Title: A Randomized, Investigator and Subjects Blinded, Sponsor Unblinded, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Escalating Multiple Doses of TAK-831 in Healthy Subjects

NCT Number: NCT03224325

Protocol Approve Date: 19 March 2018

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

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Investigator and Subject Blinded, Sponsor Unblinded, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Escalating Multiple Doses of TAK-831 in Healthy Subjects

Study Identifier: TAK-831-1005

Compound: TAK-831

Date: 19 March 2018

Version/Amendment Number: Amendment No. 02

Amendment History:

Date	Amendment Number	Region
08 June 2017	Initial version	Global
15 August 2017	01	Global
19 March 2018	02	Global

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015	**Compound:** TAK-831
Study Identifier: TAK-831-1005	**Phase:** 1
Protocol Title: A Randomized, Investigator and Subject Blinded, Sponsor Unblinded, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Escalating Multiple Doses of TAK-831 in Healthy Subjects	
Trial Design: The study is an investigator and subject blinded, sponsor unblinded, placebo-controlled clinical study progressively assessing independent cohorts of healthy subjects to continue evaluation of the safety, tolerability, and pharmacokinetics (PK) of escalating multiple doses of TAK-831 at doses higher than those achieved in the initial multiple rising dose study (TAK-831-1001). Up to 6 cohorts will be run either singly or in parallel as non- cerebrospinal fluid (CSF) cohorts with plasma analysis or CSF cohorts with CSF analysis in addition to plasma analysis to assess TAK-831 exposure and CCI levels in the central nervous system (CNS). After meeting all the selection criteria, there will be 8 subjects enrolled in each cohort. They will be randomized on Day 1 in a 1:3 ratio to receive placebo or TAK-831. In CSF cohorts, lumbar CSF samples will be collected through either a single lumbar puncture or an indwelling temporary catheter on 2 separate occasions. In CSF cohorts that use an indwelling temporary catheter on both occasions, the first collection will occur on Day 1 and the second on Day 16. In CSF cohorts where the predose CSF sample is collected through a single lumbar puncture, the first CSF sample will be collected on Day -1 prior to the start of CCI monitoring and the second collection will be obtained through use of an indwelling temporary catheter on Day 16. If an indwelling temporary catheter is being used, it will collect serial CSF samples for 24 hours. CCI Subjects in each cohort will be confined during dosing and be kept in the study unit for 24 hours after the last dose for non-CSF cohorts and 48 hours after catheter removal in CSF cohorts. The total confinement period in non-CSF cohorts will be 19 days (Day -2 to Day 17), 20 days in CSF cohorts where an indwelling temporary catheter is being used on Day 1 and Day 16 (confinement from Day -1 to Day 19); and 21 days in CSF cohorts where CSF is collected through a single predose lumbar puncture on Day -1 and through an indwelling catheter on Day 16 (confinement from Day -2 to Day 19). Follow-up assessments will occur on Day 30 (±2) for all cohorts. An exception to these minimum confinement periods will be made if a determination is made to evaluate QT/QTc intervals for additional single doses of TAK-831 in non-CSF cohorts based on the established tolerated dose range.	
Trial Primary Objective: To evaluate the safety and tolerability of TAK-831 when administered as multiple oral doses at escalating dose levels in healthy subjects. **Secondary Objectives:** To evaluate the PK of TAK-831 when administered as multiple oral doses at escalating dose levels in healthy subjects.	
Trial Subject Population: Healthy male subjects and female subjects not of childbearing potential, aged 18 to 55 years, inclusive.	
Planned Number of Subjects: Approximately 48 (8 per cohort, up to 6 cohorts)	**Planned Number of Sites:** 1

Dose Levels:	**Route of Administration:**
Starting dose TAK-831 600 mg (tablet T2 formulation, Cohort 1) and 800 mg (suspension formulation, Cohort 2) and matching placebo	Oral
Duration of Treatment:	**Planned Trial Duration:**
One day for SD part (followed by evaluation for 2 days) and then 14 days for MD part.	Approximately 58 days for each cohort: screening 28 days, treatment and assessments including follow-up 30 days (treatment Days 1 and 3 to 16; assessments Days 1 to 17 for non-CSF cohorts or 1 to 19 for CSF cohorts; follow-up: Day 30 [±2]). Maximum duration: approximately 348 days for 6 cohorts.

Main Criteria for Inclusion for Healthy Subjects:

In order to be eligible for participation, subjects must:

- Be a healthy adult male or female not of childbearing potential.
- Be aged 18 to 55 years, inclusive, at the time of informed consent and first study drug dose.
- Weigh at least 45 kg and has a body mass index between 18.0 and 30.0 kg/m^2, inclusive at Screening.

Main Criteria for Exclusion for Healthy Subjects:

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

- Has a known hypersensitivity to any component of the formulation of TAK-831.
- Has a risk of suicide according to the investigator's clinical judgment (eg, per Columbia–Suicide Severity Rating Scale), or has made a suicide attempt in the previous 6 months.

Additional Exclusion Criteria for Cohort(s) with CSF Collection:

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

- Has had CSF collection performed within 30 days before Check-in (Day -1).
- Has a known hypersensitivity to the anesthetic or its derivatives used during CSF collection, or any medication used to prepare the area of lumbar puncture.
- Has significant vertebral deformities (scoliosis or kyphosis) which, in the opinion of the investigator, may interfere with lumbar puncture procedure.
- Has a history of clinically significant back pain and/or injury.
- Has local infection at the puncture site.
- Has thrombocytopenia or other suspected bleeding tendencies noted before procedure.
- Has developed signs and symptoms of spinal radiculopathy, including lower extremity pain and paresthesia.
- Has any focal neurological deficit that might suggest an increase in intracranial pressure.
- Has any abnormal finding on ophthalmological assessment/fundoscopy suggestive of raised intracranial pressure (ie, optic disc swelling/edema; (uncontrolled) hypertensive retinopathy).
- Suffers regularly from moderate to severe headaches requiring analgesics.
- Subjects with lower spinal malformations (on physical examination or lumbar spine radiography), local spinal infection, or other abnormalities that would exclude lumbar puncture (LP).

Main Criteria for Evaluation and Analyses:

Primary Endpoints

Primary endpoints are the safety parameters of TAK-831 and will be assessed as follows:

1. Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).

2. Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
3. Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
4. Percentage of subjects who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once postdose.

Secondary Endpoints

Secondary endpoints are the plasma PK parameters of TAK-831 and will be measured as follows:

1. Maximum observed plasma concentration (C_{max}) (Day 1).
2. Maximum observed steady-state plasma concentration during a dosing interval (Day 16).
3. Time of first occurrence of C_{max} (Days 1 and 16).
4. Area under the plasma concentration-time curve during a dosing interval (Days 1 and 16).

Statistical Considerations:

Safety:

Adverse events will be presented in listings, and TEAEs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be listed and Baseline, postdose, and changes from Baseline to postdose laboratory data will be summarized. Individual results of vital signs will be listed and Baseline, postdose, and changes from Baseline in vital signs will be summarized. Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and Baseline, postdose, and changes from Baseline in quantitative ECG parameters will be summarized. All summaries will be performed by regimen for placebo, each TAK-831 dose level, and TAK-831 overall. Other safety measures (neurological examination and the ophthalmoscopic assessment of the fundus, physical examination findings and suicidality assessments [C-SSRS]) will be presented in data listings.

PK Measures:

Concentrations of TAK-831 in plasma (all cohorts) and CSF (CSF Cohort[s]) will be summarized by dose, drug formulation, and day over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. Plasma and CSF PK parameters, including dose-normalized C_{max} and AUCs, will be summarized by dose, drug formulation, and day using descriptive statistics. Changes in the PK parameters from Day 1 to Day 16 will be assessed by summarizing the ratio of Day 16 to Day 1 by dose. Dose proportionality in plasma PK parameters (C_{max} and AUCs) will be assessed graphically for Day 1 and Day 16 plasma concentrations. Additional analyses will be included as appropriate.

Biomarker Measures and Exploratory Endpoints:

CCI

Sample Size Justification:

The sample size chosen of 8 subjects for all cohorts (6 active:2 placebo) is considered to be sufficient for the determination of progression to the next cohort based on the safety and PK data. The sample size was not based on statistical power considerations.

