treatment and represent a major unmet need in the treatment of schizophrenia. Multiple clinical development programs for the treatment of CIAS have not been able to successfully demonstrate adequate evidence of efficacy. Recently sodium benzoate, a weak inhibitor of DAO, showed efficacy in multiple cognitive measures in a small phase 2 study when used as add-on therapy in schizophrenia subjects [14].

D- and L-Serine

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 drug treatment and under drug treatment [7-10]. Inhibition of DAO elevates endogenous D-serine in the cerebellum and plasma of rats. Analysis of changes in D-serine levels, and D-serine to total serine ratios will allow an evaluation of PD effects, and [redacted] will allow a preliminary evaluation of the potential utility of these biomarkers to select for patients that may benefit from treatment with TAK-831.

TAK-831 Plasma Concentrations (or PK)

TAK-831 plasma concentrations are used to measure TAK-831 PK parameters and build PK/PD relationship (see Section 11.1.3).



6.2.3.4 Safety Endpoints

TAK-831 has undergone clinical assessments in previous studies. Based on the safety and tolerability profile observed to date, standard safety endpoints and monitoring have been included in the current study, including AE documentation, psychiatric assessments, laboratory tests and biomarker evaluation.

6.2.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, collecting EBC, EEG, cognition, PK, and biomarkers in subjects with schizophrenia are the critical procedures.

- On Day -2, a baseline cognitive assessment will be conducted. On Day -1, baseline EBC, and EEG based measures will be conducted. Postbaseline EBC test, EEG, and cognitive testing will be performed sequentially on Days 7 and 8, with EBC tested approximately 1 hour postdose.
- At any postdose time point, the critical assessments need to be collected as close to the exact time point as possible.
- All other procedures should be completed as close as possible, either before or after the prescribed/scheduled time.
- The order of assessments can be changed during the study with joint agreement of the investigator and the sponsor.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a phase 2 study to explore assessment of PD profile of TAK-831 in humans. Some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data.

- In order to accommodate potential unanticipated disruptions to the planned schedule of events, subjects will be provided with 10 days of drug supply for each treatment period. In case of subject unavailability to participate in study procedures, rescheduling the subject to attend the site up to 1 day earlier or later will not be considered a protocol deviation.
- The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests) and washout currently outlined in the protocol may be modified during the study based on newly available safety, tolerability, PK, or PD/biomarker data. These changes will not increase the number of study procedures for a given subject during his/her participation in the entire study.
- Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatine kinase to serum chemistry panel that was already drawn).

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the institutional review board (IRB)/independent ethics committee (IEC) at the discretion of the investigator.

6.4 Study Beginning and End/Completion

6.4.1 Definition of Beginning of the Study

The overall study begins when the first subject signs the study informed consent form.

6.4.2 Definition of End of the Study

The overall study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit, discontinues from the study or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.4.3 Definition of Study Completion

The primary objective of this phase 2 study is to assess if cerebellar function can be improved by add-on TAK-831 therapy compared to placebo based on the EBC in subjects with schizophrenia.

It is possible that study subjects may not receive all dose levels specified in the protocol, or that the study may be stopped before all planned subjects are enrolled if this objective is achieved early in this study. This is not considered an early termination of the study, but rather an earlier than anticipated achievement of the study objective(s) or study completion.

6.4.4 Definition of Study Discontinuation

Study discontinuation due to non-safety reasons, such as:

- A finding (eg, PK, PD, biologic targets, etc) from another preclinical or clinical study using the study treatment(s) results in the study being stopped for a non-safety-related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this study become available and results in the study being stopped for a non-safety-related reason.
- The study is stopped due to non-scientific and non-safety reasons, such as slow enrollment.

Study discontinuation due to safety reasons:

- Early study termination due to unanticipated concerns of safety to the study subjects arising from clinical or preclinical studies with the study treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

6.4.5 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 medication 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.

6.4.5.1 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.

6.4.5.2 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an IRB/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 randomization or first dose.