1.1 Protocol Amendment No. 02 Summary of Changes

Rationale for Amendment No. 02

This document describes the changes in reference to the protocol incorporating Amendment No. 02. The primary reason for this amendment is to revise the study procedures to enable cohorts that obtain CCI measurements as described in the previous protocol in addition to the collection of a baseline CSF sample on Day -1 through a single lumbar puncture and serial CSF sampling on Day 16. In addition, the drug supply management has been updated. Clarifications, inconsistencies, and minor grammatical, editorial, and formatting changes are included for clarification purposes only.

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

Changes in Amendment No. 02

1. Updated study design and procedures.
2. Updated clinical study material management.

2.0 STUDY SCHEMATIC

Cohorts (up to 6 as needed)	**Pretreatment Period**		**Treatment and Assessments (a)**				
			SD Part				
	Screening	**Check-in/ Baseline**	**Treatment**	**Evaluation**	**MD Part**	**Study Exit**	**Follow-up (b)**
Non-CSF (or CSF cohorts that collect Day -1 CSF samples via a single predose lumbar puncture)	Days -28 to -3	Day -2	Day 1	Days 1 to 2	Days 3 to 16	Day 17 (non-CSF cohort) / Day 19 (CSF cohort where Day -1 CSF is collected via a single predose lumbar puncture)	Day 30 (±2)
CSF	Days -28 to -2	Day -1	Day 1	Days 1 to 2	Days 3 to 16	Day 19	Day 30 (±2)
		←		**Confinement**		→	

CSF=cerebrospinal fluid, MD=multiple dose, PD=pharmacodynamic, PK=pharmacodynamic, SD=single dose.
(a) TAK-831 dosing will be on Day 1 for SD and Days 3 through 16 for MD.
(b) The Follow-up Visit will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In these cases, subjects may then be brought back to the clinic for re-evaluation per investigator's discretion.

3.0 SCHEDULE OF STUDY PROCEDURES

	Scr-een-ing	Check in / Baseline Assessments	Treatment Day																Study Exit (a)	Early Termina-tion (b)	Follow-up
Study Day:	**-28 to -3**	**Day -2 (non-CSF or CSF cohorts) that collect baseline CSF samples via a single predose lumbar puncture or Day -1 (CSF cohorts)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Day 17 (non-CSF) / Day 19 (CSF)**		**30 (±2) (c)**
ADMINISTRATIVE PROCEDURES																					
Informed consent	X																				
Inclusion/exclusion criteria	X	X	X																		
Demographics/ medical history	X																				
Medication history	X	X																			
Concurrent medical conditions	X	X																			
CLINICAL PROCEDURES/ASSESSMENTS																					
Full physical examination	X	X																	X	X	(X)
Height	X																				
Weight and BMI (d)	X																		X	X	(X)
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (f)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Neurological examination and fundoscopy (g)		X															X				
Lumbar spine radiography (for CSF cohorts only) (h)	X																				

Study Day:	Scr-een-ing -28 to -3	Check in / Baseline Assessments Day -2 (non-CSF or CSF cohorts) that collect baseline CSF samples via a single predose lumbar puncture or Day -1 (CSF cohorts)	Treatment Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Study Exit (a) Day 17 (non-CSF) / Day 19 (CSF)	Early Termina-tion (b)	Follow-up 30 (±2) (c)
Safety ECG (i)	X	X	X									X						X	X	X	(X)
CCI																					
C-SSRS (k)	X	X																	X	X	
Study drug administration			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY PROCEDURES																					
Clinical laboratory tests (l)	X	X	X									X							X	X	(X)
Hepatitis panel (HBsAg and anti-HCV)	X																				
HIV screen	X																				
FSH (m)	X																				
hCG (n)	X	X																	X	X	(X)
Hormone laboratory tests (o)			X																X	X	(X)
Drug screen	X	X																			
PGx EVALUATIONS																					
DNA sample collection (p)			X																		
PK EVALUATIONS																					
PK blood collection (q)			X	X								X			X			X		X	
PK CSF collection (r)		X (r)	X (r)	X (r)														X			

	Scr-een-ing	Check in / Baseline Assessments	Treatment Day																Study Exit (a)		Follow-up
Study Day:	-28 to -3	Day -2 (non-CSF or CSF cohorts) that collect baseline CSF samples via a single predose lumbar puncture or Day -1 (CSF cohorts)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Day 17 (non-CSF) / Day 19 (CSF)	Early Termina-tion (b)	30 (±2) (c)
PD/BIOMARKER EVALUATIONS																					
CCI [redacted]																					
CCI [redacted]																					

AE=adverse event, anti-HCV=antibody to hepatitis C virus, BMI=body mass index, C-SSRS=Columbia–Suicide Severity Rating Scale, ECG=electrocardiogram, FSH=follicle-stimulating hormone, HbA1c=glycosylated hemoglobin, HBsAg=hepatitis B surface antigen, hCG=human chorionic gonadotropin, HIV=human immunodeficiency syndrome, PGx=pharmacogenomics, TSH=thyrotropin.
(a) Study exit for non-CSF cohorts occurs on Day 17 and for CSF cohorts on Day 19.
(b) At Early Termination, perform all procedures per Section 7.6.
(c) The Follow-up Visit will occur by telephone on Day 30 (±2) unless abnormal, clinically significant findings are observed upon discharge. In these cases, subjects must be brought back to the clinic for re-evaluation per investigator's discretion. (X) is for optional procedure.
(d) BMI will be calculated only at Screening.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Vital signs (oral temperature, respiratory rate, pulse, and blood pressure) will be obtained at Screening, Check-in, Day 1, and Days 3 through 16 at predose (within 60 minutes before dosing) and at 1, 4, and 12 hours after the morning dose, and Study Exit/Early Termination and as appropriate at the Follow-up Visit. Day 2 vital signs should be collected approximately 24 hours after the Day 1 dose is administered. Pulse and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing for all scheduled time points, with exception of Day 1, Day 2, and Day 16 in cohorts where CSF collection is performed using an indwelling catheter, when only supine measurements will be taken.
(g) Only for CSF cohorts: A neurological assessment and eye examination (ophthalmological assessment of the retina, fundoscopy) will be performed on Day -2 (baseline collection through single lumbar puncture), Day -1 (baseline collection through indwelling catheter) and Day 15.
(h) Lumbar spine radiography (for CSF cohorts only) if one has not been performed within the past 12 months prior to the screening visit.
(i) A standard 12-lead ECG (single) will be recorded at Screening, Check-in, Day 1 (predose [within 60 minutes prior to dosing], and at 1.5 hour postdose (morning dose), Day 16 (predose [within 60 minutes prior to dosing], and at 1 and 2 hours after morning dose, Day 10 (predose), and Study Exit/Early Termination and as appropriate at the Follow-up Visit.
CCI [redacted]

CCI [redacted]

(k) The C-SSRS (Lifetime/Recent) will be administered at Screening; the C-SSRS (since last visit) will be administered at Check-in and at Study Exit/Early Termination.
(l) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening, Check-in, and after a 10-hour fast at predose on Days 1, 10, and at Study Exit/Early Termination and as appropriate at the Follow-up Visit.
(m) For women only: A FSH level will be obtained on postmenopausal women at Screening only.
(n) For women only: Serum hCG will be performed at Screening, Day -1, and Study Exit/Early Termination, and at the Follow-up Visit if the subject is brought back to the clinic for re-evaluation.
(o) Hormone laboratory tests (prolactin, growth hormone, cortisol, and TSH) will be collected on Day 1 (before dosing, under fasted conditions and 3 hours postdose) and at Study Exit/Early Termination (morning values, under fasted conditions) and as appropriate at the Follow-up Visit.
(p) One blood sample (6 mL) will be collected for DNA analysis before dosing on Day 1.
(q) Blood samples (4 mL) for PK analyses will be collected on Day 1 (within 30 minutes before dosing) and at 0.5, 1, 1.5, 2, 4, 8, 12, 24, hours after the morning dose; on Day 10 (predose), Day 13 (predose), and on Day 16 at predose (within 30 minutes before dosing), and at 0.5, 1, 2, 4, 8, 12, 16, and 24 hours after the morning dose and at Early Termination.

CCI [redacted]

CCI [redacted]

4.0 INTRODUCTION

4.1 Background

Inhibition of D-amino acid oxidase (DAO) has been proposed as a potential for the treatment of schizophrenia. DAO is a peroxisomal enzyme active toward neutral D-amino acids, which is expressed in both the periphery and the brain. DAO degrades D-amino acids by oxidation. In the periphery, this action likely plays a role in the detoxification of D-amino acids from bacterial and other sources, as amino acids used for protein synthesis and other metabolic processes are L-amino acids. Few D- amino acids are known to play a biological role in humans, but D-serine in the brain has been connected to the regulation of glutamatergic neurotransmission [1], and D-serine has been shown to be an obligatory co-agonist of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors, binding to the glycine site. Inhibition of DAO elevates endogenous D-serine in the cerebellum, increasing Purkinje cell long term depression via activation of δ2 glutamate receptor and/or NMDA receptors with subsequent internalization of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptors [2].

Hypofunction of NMDA receptors is considered a possible mechanism in the pathophysiology of schizophrenia, which could be mitigated by increasing D-serine levels in the brain [3]. Changes in D-serine levels or in the ratio of D-serine to total serine have been reported in the plasma of patients with schizophrenia, both naive and under drug treatment [4-7]. 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 study analysis, indicating the biological relevance to schizophrenia of the genetic pathway in which DAO sits [8].

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 [9].

While current medications mitigate positive symptoms of schizophrenia and to some extent the negative symptoms, cognitive impairment represents an area of unmet medical need. Moreover, cognitive 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 Rationale for the Proposed Study

TAK-831 is a highly selective and potent inhibitor of DAO. 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 negative symptoms of schizophrenia (NSS) and cognitive impairment associated with schizophrenia (CIAS), as well as for cerebellar ataxias such as Friedreich ataxia. In addition to safety and tolerability, the current proposed study is aimed at providing information on the relationship between concentrations of TAK-831 CCI [redacted]

4.3 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. Procedures may be added during the study if necessary based on evaluation of any additional clinical or nonclinical safety data.

- TAK-831 has been used in a prior single dose (up to 750 mg in oral suspension and 100 mg in tablet T1 formulation and 14 days multiple dose (up to 400 mg QD in oral suspension) study in healthy subjects (TAK-831-1001) with good safety and tolerability, as well as a single dose PET study (TAK-831-1003), and these studies have not resulted in a safety signal that would prevent additional studies. Additionally, a T2 tablet formulation is currently under assessment in a single dose food effect study (TAK-831-1004) that will contribute additional data to inform dose selection during the conduct of this study.
- 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.
- Study procedure–specific risks include issues relating to blood collection for safety assessment/PK and PD monitoring (venipuncture may cause bruising), and the placement of ECG pads, which may cause some local redness and/or erythema/itching.
- The risk of pain or discomfort at the site of CSF collection and the risk of headache in cohorts where CSF will be collected for PK and PD assessment. Severe headaches may require a blood patch procedure. There is a small risk of infection with indwelling catheters.
- The investigator has discretion to use his/her clinical judgment as to whether to allow a subject to proceed in the study or whether to unblind the subject in order to determine his/her treatment allocation.
- The C-SSRS will be administered to monitor emergent suicidality.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Trial Objectives

5.1.1 Trial Primary Objective

To evaluate the safety and tolerability of TAK-831 when administered as multiple oral doses at escalating dose levels in healthy subjects.

5.1.2 Trial Secondary Objective

To evaluate the PK of TAK-831 when administered as multiple oral doses at escalating dose levels in healthy subjects.

5.1.3 Trial Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

Primary endpoints are the safety parameters of TAK-831 and will be assessed as follows:

1. Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE)
2. Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
3. Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
4. Percentage of subjects who meet the markedly abnormal criteria for safety ECG parameters at least once postdose.

5.2.2 Secondary Endpoints

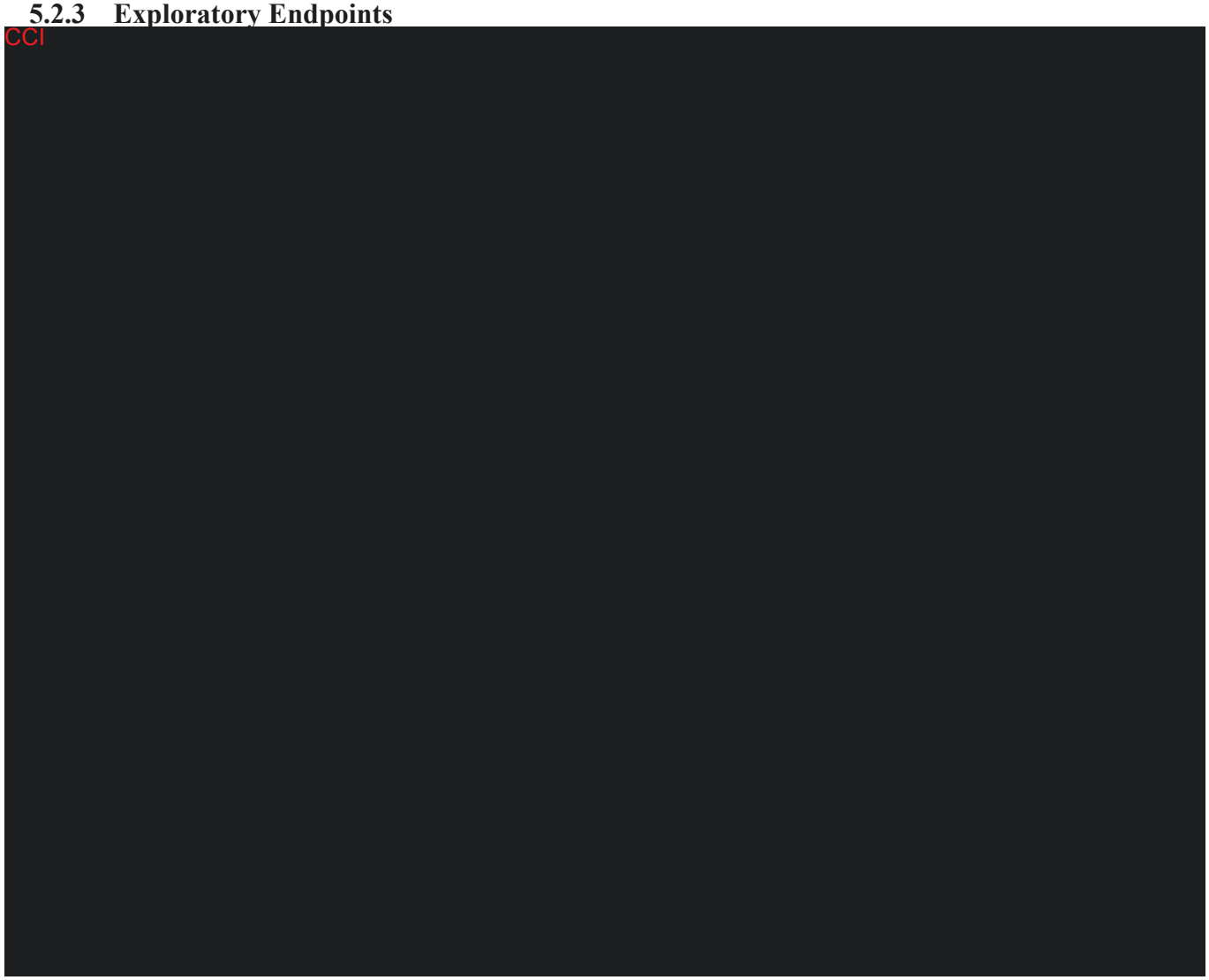
Secondary endpoints are the plasma PK parameters of TAK-831 and will be measured as follows:

1. Maximum observed plasma concentration (C_{max}) (Day 1).
2. Maximum observed steady-state plasma concentration during a dosing interval (Day 16).

3. Time of first occurrence of C_{max} (Days 1 and 16).
4. Area under the plasma concentration-time curve during a dosing interval (Days 1 and 16).

5.2.3 Exploratory Endpoints

CCI



6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

The study is an investigator and subject blinded, sponsor unblinded, placebo-controlled clinical study progressively assessing independent cohorts of healthy subjects to continue evaluation of the safety, tolerability, and PK of escalating single doses (SD) and multiple doses (MD) of TAK-831, as either a suspension or T2 tablet formulation, at levels higher than those achieved in the initial single and multiple rising dose (SRD/MRD) Study TAK-831-1001.