7.1 Inclusion Criteria

In order to be eligible for participation in this study, the subject or caregiver must:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions (see Sections 7.3 and 7.4 for a summary of restrictions).
3. Be male or a female aged 18 to 60 years, inclusive, at the Screening Visit.
4. Have a body BMI ≥18.5 and ≤40.0 (kg/m^2) at the Screening Visit.
5. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and prior to administration of the initial dose of study drug/invasive procedure.
6. Meet the following birth control requirements:
   - Is a male subject who is sterile or agrees to use a barrier method of contraception (eg, condom with or without spermicide) from study drug administration on the first day of the first dose until 95 days after the last dose of study drug administration. No restrictions are required for a vasectomized male subject provided the subject is at least 1 year post-bilateral vasectomy procedure prior to study drug administration on first day of the first dose. A male subject whose vasectomy procedure was performed less than 4 months prior to study drug administration on the first day of the first dose must follow the same restrictions as a nonvasectomized male. Appropriate documentation of surgical procedure should be provided.
   - Is a male subject who agrees to not donate sperm from study drug administration on the first day of the first dose until 95 days after the last dose of study drug administration.
   - Is a female subject with no childbearing potential, defined by at least 1 of the following criteria:
     a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years, 6 months of spontaneous amenorrhea in females aged >45 years with serum FSH levels >40 mIU/mL). Appropriate documentation of FSH levels is required.
     b) Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
     c) Had a tubal ligation with appropriate documentation of surgical procedure.
     d) Has a congenital condition resulting in no uterus.

- Is a female subject with child-bearing potential must have the following criteria:
  a) A negative pregnancy test at Screening and Baseline.
  b) Agrees to use a highly effective method of contraception from signing of informed consent throughout the duration of the study and for 35 days after the last dose. (see Appendix D for definitions of highly effective contraception).
  c) Is not breastfeeding.

7. Meets a current DSM-5 diagnosis of schizophrenia.
8. PANSS NSFS ≥15, stable screening and baseline PANSS NSFS (<25% change).
9. PANSS total score ≤90; stable screening and baseline PANSS total score (<20% change).
10. Receiving stable (no increase, no decrease >25% in dose in the preceding 2 months) antipsychotic medication at doses not to exceed risperidone 6 mg or its equivalent. Concomitant treatment with a subtherapeutic dose of a second antipsychotic may be permitted with sponsor or designee approval if used as a hypnotic (maximum of quetiapine 300 mg or its equivalent once daily at bedtime) and subject does not show morning sedation as per the investigator opinion, but not if it is used for refractory positive psychosis symptoms. Under this exception, the total daily dose the second antipsychotic will not have to be included in the calculation of the 6 mg/day risperidone-equivalent limit.
11. Able to swallow study drug in tablet form.
12. Should a patient require a caregiver to accompany him/her during the study, the caregiver should be available for the full duration of the study.

7.2 Exclusion Criteria

The subject must be excluded from participating in the study if the subject:

1. Has participated in another investigational study within 30 days prior to the prestudy (screening) visit or <5 half-lives prior to the first dose. The 30 days window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the prestudy/Screening Visit of the current study.
2. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of the study site personnel or of the Sponsor.
3. Has a history of cancer (malignancy) excluding treated basal cell carcinoma or treated stage 0 (in situ) cervical carcinoma.
4. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
5. Subject has a QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females) confirmed with one repeat testing, at the Screening Visit or Check-in.

6. Has a positive alcohol or drug screen for disallowed substances, including amphetamines, barbiturates, cocaine, marijuana, methadone, methamphetamine, 3,4-methylenedioxymethamphetamine, 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 patient may either be re-screened after a sufficient washout period or may continue screening process and a drug screen must be performed on Baseline Day -2 of each treatment period and at all subsequent outpatient 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.
7. Has a positive pregnancy test or plan to become pregnant during the study (female subjects only).
8. Is positive for HBsAg, hepatitis C antibodies, or has HIV by history (confirmatory testing is allowed; most sensitive test should take precedence).
9. Had major surgery, donated or lost 250 mL of blood within 4 weeks prior to the prestudy (screening) visit.
10. Use of disallowed concomitant medications.
11. Is unable to refrain from or anticipates the use of any medication (except those prescribed), including prescription and nonprescription drugs or herbal remedies beginning approximately 7 days prior to administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted, see Section 7.3.
12. Unwilling or unable to comply with the requirements of the protocol.
13. Subject has a known hypersensitivity to any component of the formulation of TAK-831.
14. If male, the subject intends to donate sperm during the course of this study or before 95 days have elapsed since the last dose of study drug.
15. Subject has a history of significant skin reactions (hypersensitivity) to adhesives, metals or plastic.
16. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or subjects who within the past year prior to Screening have attempted suicide. Subjects who have positive answers on item 4 or 5 on the C-SSRS (based on the past year) prior to randomization are excluded.

17. Ongoing disability, medical, neurological, or psychiatric history, cognitive impairment or conditions that, in the opinion of the investigator, may interfere with study conduct or clinical assessments.
18. The subject has a recent (within the last 6 months) diagnosis of panic disorder, depressive episode, or other comorbid psychiatric conditions requiring clinical attention based on the DSM-5 and the general psychiatric evaluation.
19. The subject has a diagnosis of substance use disorder (with the exception of nicotine dependence) within the preceding 6 months based on DSM-5 and the general psychiatric evaluation.
20. 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.
21. The subject has evidence of depression as measured by a CDSS >11 at Screening. Subjects with a CDSS score of 9 to 11 must be discussed with the sponsor and will also be excluded if the item scores are determined to reflect the presence of depression rather than schizophrenia negative symptoms.
22. Hearing deficits that in the investigator's opinion prevent participation in event related potential testing.
23. History of brain trauma associated with loss of consciousness for >15 minutes.

7.3 Excluded Medications, Supplements, Dietary Products

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)		
	Chronic Use	**Episodic Use**	**Comments or Exceptions**
Any investigational drug	X	X	<30 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	Maximum dose of chronic anticholinergic treatment is 2 mg/day of benztropine or equivalent.
Antithrombic agents and anticoagulants (excluding warfarin, which is excluded)		X	
Anticonvulsants	X	X	Exception: gabapentin and pregabalin are permitted if they are prescribed at a stable dose for ≥2 months prior to Screening and throughout study treatment. Subjects taking other anticonvulsants should not be considered for participation in the study, as their discontinuation could lead to symptom instability.
Antidepressants (excluding tricyclic antidepressants, MAOIs, and 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.
Antihistamines	X	X	Except loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine.
Antihypertensives			Clonidine NOT allowed.
Antipsoriatic agents	X	X	Topical agents are allowed.
Antipsychotics		X	Clozapine is excluded; all other treatments must adhere to requirements outlined in the study entry criteria. As an exception, occasional use of an additional dose of the background antipsychotic may be permitted with sponsor or designee approval.

Footnotes are on last table page.

Table 7.a Excluded Medications and Dietary Products (continued)

Drug Class		Disallowed (X) During the Study (sections without [X] indicate no restriction)		
		Chronic Use	**Episodic Use**	**Comments or Exceptions**
Herbal remedies, which are psychoactive (eg, St John's Wort, kava, valerian, ginkgo biloba, melatonin)		X	X	Must be discontinued ≥14 days prior to randomization.
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 for the treatment of anxiety or agitation as needed is permitted up to 2 mg/day lorazepam (or the equivalent dose of another benzodiazepine) up to 3 times per week, but cannot be taken within 8 hours of the administration of study assessments.
Insulin		X	X	
Mood stabilizers		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.
UGT enzyme inhibitors (probenecid and valproic acid)				Not within 14 days of dosing.

BZ=benzodiazepine, MAOI=monoamine oxidase inhibitor, RIMA=reversible inhibitor of monoamine oxidase type A, UGT=uridine 5'-diphosphate-glucuronosyltransferase.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Study drug can be taken with water or milk. Subjects should avoid drinking juices 1 hour before and 1 hour after taking study drug.

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc) from the Screening Visit until the poststudy visit.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

1. The subject experiences an 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 AE. The primary reason for discontinuation or withdrawal of the subject form the study or study drug should be recorded in the electronic case report form (eCRF).

2. Drug-Induced Liver Injury (DILI).

   Study medication 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 medication treatment:

   – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or

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

   – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5.

3. Significant protocol deviation. The discovery postrandomization 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. Subject inability to adhere to medication intake or study procedures may also be considered a reason for early subject discontinuation.
4. Lost to follow-up. The subject did not return to the unit and multiple attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study.

   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).

6. Study termination. The sponsor, IRB/independent ethics committee, or regulatory agency terminates the study.

7.6 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 7.5. 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.

7.7 Subject Replacement

If a subject discontinues from the study, a replacement subject may be enrolled, if deemed appropriate by the investigator and Sponsor. The study site should contact the IRT for the replacement subject's treatment assignment and identification number.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation, of the active drug and placebo, can be found in the pharmacy manual or in the referenced compounding manual when applicable. Study drug will be packaged to support enrollment and replacement subjects as required.

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and remain in the original container until dispensed. The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

8.1.3 Clinical Study Drug Blinding

The study drug blind will be maintained using the IRT.

8.1.4 Randomization Code Creation and Storage

IRT system will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

The study drug blind will be maintained using the IRT.

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. If possible, the medical monitor should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator is responsible for keeping accurate records of the study drug received from the sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the end of the study. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction.