Up to 6 cohorts will be run either singly or in parallel as non- cerebrospinal fluid (CSF) cohorts with plasma analysis or CSF cohorts with CSF analysis in addition to plasma analysis to assess TAK-831 exposure and CCI levels in the central nervous system (CNS). After meeting all the selection criteria, there will be 8 subjects enrolled in each cohort. They will be randomized on Day 1 in a 1:3 ratio to receive placebo or TAK-831.

All cohorts will start with an initial, in-house SD period to include predose PD assessments on Day -1, Day 1 TAK-831 dosing, and a 48-hour in-house observation period with full PK collections. The SD PK collection and observation phase will be followed by 14 days of in-house MD.

In CSF cohorts, lumbar CSF samples will be collected through either a single lumbar puncture or an indwelling temporary catheter on 2 separate occasions. In CSF cohorts that use an indwelling temporary catheter on both occasions, the first collection will occur on Day 1, and the second on Day 16. In CSF cohorts where the pre-dose CSF sample is collected through a single lumbar puncture, the first CSF sample will be collected on Day -1 prior to the start of CCI monitoring and the second collection will be obtained through use of an indwelling temporary catheter on Day 16. If an indwelling temporary catheter is being used, it will collect serial CSF samples for 24 hours.

CCI

Subjects in each cohort will be confined during dosing and be kept in the study unit for 24 hours after the last dose for non-CSF cohorts and 48 hours after catheter removal in CSF cohorts. The total confinement period in non-CSF cohorts will be 19 days (Day -2 to Day 17), 20 days in CSF cohorts where an indwelling temporary catheter is being used on Day 1 and Day 16 (confinement from Day -1 to Day 19); and 21 days in CSF cohorts where CSF is collected through a single predose lumbar puncture on Day -1 prior to the start of CCI and through an indwelling catheter on Day 16 (confinement from Day -2 to Day 19). Follow-up assessments will occur on Day 30 (±2) for all cohorts. An exception to these minimum confinement periods will be made if a determination is made to evaluate QT/QTc intervals for additional single doses of TAK-831 in non-CSF cohorts based on the established tolerated dose range.

The Study Schematic and Schedule of Study Procedures are provided in Section 2.0 and Section 3.0, respectively.

6.2 Dose Escalation

In Cohort 1, the proposed starting dose is TAK-831 600 mg QD, administered as a tablet formulation (Formulation T2) and, in Cohort 2, the starting dose is TAK-831 800 mg QD administered as a suspension formulation. Cohort 1 and Cohort 2 will run in parallel.

The proposed dose and dose escalation is provided in Table 6.a.

Table 6.a Proposed Doses and Cohort Dose Escalation

Cohort	Proposed Dose, (Estimated)	Formulation	Rationale
1 (with CSF)	600 mg/day (QD)	Tablet formulation T2	T2 tablet formulation at 600 mg is expected to deliver exposures comparable to 400 mg administered as a suspension. This exposure level demonstrated acceptable safety and tolerability with multiple dosing in Study TAK-831-1001; CCI [redacted]
2 (with CSF)	800 mg/day (QD)	Suspension formulation	Cohort 2 will be run in parallel with Cohort 1. TAK-831 750 mg single dose administered as a suspension was found to have acceptable tolerability in Study TAK-831-1001. The highest multiple dose level in that study was 400 mg suspension. CCI [redacted]
3	1200 mg/day (a)	Suspension	Evaluate safety, tolerability, PK and PD effects of increased doses of TAK-831 administered as a suspension as tolerated up to the maximum exposure defined below. Once this objective is met, possible additional doses and dose regimens (eg, BID, single doses), with or without CSF collections and CCI [redacted] (in non-CSF cohorts or in CSF cohorts where Day -1 CSF is being collected through a single lumbar puncture), will be examined, pending PK-PD results of Cohorts 1 and 2.
4 (with CSF)	100 mg/day (a)	Tablet formulation T2	
5 (with CSF where Day -1 CSF is collected through a single lumbar puncture)	15 mg	Suspension	CCI [redacted]
6	TBD (a)	Tablet formulation T2 or suspension	

TBD=to be determined.
(a) No selected dose will have exposures projected to exceed the study exposure limits or a maximum 2000 mg dose, whichever is lower.

Exposure levels in each cohort will be monitored closely and will not exceed exposures seen at the end of a 13-week repeat dose toxicity studies in monkeys (see Section 6.3.2).

Since, the highest dose tested in single rising dose portion of Study TAK-831-1001 was 750 mg administered as a suspension, all dose levels above 750 mg/day will be tested first in SD setting before MD in subsequent cohorts.

All decisions concerning dose escalation will be made by Takeda (at a minimum, the clinical science representative[s], quantitative clinical pharmacologist, study statistician and pharmacovigilance physician) and the principal investigator. The investigator and subjects will remain blinded throughout the study, but at the completion of each cohort, specific Takeda personnel listed in associated study documentation may be unblinded to analyze data considered necessary to determine subsequent doses and cohort management decisions. All data presentations prepared for discussions with the investigator and site staff will contain only blinded study data, except in the event that formal study unblinding procedures detailed in Protocol Section 8.1.5 have been followed and discussion of related data is required.

If agreement regarding a dose escalation decision cannot be reached between the principal investigator and Takeda, the study will be stopped.

Based on emerging safety and tolerability and PK data, the planned dose levels may be modified.

All adverse events reported during the Treatment Period, both within and across cohorts, up to the time of discharge will be evaluated to assess the need for subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (Section 6.5).

Following assessment of the adverse event data and predefined criteria for study termination, dose escalation may be interrupted/stopped if these criteria are met. Based on review of study data as outlined above, Takeda, in consultation with the principal investigator, will decide if and how it is appropriate for the study to proceed.

Dose escalation may be interrupted/stopped if:

- Exposures in any cohort exceed those observed at the top dose tested in the monkey toxicity study, that is, a mean C_{max} of 3680 ng/mL or a mean AUC_{24} of 35,700 hr*ng/mL.
- The exposures reach the plasma exposure plateau in the 2 highest dose cohorts.
- One or more subjects in any single cohort or across more than 1 cohort experience an SAE or 2 severe or clinically significant AEs occur that are considered related to study drug.
- One or more subjects in any single cohort or across more than 1 cohort experience severe psychiatric symptoms, including any level of treatment-emergent suicidal ideation* that are considered related to study drug.

  [*Treatment-emergent suicidality compared to Baseline, as measured by an increase in suicidal ideation or behavior category (on the C-SSRS) during treatment from the maximum suicidal ideation/behavior category at Baseline, or any suicidal ideation/behavior during treatment if there was none at Baseline].

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

In addition to assessing safety, tolerability, and PK of TAK-831, the proposed study is aimed at providing information on the relationship between concentrations of TAK-831 and CCI [redacted] to be explored in both plasma and CSF in healthy subjects in order to support dose selection for the follow-up studies planned to evaluate PD effects of TAK-831 in subjects with schizophrenia. CCI [redacted] assessments will be conducted in non-CSF cohorts for exposure-response analysis of ECG parameters, or in CSF cohorts where the first CSF sample is collected through single lumbar puncture prior to the start of CCI [redacted] on Day -1.

6.3.2 Rationale for Dose

Based on the results of toxicology studies, the monkey is considered the more sensitive species. The NOAEL in the 13-week repeat dose study was based on adverse findings of vomiting, diarrhea, and loose stool at the top dose of 600 mg/kg/day. Therefore, the next lower dose tested, 100 mg/kg/day, was assigned the NOAEL for both sexes. This NOAEL was associated with mean C_{max} values of 1340 and 1270 ng/mL and mean AUC_{24} values of 7490 and 9190 h*ng/mL for males and females, respectively, on Day 91.

As the adverse effects of treatment in the monkey (vomiting, diarrhea, and loose stool) are easily monitored in humans, exceeding the NOAEL of 100 mg/kg/day in monkeys may be warranted in order to achieve adequate CNS exposures in humans. The targeted maximum exposure in humans is that attained in monkeys at 600 mg/kg/day. Dose escalation will be stopped if significant vomiting or diarrhea is observed in humans. In monkeys, at 600 mg/kg/day (dosed as 300 mg/kg, BID), respective mean C_{max} and AUC_{24} values on Day 91 were 3680 ng/mL and 35,700 h*ng/mL, sexes combined.