8.1.7 Ancillary Supplies

All ancillary supplies will be provided by either the study site or the sponsor or designee, based upon availability. The list of ancillary supplies and source information can be found in the pharmacy manual or in the referenced compounding manual when applicable. If provided by the sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the sponsor or designee.

9.0 STUDY PROCEDURES

The following sections describe the study procedures and data to be collected as indicated in the Schedule of Study Procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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] informed consent is a component of the overall study informed consent. The requirements of informed consent are described in Section 13.2.

When subjects have performed screening assessments prior to study, the data from screening using a generic screening consent form can be used in this study for those who were subsequently enrolled, as long as the procedure was performed within the protocol screening to enrollment window.

[redacted]

9.1.1.1 Assignment of Screening and Randomization Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening event.

All eligible subjects will be randomized by contacting the IRT for treatment assignment. The randomization number will be assigned to each subject; however, it will not be provided to the site or entered into the eCRF. The subject identification (ID) number will be the number that identifies the subjects for all procedures. Once a randomization number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than 1 randomization number.

9.1.1.2 Clinical Study Drug Assignment

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

9.1.2 Inclusion and Exclusion Criteria

Each subject is assessed through randomization, according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demographics

Qualified site personnel are to collect subject significant medical history (past and ongoing) per the site's standard of care and appropriate clinical judgment as well as subject demographics.

9.1.4 Prior and Concomitant Medication Review

Medications are defined as prescription and over-the-counter drugs, vitamin supplements, nutraceuticals, and oral herbal preparations. Qualified site personnel are to review subject medication use.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Examination

Qualified site personnel will conduct full physical including neurological examinations.

9.2.2 Psychiatric Examination

The presence of extrapyramidal symptoms will be determined using the SAS. The presence of dyskinesias will be documented with the AIMS.

9.2.2.1 SAS

The SAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale, and address rigidity, gait (bradykinesia), tremor, glabellar tap, and salivation [36]. The SAS will be administered by a qualified rater at the site.

9.2.2.2 AIMS

The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions, including the facial area, extremities, and trunk. There are two items related to dental status, as well as three global impression items assessing overall severity, incapacitation, and the subject's awareness of abnormal movements [37,38]. The AIMS raters will be required to meet specific credential and educational criteria before they are certified to rate for this study. The AIMS will be administered by a qualified rater at the site.

9.2.3 Height and Weight

Body weight and height will be obtained with the subject's shoes off, and jacket or coat removed.

9.2.4 BMI

BMI equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Body weight and height will be obtained with the subject's shoes off and jacket or coat removed.

BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

9.2.5 Vitals (Body Temperature, Heart Rate, Blood Pressure)

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

Subjects should rest in a semirecumbent position for at least 5 minutes prior to having vital sign measurements obtained. Vital signs will include heart rate (HR) and systolic and diastolic blood pressure. 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.

9.2.6 12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove their bra.

Subjects should be resting in a semirecumbent position for at least 5 minutes prior to each ECG measurement.

QTcF will be used to calculate QT intervals in this study.

Prior to each treatment period/cohort, a predose ECG will be obtained on Day -2. This measurement will be used as the baseline. The principal investigator should arrange to have a study cardiologist available as needed to review ECG tracings with abnormalities.

During each treatment period, if a subject demonstrates an increase in QTcF interval ≥40 msec compared with a predose baseline measurement, the ECG will be repeated within 5 minutes. The average value of the QTcF interval from the 2 ECGs will represent the value at that time point. If the average QTcF interval increase from Baseline for any postdose time point is ≥40 msec, the subject will continue to be monitored by repeat 12-lead ECGs every 60 minutes for at least 4 hours or until the QTcF is within 40 msec of the baseline value. If prolongation of the QTcF interval ≥40 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTcF interval is ≥500 msec on repeat measurements, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be monitored (until the QTcF is <500 msec) or should be considered for transfer to a location where closer monitoring is available.

If the subject has unstable hemodynamics, or has any clinically significant dysrhythmias noted, the subject should be immediately transferred to an acute care setting for definitive therapy.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

The following ECG parameters will be recorded: HR, PR-interval, QRS-duration, QT-interval, QTcF-interval, and the interpretation of the ECG profile by the principal investigator.

9.2.7 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. 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.

Suicidality will be assessed by the use of the C-SSRS, a 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 (actually, interrupted, and aborted attempts at suicide). Two versions of the C-SSRS will be used in this study: the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS.

9.2.8 CDSS

The CDSS was developed to assess symptoms of major depressive disorder in patients with schizophrenia, and specifically designed to assess comorbid depressive symptoms. The CDSS consists of nine 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.

9.2.9 PANSS

The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure is comprised of 30 items and 3 scales: the Positive scale assesses hallucinations, delusions, and related symptoms; the Negative scale assesses emotional withdrawal, lack of motivation, and similar symptoms; and the General Psychopathology scale addresses other symptoms such as anxiety, somatic concern, and disorientation. An anchored Likert scale from 1 to 7, where values of 2 and above indicate the presence of progressively more severe symptoms, is used to score each item. Individual items are then summed to determine scores for the 3 scales, as well as a total score. A Composite scale score (Positive scale score minus Negative scale score) can also be calculated to show the relative valence of positive and negative symptoms. Total time required for the PANSS interview and scoring is approximately 30 to 40 minutes [39-41]. PANSS raters will be required to meet specific training and education criteria

before they are certified to rate for this study. In addition, raters will receive specific training and education regarding all of the assessments prior to study initiation.

9.2.10 Study Drug Administration

This is a double-blind study; therefore, TAK-831 or matching placebo will be administered orally, once a day for 8 days in a blinded fashion.

9.2.10.1 Monitoring Subject Treatment Compliance

Compliance will be assessed via study drug count and subject or informant report. Subjects will also be required to bring study medication containers to each clinic visit, regardless of whether the study medication container is empty.

All subjects who are noncompliant 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. Subjects will be required to bring study medication containers/unused medications to the site visit during the study.

9.2.11 Cognitive Assessments

In order to obtain early estimates of potential treatment effects of TAK-831 on cognitive function, the BACS battery will be included in this study [42]. These neurocognitive domains may be potentially improved by TAK-831 based on preclinical efficacy data as well as the results of the phase 2 sodium benzoate study [14].

The set of tests is of approximately 35 to 40 minutes duration and may be conducted using either paper and pencil or a comparable version delivered electronically [43].

9.2.12 ERPs

This test takes approximately 45 minutes.

The ERPs to be measured (via scalp EEG) include the MMN potential during the oddball paradigm (MMN), the P300 wave during the oddball task, and the ASSR task. These tests have been linked to NMDA receptor function [21-24] and have demonstrated differences between subjects with schizophrenia and control subjects. Further details will be provided in the manual of procedure (MOP) for event related potentials and EEG based measures.

Frequency analysis during resting state will be recorded as quantitative electroencephalogram as indicated in the Schedule of Study Procedures (Section 3.0).

9.2.13 Delay EBC Test

EBC enables evaluation of cerebellar-dependent learning and is the primary endpoint in this study. Briefly, the procedure involves an initial set of 8 unconditioned stimuli (unconditioned stimulus: corneal air puff, 50 msec, 10 psi at source) presented with an intertrial interval of 15 seconds. The acquisition phase will then follow, consisting of 5 blocks of trials (mean intertrial interval = 15 seconds; range = 10 to 20 seconds). Each block will contain 18 trials in which the conditioned

stimulus (1 KHz tone; 400 msec; sound pressure level: 80 dB) will be paired with the unconditioned stimulus and 2 trials in which the conditioned stimulus will be presented alone. In trials in which the conditioned and unconditioned stimuli are paired, the unconditioned stimulus air puff will be coterminated with the conditioned stimulus tone. The overall duration of this task is between 30 to 60 minutes. Further details will be provided in the MOP for EBC test (including modifications for administration at the Screening Visit).

9.2.14 AE Monitoring

AE monitoring begins following signing of informed consent. Changes in subject health status from baseline assessment to trial drug administration should be captured in the subject's medical history. A complete description of AE collections and procedures is provided in Section 10.0.

9.2.15 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be taken on the days stipulated in the Schedule of Study Procedures (Section 3.0).

9.2.15.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells)	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells [WBCs]) with absolute differential	

Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrite

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of red blood cell/high-power field, white blood cell/high-power field, and casts.

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total), if above ULN total bilirubin will be fractionated
Protein (total)	

9.2.15.2 Diagnostic Screening

Serum

Serum diagnostic evaluations will include the following tests:

β-hCG (females only)	FSH (females only)
Hepatitis Screen (HBsAg, HCV antibody)	

Urine

A urine drug screen will include the following tests:

Amphetamines	3,4-methylenedioxy-methamphetamine
Barbiturates	Methadone / Metabolite
Benzodiazepines	Opiates
Buprenorphine / Metabolite	Oxycodone / Oxymorphone
Cannabinoids	Phencyclidine
Cocaine / Metabolites	

9.3 Biomarker, PK, PD, and [redacted], Samples

Samples for PK and PD (D- and L-serine) will be collected as specified in the Schedule of Study Procedures (Section 3.0). Please refer to the Laboratory Manual for information on the collection, processing, and shipment of samples to the Central Laboratory.