The highest dose tested in the MRD portion of Study TAK-831-1001 was 400 mg daily of the oral suspension formulation for 14 days. At this dose level, there were no significant adverse effects reported, and C_{max} exposures had reached those of female monkey at the NOAEL dose (C_{max} 1270 ng/mL and AUC_{24} 3454 h*ng/mL) (Table 6.b).

Table 6.b Exposure Margins

Species-Study	Dose (mg/kg/day or mg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	Margin (a)	
				C_{max}	AUC_{24}
Rat 13-week (Day 91)	1000 (NOAEL)	11,000 (M) 26,100 (F)	162,000 (M) 355,000 (F)	8.7 (M) 20.6 (F)	46.9 (M) 102.8 (F)
Monkey 13-week (Day 91)	100 (50 BID) (NOAEL)	1340 (M) 1270 (F)	7490 (M) 9190 (F)	1 (M) 1 (F)	2.2 (M) 2.7 (F)
	600 (300 BID) (vomiting, diarrhea)	4650 (M) 2710 (F)	45,500 (M) 25,900 (F)	3.7 (M) 2.1 (F)	13.2 (M) 7.5 (F)
Human MRD (Day 14)	400 mg QD (suspension form)	1270 (M)	3454 (M)	-	-

F=female, M=male.
(a) Margins relative to Day 14 exposures in humans administered 400 mg/day.

Based on these data, the proposed doses in the current study are as follows:

Cohort 1 subjects will receive a starting dose of TAK-831 600 mg QD as a T2 tablet formulation, which is expected to achieve geometric mean TAK-831 C_{max} and AUC_{24} about 60% and 83%, respectively of that of 400 mg suspension formulation under fasted conditions.

In parallel to Cohort 1, Cohort 2 will test the suspension formulation with 800 mg dose. Subsequent cohorts will have dose escalated as tolerable. Dose escalation will be stopped according to the stopping rules detailed in Section 6.2.

Proposed dose levels as well as dosing intervals for the subsequent cohorts may be adjusted after reviewing safety, tolerability, PK, and/or PD data of Cohorts 1 and 2.

6.3.3 Rationale for Endpoints

6.3.3.1 Primary Endpoint

The primary endpoint for this trial is the composite of safety variables to determine the safety and tolerability of oral multiple doses of TAK-831, and dose-limiting effects of TAK-831 and are common for this type of study.

6.3.3.2 Secondary Endpoint

The secondary endpoints consist of standard plasma PK variables to determine drug exposure at each dose to facilitate dose escalation.

6.3.3.3 Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, collecting safety data and collecting blood in all cohorts and CSF samples in one or more cohorts for TAK-831 PK and PD are the critical procedures.

- At any postdose time point, safety data need should be collected as close to the exact time point as possible.
- At any postdose time point, the blood and/or CSF sample for TAK-831 PK, and PD needs 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 priority can be changed during the trial 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.

6.4 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a phase 1 assessment of TAK-831 in healthy subjects. The PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 dose rising trials. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined in Section 6.1 and 6.2 may be required to achieve the trial objectives and to ensure the safety of the trial subjects.

Some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose/exposure detailed in Section 6.3.2, may not exceed those currently outlined.

- Additional cohorts may be added.
- Repeat of or decrease in the dose of the trial drug administered.
- Entire cohorts may be omitted.
- Increase/decrease in the duration of trial drug administration (eg, number of days), including evaluation of single doses of TAK-831 on QT/QTc intervals based on the established tolerated dose range.
- Adjustment of the dosing interval, for example, divided doses BID to QD, QD to BID, 3 times daily, or vice versa.

- A planned PK data review may be eliminated if agreed to by the sponsor and investigator and if no further increases in total daily dose occur.
- Addition of a PK data review.
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data (ie, food effect is known).
- The planned CSF sample may be eliminated, if agreed to by the sponsor and the investigator.

The PK/PD sampling scheme currently outlined in the protocol may be modified during the trial based on newly available PK or PD data (eg, to obtain data closer to the time of peak plasma concentrations). CCI [redacted].

Up to an additional 50 mL of blood may be drawn for PK and/or biomarker analyses. This may include repeat samples or modified PK/PD time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial.

The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, PK, or PK/PD data (eg, to obtain data closer to the time of peak plasma concentrations). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

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 trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the sponsor in a letter to the Trial 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.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

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

6.5.2 Definition of End of the Trial

The overall trial ends when the last subject completes the last planned or Follow-up Visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the trial, or is lost to follow-up (ie, the investigator is unable to contact the subject); or dosing of future cohorts is stopped based on the dose escalation rules.

6.5.3 Definition of Trial Completion

The primary objective of this phase 1 trial is to identify safety and tolerability of multiple rising doses. Therefore, it is possible that not all planned doses to be administered, if this objective is achieved at lower dose levels in this trial. This is not considered an early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s) or trial completion. Therefore, the definition of trial completion follows the same rules as definition of end of trial (Section 6.5.2) for the dosing group achieving the primary objective.

6.5.4 Definition of Trial Discontinuation

Trial discontinuation because of nonsafety reasons, such as:

- A finding (eg, PK, PD, efficacy, biologic targets) from another nonclinical or clinical trial using the trial treatment(s) results in the trial being stopped for a non–safety-related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this trial become available and results in the trial being stopped for a non–safety-related reason.
- The trial is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.

Trial discontinuation because of safety reasons:

- Early trial termination because of unanticipated concerns of safety to the trial subjects arising from nonclinical or clinical trials with the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial.

6.5.5 Criteria for Premature Termination or Suspension of the Trial

6.5.5.1 Criteria for Premature Termination or Suspension of Trial

The study will be completed as planned unless 1 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 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.
- Meeting study-specific criteria for terminating the study (eg, study meets predefined rule for futility or benefit, study meets predefined stopping rules within or between cohorts per Section 6.2).
- Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 times the upper limit of normal (ULN) in the absence of a concomitant bilirubin increase (see point 3 below)*. If 2 subjects in 1 dose level after dosing show the following findings in 2 consecutive measurements within 24 hours:

- ALT or AST ≥3×ULN, or
- ALT or AST ≥2×ULN and ALT or AST ≥5×baseline value, or
- Total bilirubin ≥2×ULN or
- International normalized ratio (INR) >1.5 or
- ALT and/or AST elevations >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%) without findings of cholestasis or other alternate etiology to explain the elevations (ie, "Hy's Law cases").

*Please note that the study may be terminated early before full attainment of these criteria (eg, if just 1 subject experiences 1 of these events) if warranted by safety data from the other subjects dosed in the study to date.

6.5.6 Criteria for Premature Termination or Suspension of a Site

A trial 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 trial, or as otherwise permitted by the contractual agreement.

6.5.7 Procedures for Premature Termination or Suspension of the Study or a Site

If the sponsor, an IRB, or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before the first dose.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization before the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is a healthy male or female not of childbearing potential adult who is aged 18 to 55 years, inclusive, at the time of informed consent and first study drug dose.
4. The subject weighs at least 45 kg and has a BMI from 18.0 to 30.0 kg/m2, inclusive at Screening.
5. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 90 days plus 5 half-lives (95 days) after last study drug dose.

   *Definitions and acceptable methods of contraception are defined in Appendix D.
6. A female subject with no childbearing potential, defined as a subject that has been surgically sterilized (hysterectomy, tubal ligation, or bilateral oophorectomy) or who is postmenopausal (defined as continuous amenorrhea of at least 12 months and FSH >40 IU/L).

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 4 weeks before Screening Visit. The 4-week window will be derived from the date of the last trial procedure and/or AE related to the trial procedure in the previous trial to the Screening Visit of the current trial.
2. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
3. The subject has uncontrolled, clinically significant neurological (including seizure disorders), cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, or psychiatric disorder, or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the Takeda Medical Monitor may be warranted.
4. The subject has a known hypersensitivity to any component of the formulation of TAK-831.

5. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in.
6. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as >3 drinks per day) within 5 year before the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study. (1 drink=12 oz. beer=5 oz. wine=1.5 oz. liquor.)
7. The subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products table listed in Section 7.3.
8. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 35 days after participating in this study; or intending to donate ova during such time period.
9. If male, the subject intends to donate sperm during the course of this study or for 90 days plus 5 half-lives (95 days) after the last dose of study medication.
10. The subject has evidence of current significant cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-831, or a similar drug in the same class, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
11. The subject has a QT interval with Fridericia's correction method (QTcF) >450 ms (male subjects) or >470 ms (female subjects) or PR outside the range of 120 to 220 ms, confirmed with 1 repeat testing, at the Screening Visit and Check-in. If repeat testing is required, QTcF and PR values should be based on the average of the assessments.
12. The subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
13. The subject has a history of cancer, except basal cell carcinoma that has been in remission for at least 5 years before first dose of study medication.
14. The subject has a positive test result for HBsAg, anti-HCV, or HIV antibody/antigen at Screening.
15. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 28 days before Check-in. Cotinine test is positive at Screening or Check-in.
16. The subject has poor peripheral venous access.

17. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 45 days before the first dose of study medication.
18. The subject has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by the principal investigator or designee.
19. The subject has a supine blood pressure outside 90 to 140 mm Hg for systolic and 50 to 90 mm Hg for diastolic, confirmed on repeat testing within a maximum of 30 minutes, at the Screening Visit or Check-in.
20. The subject has a resting heart rate outside 40 to 100 beats per minute confirmed on repeat testing within a maximum of 30 minutes, at the Screening Visit or Check-in (heart rate from the ECG does not apply).
21. The subject has abnormal Screening or Check-in laboratory values, confirmed by repeat assessment), that suggest a clinically significant underlying disease or subject with the following lab abnormalities: ALT and/or AST >1.5×ULN.
22. The subject has a risk of suicide according to the Investigator's clinical judgment (eg, per C-SSRS), or has scored "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior", if this behavior occurred in the past 2 years.
23. The subject has received TAK-831 in a previous clinical study.

7.2.1 Additional Exclusion Criteria for Cohort(s) With CSF Collection

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

1. The subject has had CSF collection performed within 30 days before Check-in.
2. The subject has a known hypersensitivity to the anesthetic or its derivatives used during CSF collection, or any medication used to prepare the area of lumbar puncture, or any allergy-related indications to medication used for dilation during the eye examination.
3. The subject has significant vertebral deformities (scoliosis or kyphosis), which, in the opinion of the investigator, may interfere with lumbar puncture procedure.
4. The subject has a history of clinically significant back pain and/or injury.
5. The subject has local infection at the puncture site.
6. The subject has thrombocytopenia or other suspected bleeding tendencies noted before procedure.
7. The subject has developed signs and symptoms of spinal radiculopathy, including lower extremity pain and paresthesias.

8. The subject has any focal neurological deficit that might suggest an increase in intracranial pressure.
9. The subject has any abnormal findings on ophthalmological assessment/fundoscopy suggestive of raised intracranial pressure (ie, optic disc swelling/edema; (uncontrolled) hypertensive retinopathy).
10. Subject suffers regularly from moderate to severe headaches requiring analgesics.
11. Subjects with lower spinal malformations (on physical examination or lumbar spine radiography), local spinal infection, or other abnormalities that would exclude lumbar puncture (LP).

7.3 Excluded Medications, Supplements, Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until subject is discharged from the unit.

Table 7.a Prohibited Medications, Supplements, and Dietary Products

28 Days Before Check-in	7 Days Before Check-in	72 Hours Before Check-in
Prescription medications	OTC medications including aspirin or aspirin containing products (a)	Products containing caffeine or xanthine
Neutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	poppy seeds
Immunization/Vaccines (b)	Foods or beverages containing grapefruit or grapefruit juice, star fruit or star fruit juice, Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juices, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	
Nicotine-containing products	Alcohol containing products	
Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 (c)		

CYP=cytochrome P-450, OTC=over-the-counter.
(a) Occasional use of paracetamol (≤1 g/day) or other medication as approved by Takeda on a case-by-case basis is allowed. Lidocaine and epinephrine or other local anesthetics are not excluded for subjects undergoing lumbar puncture. Ibuprofen or acetaminophen may be used for any spinal headaches that may occur as a result of lumbar puncture.
(b) Inclusive of but not limited to H1N1 and other flu vaccinations.
(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine.

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

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Subjects in each cohort will be confined during dosing and be kept in the study unit for 24 hours after the last dose for non-CSF cohorts and 48 hours after catheter removal in CSF cohorts.

The total confinement period in non-CSF cohorts will be 19 days (Day -2 to Day 17), 20 days in CSF cohorts where an indwelling temporary catheter is being used on Day 1 and Day 16 (confinement from Day -1 to Day 19), and 21 days in CSF cohorts where CSF is collected through a single predose lumbar puncture on Day -1 and through an indwelling catheter on Day 16 (confinement from Day -2 to Day 19). Follow-up assessments will occur on Day 30 (±2) for all cohorts. (See Section 3.0). An exception to these minimum confinement periods will be made if a determination is made to evaluate QT/QTc intervals for additional single doses of TAK-831 in non-CSF cohorts based on the established tolerated dose range.

During the confinement period, subjects will be given a menu that will include 3 meals and an evening snack, each containing approximately 30% fat (relative to the total calories). The meals served on dosing and PK assessment days (Days 1 and 16) should be identical; no breakfast will be served; also on these days, record whether the meals were fully consumed (100%), or if not, record the percentage consumed (0, 25%, 50%, 75%). The study menu should be recorded and submitted to the study file with a copy provided to the sponsor before the start of the study (for PK days only).

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

TAK-831 (as a tablet or suspension formulation) or placebo will be administered in the morning (QD on Day 1 and Days 3 through 16 in Cohorts 1 and 2) after a fast of at least 10 hours; subjects will be instructed to fast for an additional 4 hours on Days 1, 3, and 16 and 2 hours for all other dose administration days. For cohorts with T2 formulation tablets, dose administration will be followed by a 240 mL of water. For cohorts with suspension formulation, dose administration will be followed by two rinses of 80 mL of water each (total volume of rinse water=160mL). All subjects may then consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. Subjects do not have to fast when no dosing is scheduled or for additional doses administered on the same day if TAK-831 is administered more than once per day.

7.4.2 Activity

Subjects will remain upright (seated, standing, or ambulatory) for 4 hours following the dose administration, except as necessitated by the occurrence of an AE or study procedures (eg, obtaining 12-lead ECG).

Subjects will refrain from strenuous and/or unaccustomed exercise throughout the entire course of the study, from Check-in through Study Exit/Early Termination.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the electronic case report form (eCRF) using the following categories.

1. AE. The subject has experienced 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.
   a. Liver Function Test (LFT) Abnormalities

      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, see Section 10.2.8.5), if the following circumstances occur at any time during study medication treatment:

      – ALT or AST >8×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, or
      – ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

   b. Subject discontinuation should be considered if there is a marked prolongation of the QTcF interval during treatment with the study drug, especially if the measurements are confirmed from more than 1 ECG. The thresholds for marked corrected QT (QTc) interval increases are considered to be >500 ms on any given QTcF measurement or >60 ms over baseline QTc and should be discussed with Takeda.
2. 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.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal because of an AE).

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

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

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 6.5.5. 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. Discontinued or withdrawn subjects may be replaced to ensure that a minimum of 6 subjects are completed for each cohort. This will be examined by the team on a case-by-case basis.

7.7 Subject Replacement

Subjects may be replaced on a case-by-case basis at the discretion of the sponsor.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Details regarding the active drug and placebo in tablet dosage form and the extemporaneous preparation can be found in the IB and compounding manual respectively. Clinical study drug will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the sponsor needs to be contacted prior to dosing.

8.1.1 Clinical Study Drug Labeling

Clinical study drug will be affixed with a clinical label in accordance with regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

Clinical study drug must be stored in a secure, limited-access location and remained in the original container until dispensed. The storage condition and temperature excursion information can be found in the compounding manual. Receipt and dispensing of study drug must be recorded by authorized personnel at the trial site.

8.1.3 Clinical Study Drug Blinding

This is an investigator and subject blinded, sponsor-open study. The investigator and subjects are blinded to treatment assignment. The unblinded study drug supply will be provided to an unblinded pharmacist or other qualified trial site personnel who will blind the trial supplies. Treatment identity (name and strength or potency) will be included on the study drug container label; randomization code/disclosure envelopes or lists will be provided as per site procedure.

8.1.4 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigational drug blind is maintained through a randomization schedule held by the randomization personnel.