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of PK/biomarkers will be determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples

may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional biomarkers.

It is anticipated that the total blood volume drawn for the study will be approximately 220 ml.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use
Blood sample for PK	Blood	Plasma	Plasma sample for PK analysis
Blood sample for PD assessment (D- and L-serine)	Blood	Plasma	Plasma sample for PD analysis
[redacted]			

9.3.1 PK Measurements

9.3.1.1 PK Sample Collection

Serial blood samples (one 4-mL sample per scheduled time) for PK analysis of TAK-831 plasma concentrations will be collected into chilled Vacutainers containing the anticoagulant potassium ethylenediamine tetraacetic acid (K_2EDTA), as specified in Schedule of Study Procedures (See Section 3.0).

The actual date and time of each PK sample collection as well as the date and time of study drug dosing for the most recent dose will be recorded accurately in the eCRF.

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

9.3.1.2 Bioanalytical Methods

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

9.3.2 Biomarker Measurements

9.3.2.1 PD Sample Collection

Serial blood samples (one 6-mL sample per scheduled time) for PD (D-serine and L-serine) analysis of TAK-831 will be collected into chilled Vacutainers containing the anticoagulant K_2EDTA, according to the schedule shown in in Schedule of Study Procedures (See Section 3.0).

The actual time of 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 processing and shipment are provided in the laboratory manual.

9.3.2.2 PD Analysis

Plasma concentrations of D- and L-serine will be measured by a validated HPLC with tandem mass spectrometry. Additional D- and L- amino acids may also be analyzed, including but not limited to alanine.

9.3.2.3 PD Parameters

PD parameters will be determined for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The PD parameters of plasma D- and L-serine, and the ratio of D-serine to total serine in plasma will be assessed. Individual PD data may be combined with other study data and analyzed using a population PK/PD modeling approach.

9.3.4 Confinement

The study will include 2 inpatient stays at the clinic in each period. The first will be 2 days (including night stays on Days -2 to -1) and the second will be on Days 7 to 8 (including a night stay on Day 7). In between these stays, subjects will report to the study site as and when required per schedule of assessments.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

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 an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered to be 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 re-test and/or continued monitoring of an abnormal value 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 an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication

of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). 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 condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, 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:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered 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 captured appropriately as an 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 AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- 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. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 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 AE List

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

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Section 10.2.8.3).

10.1.2 Special Interest AEs

No AEs of special interest have been identified for this compound.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

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

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(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 a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs 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.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Concerning Study Drug

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

10.2.7 Outcome

- Recovered/resolved - subject returned to first assessment status with respect to the AE.
- Recovering/resolving - the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE 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 become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae - the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal - an AE that is considered as the cause of death.
- Unknown - the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and DILI

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and DILI) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up visit 10 to 14 days after the last dose of investigational product. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

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 an SAE prior to the first exposure to investigational product 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 that begin prior to the first exposure to investigational product, 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 medication 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 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:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with trial drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Appendix 14.1.1.

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

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and

fax it immediately 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.

10.2.8.4 Reporting Special Interest AEs

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

10.2.8.5 Reporting of DILI

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, a DILI 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 elevated >3 × ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, a DILI 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 10.2.8.3. The investigator must contact the Medical Monitor 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 as described in Section 9.2.15 must also be performed. In addition, a DILI eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 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, 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 Sponsor's designee, SUSARs will be submitted 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 an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (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. In cases of inconsistencies between the protocol and the SAP in regard to data analysis, the SAP is to take precedence over the protocol. Due to this clear understanding of precedence, the statistical analysis section will not necessarily be updated to match the SAP when the protocol is amended.

A targeted 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.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

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

11.1.1.2 PK Set

The PK Set will include all randomized subjects who receive at least one dose of double-blind study medication and who have any available plasma concentration data.

11.1.1.3 PD Set

The PD set will consist of all subjects who receive at least 1 dose of study drug and have at least 1 postdose PD result.

11.1.2 Analysis of Demographics and Other Baseline Characteristics

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

Baseline values for selected PD assessments will also be summarized by treatment sequence and overall based on the Safety Set.