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. The investigator should perform all study assessments and causality evaluation, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor or designee should be contacted before the investigational drug blind is broken to discuss the need for unblinding. The sponsor must be notified as soon as possible if the investigational drug blind is broken.

Individual code break envelopes will be provided for all subjects to the investigator or designee by the sponsor or designee. Each sealed envelope containing the randomization code and treatment will be kept in a medication storage room, which is locked with restricted access. If opened, the name of the person who opened it, the date and time of opening and the reason for opening must be written on the envelope. A similar mechanism may be substituted for envelopes (eg, scratch-off cards).

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

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

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 before the subject entering into the study and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations. PGx 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 before 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.

The sampling of whole blood for PGx analysis is mandatory; every subject must sign informed consent to participate in the study. A separate optional informed consent may be required for PGx.

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 before randomization or allocation. Each subject will be assigned only 1 screening number. 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.

Subjects who qualify for the study will be assigned a 4-digit randomization sequence number starting with X001 in the order in which they are enrolled into their respective Cohort X, and ended with X008. For example, for Cohort 2, the randomization numbers will be 2001 to 2008. The number will be assigned by the clinic site personnel in sequential order beginning and ending with the numbers specified for each cohort. The 4-digit randomization number will dictate which treatment will be assigned to each subject based on the randomization schedules distributed only to the authorized personnel (eg, pharmacist). 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.

For a subject's replacement, the randomization number will be X9XX, where X's are the same as those for the original subject. For example, the replacement number for Subject 3005 will be 3905. The replacement will be given the same drug as that for the original subject.

9.1.1.2 Study Drug Assignment

On Day 1, subjects will be assigned a randomization number in ascending numerical order at the study site. The randomization number encodes the subject assignment to either the TAK-831 or the placebo arm of the study, according to the randomization schedule generated before the study by the sponsor's Statistics Department or designee. Each participant will be dispensed blinded study treatment, labeled with his/her unique randomization number, throughout the study. If a subject is discontinued before the first dose on Day 1, the replacement subject will have the same randomization number as the discontinued subject.

9.1.2 Inclusion and Exclusion

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

9.1.3 Medical History/Demography

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

9.1.4 Medication History/Concomitant Medications

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 examinations.

A comprehensive clinical neurological assessment (with a focus on cerebellar signs), will be performed on all subjects (except on CSF collection days in CSF cohorts) as indicated in the Section 3.0 Schedule of Study Procedures.

The neurological examination will include: 1. Mental status, 2. Cranial nerves I – XII; 3. Motor (muscle bulk; tone; power; reflexes); 4. Sensory (pain; temperature, light touch and proprioception); 5. Cerebellar function: a) Gait; b) Walk heel-toe in a straight line; c) Romberg's test; d) Intention tremor; e) Assess tone at shoulder, elbow and wrist; f) Test for dysdiadochokinesis by rapid alternating movements of hands; g) Test for dysmetria by finger-nose test and heel-shin test; h) Assess eye movements for nystagmus; i) Assess speech for staccato cerebellar speech; j) Assess for titubation.

For the eye examination: a baseline (Day -2 for single lumbar puncture, Day -1 for indwelling catheter, and Day 15) ophthalmological assessment of the retina (fundoscopy), as well as a repeat assessment before performing the lumbar puncture for CSF collection.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a pretreatment event or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately before the first dose of the investigational drug on Day 1 in each cohort must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the AE eCRF described in Section 10.0.

9.2.2 Height and Weight

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

9.2.3 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.

9.2.4 Vital Signs

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 supine position for at least 5 minutes before having vital sign measurements obtained. Vital signs will include heart rate, respiration rate, 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.

9.2.5 ECGs

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before 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 supine position for at least 5 minutes before each ECG measurement.

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

9.2.5.1 Safety ECG

Standard 12-lead ECG (singlet) will be recorded. When an ECG is scheduled at the same time as blood draws, or vital signs then the ECG will take priority followed by vital signs and then the blood draw. Vitals will be collected within approximately 0.5 hour before the scheduled timepoint. The blood draw will be then performed as closely as possible to the ECG. If an ECG coincides with a meal or CSF collection, ECG will take precedence followed by CSF collection and then the meal.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be resting in a supine position for at least 5 minutes prior to each ECG measurement. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

Before each Treatment Period/cohort, a predose ECG will be obtained within approximately 1 hour before dosing TAK-831. 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.

If a subject demonstrates an increase in QTcF interval ≥40 msec compared with a predose baseline measurement, the ECG will be repeated within 30 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: heart rate, PR-interval, QRS-duration, QT-interval, QTcF interval, and the interpretation of the ECG profile by the principal investigator.

9.2.5.2 CCI [redacted]

CCI [redacted]

CCI

[redacted]

9.2.6 C-SSRS

Suicidality will be assessed by the use of the C-SSRS [10,11]. 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 trial 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 Screening/Baseline C-SSRS (Lifetime) will be administered at Screening for all subjects, by the principal investigator or a trained designee.

9.2.7 Study Drug Administration

This is an investigator and subject blinded study; therefore, TAK-831 or matching placebo will be administered orally on Day 1 and Days 3 through 16 in a blinded fashion.

9.2.7.1 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.2.8 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.

9.2.9 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).

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells)	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells) with absolute differential	Coagulation panel (PT/INR, aPTT) for CSF cohort subjects

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)	

9.2.9.2 Diagnostic Screening

Serum/Blood

Serum diagnostic evaluations will include the following tests:

Alcohol	Hepatitis Screen (HBsAg, HCV antibody)
hCG (female subjects only)	HIV
	FSH (female subjects only)

Urine

A urine drug screen will include the following tests:

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

9.3 PK, PD, and PGx, Samples

CCI [redacted]

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	Sample Collection
CCI [redacted]				

(a) Only in selected cohort(s).

9.3.1 PK Measurements

The PK parameters of TAK-831 will be derived using noncompartmental analysis methods and will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times for plasma PK parameters.

9.3.1.1 PK Sample Collection

PK blood and CSF samples for TAK-831 concentrations will be collected as specified in the Schedule of Trial Procedures (See Section 3.0).

The actual date and time of each PK (blood and CSF) 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 processing and shipment are provided in the laboratory manual.

9.3.1.2 PK Sample Analysis

Plasma and CSF concentrations of TAK-831 will be measured by a validated HPLC with tandem mass spectrometry assay.

Part of the archival plasma and CSF samples will be used for potential analysis of unknown metabolite characterization, if appropriate.

9.3.2 PD Measurements

CCI

[redacted]

9.3.2.1 PD Sample Collection

Blood

CCI

[redacted]

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.

CSF

CCI

[redacted]

9.3.2.2 PD Sample Analysis

CCI

[redacted]

9.3.3 PGx Measurements

The sampling of whole blood for PGx and genotyping analysis is mandatory; every subject must sign informed consent in order to participate in this study. DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms. Also, since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of this gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

The samples will be stored for no longer than 15 years after completion of the TAK-831 study and/or until the drug development of TAK-831 is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. “Stored samples” are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

9.3.4 Total Blood Volume

Approximately 380 mL of total blood volume will be collected.

9.3.5 Confinement

Subjects in each cohort will be confined during dosing and be kept in the study unit for 24 hours after the last dose for non-CSF cohorts and 48 hours after catheter removal in CSF cohorts. The total confinement period in non-CSF cohorts will be 19 days (Day -2 to Day 17), 20 days in CSF cohorts where an indwelling temporary catheter is being used on Day 1 and Day 16

(confinement from Day -1 to Day 19); and 21 days in CSF cohorts where CSF is collected through a single predose lumbar puncture on Day -1 and through an indwelling catheter on Day 16 (confinement from Day -2 to Day 19). Follow-up assessments will occur on Day 30 (±2) for all cohorts. An exception to these minimum confinement periods will be made if a determination is made to evaluate QT/QTc intervals for additional single doses of TAK-831 in non-CSF cohorts based on the established tolerated dose range.

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 or 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 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) 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 Baseline 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 before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of 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 10.2.8.