11.1.3 PK Analysis

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

Individual concentration-time data will be pooled to describe the population PK of TAK-831. As data permit, a nonlinear mixed effects modeling approach (NONMEM software) will be used to

assess TAK-831 exposure. PK information generated in this study will be further utilized in subsequent population PK-PD analyses. The relationships between TAK-831 plasma concentrations and drug response will be explored. As appropriate, historical data may be used in this analysis to increase the robustness of the model and precision of estimated parameters. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses may be reported separately.

11.1.4 PD Analysis

11.1.4.1 Analysis of Primary PD Endpoint

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

A frequentist analysis will be done for the full data set, using simulations to adjust for the effect of the interim analysis on the type I error rates. The results of the primary endpoint will be considered statistically significant at either of the 2 doses (as applicable) if the one-sided $p<0.05$, without adjustment for multiplicity (ie, the type I error rate will be separately controlled for each dose).

In addition, the primary endpoint will be analyzed using a Bayesian normal linear model with treatment sequence, period, and treatment as fixed effects and subject within sequence as a repeated factor. The dependent variable is the change in response from the period baseline assessment to the final treatment day for each period. The response data will be logit transformed before the change is calculated. A diffuse normal distribution will be used as a prior for the regression coefficients and a diffuse inverse gamma for the residual variance. The Bayesian model will be used to estimate the posterior distribution of the treatment effect from each dose (as applicable).

11.1.4.2 Analysis of Other PD Endpoints

The secondary EEG endpoints will be analyzed using an ANOVA model as described in Section 11.1.4.1.

The cognitive battery composite score, the BACS, will be analyzed as follows. The primary measure from each test is standardized by creating z-scores whereby the mean of the test session of a healthy participant is set to 0 and the standard deviation set to 1 [44]. A composite score will be calculated by averaging the 4 measures from the BACS used in the study, and then calculating a z-score of the composite. The composite z-score indicates how much higher or lower the participant's cognition is compared to a healthy person. An ANOVA will be performed on the change from baseline for the composite BACS score, using a similar model to that used for primary endpoint.

For each regimen, the concentrations of D-serine, L-serine, and the ratio of D-serine to total serine with change and percent change from Baseline will be summarized at each time point of each dose level using descriptive statistics. In addition, mixed effects regression models will be fitted to the change from Baseline in these concentrations. Pairwise comparisons between the test regimens (high dose, low dose and placebo) will be made and the CIs for the difference in the LS means will be constructed for selected time points. Additional details and further analyses will be specified in the statistical analysis plan.

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

Analysis of exploratory PD endpoints will be described in the SAP.

11.1.5 Safety Analysis

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

11.1.5.1 AEs

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

11.1.5.2 Clinical Laboratory Evaluation

Individual results of 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.

11.1.5.3 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.

11.1.5.4 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.

11.1.5.5 Other Safety Parameters

Physical examination findings will be presented in the data listings.

11.2 Interim Analysis and Criteria for Early Termination

A planned unblinded interim analysis of the primary PD endpoints will be conducted when approximately 14 patients have been completed the primary endpoint. The site will be allowed to continue enrollment to the high/placebo comparison, with the goal that approximately 16 patients will be randomized by the time the interim analysis is complete. (The additional approximately 2 subjects will be included in the final analysis but not the interim analysis.) The purpose of the interim PD analysis will be to determine whether to continue enrolling subjects to the high-dose/placebo comparison, switch enrollment to the low-dose/placebo comparison, or discontinue enrollment. The decision rule will be specified in an interim analysis plan before the data are unblinded for the interim analysis. In addition, a decision to switch to the low dose may be made based on safety or tolerability of the high dose.

11.3 Determination of Sample Size

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

The expected effect size, defined as the ratio between the mean difference between treatment and placebo divided by the standard deviation of this difference, is 0.6 for the primary endpoint. This effect size is a conservative estimate based on data from [20], which showed an effect size of 0.74 for EBC at 24 hours after initiation of treatment with secretin. In this study of a schizophrenic population, subjects on secretin showed a 24% higher rate of correct responses compared to subjects on placebo (70% vs 46%).

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

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's 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, and review of 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.

12.2 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, 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.

Significant 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.

12.3 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 the medication 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 the US 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 guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 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 International Conference on Harmonisation (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 A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 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 (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). 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 will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

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 its designee.

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

13.2 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] Notify Sponsor of consent withdrawal.

13.3 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 study database or documentation via a unique identification 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 identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, 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 13.2).

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).

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 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 clinical 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 Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical studies 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 studies 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 investigators in the United States), 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 study information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study 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.

13.4.3 Clinical Study Results Disclosure

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

13.5 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 Sponsor's 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 Sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
SAE and pregnancy reporting	Takeda Pharmacovigilance Takeda Development Center Americas, Inc Fax: 224-554-1052 Email: PVSafetyAmericas@tpna.com

14.1.2 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 Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AST	aspartate aminotransferase
ASSR	auditory steady-state response
ANOVA	analysis of variance
BACS	Brief Assessment of Cognition in Schizophrenia
beta-hCG	beta human chorionic gonadotropin
BMI	body mass index
CDSS	Calgary Depression Scale Score
CIAS	cognitive impairment in schizophrenia
CRO	contract research organization
CR	conditioned response
CS	conditioned stimulus
C-SSRS	Columbia Suicide Severity Rating Scale
Cz	midline central electrode
DAO	D-amino acid oxidase
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBC	eyeblink conditioning
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalography
EDS	extra-dimensional set shifting
ERP	event related potential
FDA	Food and Drug Administration of the United States
FSH	follicle stimulating hormone
Fz	midline frontal electrode
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HPLC	high performance liquid chromatography
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
IDS	intra-dimensional shift
IEC	Independent Ethics Committee
IRB	institutional review board
IRT	interactive response technology

K_2EDTA	Potassium ethylenediaminetetraacetic acid
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMN	mismatch negativity
MOP	manual of procedure
MRD	multiple-rising dose
NMDA	N-methyl-D-aspartate
NSFS	negative symptom factor score
PANSS	Positive and Negative Symptom Scale
PCP	phencyclidine
PD	pharmacodynamics
PET	positron emission tomography
[redacted]	[redacted]
PK	pharmacokinetic
PT	preferred term
Pz	midline parietal electrode
QD	once daily
QTcF	QT interval with Frederica correction method
RNA	ribonucleic acid
Rs	resting state
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SBP	systolic blood pressure
SOC	system organ class
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	unconditioned response
WBC	white blood cell

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 CRFs (Electronic and Paper)

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

The Sponsor or its designee will supply investigative sites with access to eCRFs. The Sponsor 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 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 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. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date 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 clinical 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 sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its 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.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 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), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its 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, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (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 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 Clinical Study Site Agreement between the investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

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17.0 APPENDICES

Appendix A 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 that will assist in the protocol.
3. 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.
4. 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.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. 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.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B 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 medication(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 highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 35 days after the last dose of study drug. 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 study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use a barrier method of contraception (eg, condom with or without spermicide) as defined in the informed consent from signing the informed consent throughout the duration of the study and for 95 days after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C 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 medication.
- 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 D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

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 a highly effective/effective method of contraception (from the list below).

For studies in which teratogenicity/genotoxicity/embryotoxicity has been demonstrated (investigational medicinal product or comparator or background medication), or there is a lack of adequate reproductive toxicity data, female subjects should be instructed to use two highly effective methods of contraception/one highly effective and one effective method (from the list below).

In addition they must be advised not to donate ova during this period.

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 post-menopausal 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 FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) 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 post-bilateral 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. Highly effective methods of contraception are defined as “those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and

correctly). In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are:

- Non-Hormonal Methods:
  - Intrauterine device.
  - Bilateral tubal occlusion.
  - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant 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.

2. Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
4. Subjects will be provided with information on 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, donation of ova, and sperm donation during the course of the study.
5. During the course of the study, regular serum hCG pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study
   b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) Assessment of subject compliance through questions such as
      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?

6. 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), a negative serum hCG pregnancy test at predose on Day 1 prior to receiving any dose of study medication. In addition, subjects must also have a negative serum/urine hCG pregnancy test at any time during the study, if requested by the clinical site.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
    - Is there a chance you could be pregnant?

Pregnancy

Women of childbearing potential will be included in this study.

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug and should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 95 days after the last dose should also be recorded following authorization from the subject's partner.

Should the pregnancy occur during or after administration of blinded 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 the female subject or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the 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, including female partners of male subjects, in subjects on active study drug (including comparator, if applicable) 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.

Appendix E Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 06 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Updated entry criteria.

The primary changes occur in Section 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

Initial wording:	7.1 Inclusion Criteria ... 3. Be male or a female aged 18 to 50 years, inclusive, at the Screening Visit. .....
Amended or new wording:	7.1 Inclusion Criteria ..... 3. Be male or a female aged 18 to 60 years, inclusive, at the Screening Visit. ....

Rationale for change: Inclusion criterion 03 revised to increase the maximum subject age from 50 to 60 years, which will allow for increasing patient recruitment.

The following sections also contain this change:

- Section 1.0 STUDY SUMMARY
- Section 6.1 Study Design and Description

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

ELECTRONIC SIGNATURES

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