- 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 Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

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

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	An AE 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 AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 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, that is, 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 AE (Frequency)

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

10.2.6 Action Taken With Study Treatment

- Drug withdrawn: a study medication is stopped because of 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, for example, 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 because of the particular AE.
- Dose increased: the dose was increased because of 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 because of 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 Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call on Day 30 (±2 days), approximately 15 days after the last dose of investigational product. For subjects who discontinue before 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 before 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 before 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 Section 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 is 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 Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases 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 9.2.9 must also be

performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

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

A blinded targeted data review will be conducted before the database lock for the entire study. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

For analyses where baseline and/or change from baseline will be evaluated, the baseline is defined as the last available results prior to first dose of study drug except for CCI parameters. For CCI parameters, the baseline is defined as the average of the 3 measurements (average of triplicate measurements) on Day -1 at time points that are matched with those on Day 1.

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 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 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.

If any subject is found to be noncompliant with the dosing schedule or has incomplete data, a decision will be made on a case-by-case basis as to whether that subject should be included in the PK and PD analyses; however, data for all subjects will be presented in the data listings.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for subjects in the safety set by pooled placebo, each TAK-831 dose level, summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables (age, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (sex, ethnicity, and race).

Individual subject demographic and baseline characteristic data will be listed. Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for

subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

11.1.3 PK Analysis

Concentrations of TAK-831 in plasma (all cohorts) and CSF (CSF Cohort[s]) will be summarized by dose, drug formulation, and day over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing.

PK parameters of TAK-831 will be derived using noncompartmental analysis methods. The PK parameters of TAK-831 will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. Plasma and CSF PK parameters, including dose-normalized C_{max} and AUCs, will be summarized by dose, drug formulation, and day using descriptive statistics. Changes in the PK parameters from Day 1 to Day 16 will be assessed by summarizing the ratio of Day 16 to Day 1 by dose and drug formulation. Dose proportionality in plasma PK parameters (C_{max} and AUCs) will be assessed graphically for Day 1 and Day 16 plasma concentrations for each formulation. Additional analyses will be included if appropriate.

11.1.4 PD Analysis

CCI

[redacted]

11.1.5 Safety Analysis

The safety set will be used for all summaries of safety parameters. Summaries will be presented by pooled placebo, each TAK-831 dose level, drug formulation, TAK-831 overall, and overall.

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.

CCI

[redacted]

11.1.5.5 Other Safety Parameters

Physical and neurological examination findings and suicidality assessments (C-SSRS) will be presented in data listings.

11.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned. As described in Section 6.2, specific Takeda personnel listed in associated study documentation may be unblinded to analyze data considered necessary to determine subsequent doses and cohort management decisions during the conduct of the study. In addition, sponsor may perform preliminary analysis to inform dose selection for future development.

11.3 Determination of Sample Size

The sample size chosen of 8 subjects for all Cohorts (6 active:2 placebo) is considered to be sufficient for evaluation of safety, tolerability, and PK of each cohort to determine the dose for the next cohort. The sample size was not based on statistical power considerations.

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 (contract research organization) 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, trial 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 trial 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 those of foreign governments (eg, the Food and Drug Administration, 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 because of 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 trial. 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 before 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 before 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 before 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.

Subjects who consented and provided a PGx sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. 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 Trial 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 Trial Registration

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

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

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

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials 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	PPD

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.
- ICH, E6 GCP: 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
ALT	alanine aminotransferase
anti-HCV	antibody to hepatitis C virus
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from 0 to 24 hours
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval
BID	twice daily
BMI	body mass index
$C_{av,ss}$	average plasma concentration at steady state
CFR	Code of Federal Regulations
CIAS	cognitive impairment associated with schizophrenia
C_{max}	maximum observed plasma concentration
$C_{max\ CSF}$	maximum observed CSF concentration
CNS	central nervous system
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
DAO	D-amino acid oxidase
ECG	electrocardiogram
eCRF	electronic case report form
E_{max}	maximum drug-induced effect
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	institutional review board

LFT	liver function test
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple rising dose
NCS	not clinically significant
NMDA	*N*-methyl-D-aspartate
NOAEL	no-observed-adverse-effect level
NSS	negative symptoms of schizophrenia
PD	pharmacodynamics
PGx	pharmacogenomics
PK	pharmacokinetic
PT	preferred term
QD	once daily
QTc	corrected QT (interval)
QTcF	QT interval with Frederica correction method
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

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.

16.0 REFERENCES

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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, before 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 Code of Federal Regulations (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. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
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 (5 half-lives PLUS 30 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 highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for (5 half-lives PLUS 90 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 the 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 (5 half-lives PLUS 90 days, which for TAK-831 is 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 partners 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.

In studies with no risk of fetotoxicity/teratogenicity/genotoxicity: male subjects are not required to use barrier contraception.

Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for (5 half-lives PLUS 30 days, which for TAK-831 is 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 (IMP 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, that is, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, tubal ligation, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years 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 men 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 before the first dose until 5 half lives PLUS 30 days after last dose.
   - Hormonal methods: hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method (evaluate on compound-by-compound and protocol – by-protocol basis and obtain clinical pharmacology justification).
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
       - Oral †.
       - Intravaginal † (eg, ring).
       - Transdermal †.
     - Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
       - Oral †.
       - Injectable.
       - Implantable.

5. If genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drug, comparator, background therapy or standard of care medications effective methods of contraception (there may be a higher than 1% failure rate) are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
6. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
7. Subjects will be provided with information on highly effective/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.
8. 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 male subjects 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?
9. 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 specify time before receiving any dose

of study medication. In addition, subjects must also have a negative serum hCG pregnancy test specify time before receiving first dose of investigational drug as close as possible and before first dose of investigational drug, preferably on the same day.

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 not 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 should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for (5 half-lives PLUS 90 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 partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the 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. 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Updated study design and procedures.

The primary change occurs in Section 6.1 Trial Design

Initial wording:	The study is a double-blind, placebo-controlled clinical study progressively assessing independent cohorts of healthy subjects to continue evaluation of the safety, tolerability, PK, and PD of escalating single doses (SD) and multiple doses (MD) of TAK-831, as either a suspension or T2 tablet formulation, at levels higher than those achieved in the initial single and multiple rising dose (SRD/MRD) Study TAK-831-1001. …. In all CSF cohorts, serial lumbar CSF samples will be collected through an indwelling temporary catheter on 2 separate occasions: the first from Day 1 through Day 2, and the second from Day 16 through Day 17, for 24 hours each. …. Subjects in each cohort will be confined during dosing and be kept in the study unit for 24 hours after the last dose for non-CSF cohorts and 48 hours after catheter removal in CSF cohorts. The total confinement period in non-CSF cohorts will be 19 days (Day -2 to Day 17) and 20 days in CSF cohorts (Day -1 to Day 19). Follow-up assessments will occur on Day 30 (±2) for all cohorts. An exception to these minimum confinement periods will be made if a determination is made to evaluate QT/QTc intervals for additional single doses of TAK-831 in non-CSF cohorts based on the established tolerated dose range.
Amended or new wording:	The study is ~~a double-blind~~**an investigator and subject blinded, sponsor unblinded**, placebo-controlled clinical study progressively assessing independent cohorts of healthy subjects to continue evaluation of the safety, tolerability, **and** PK~~, and PD~~ of escalating single doses (SD) and multiple doses (MD) of TAK-831, as either a suspension or T2 tablet formulation, at levels higher than those achieved in the initial single and multiple rising dose (SRD/MRD) Study TAK-831-1001. …. In ~~all~~ CSF cohorts, ~~serial~~ lumbar CSF samples will be collected through **either a single lumbar puncture or** an indwelling temporary catheter on 2 separate occasions. **In CSF cohorts that use an indwelling temporary catheter on both occasions,** the first ~~from~~**collection will occur** on Day 1~~ through Day 2~~, and the second ~~from~~**on** Day 16**. In CSF cohorts where the predose CSF sample is collected through a single lumbar puncture, the first CSF sample will be collected on Day -1 prior to the start of** CCI [redacted] **monitoring and the**

second collection will be obtained through **use of an indwelling temporary catheter on** Day ~~17,~~**16. If an indwelling temporary catheter is being used, it will collect serial CSF samples** for 24 hours~~ each.~~

….

Subjects in each cohort will be confined during dosing and be kept in the study unit for 24 hours after the last dose for non-CSF cohorts and 48 hours after catheter removal in CSF cohorts. The total confinement period in non-CSF cohorts will be 19 days (Day -2 to Day 17~~) and 20 days in CSF cohorts (Day -1 to Day 19).~~**, 20 days in CSF cohorts where an indwelling temporary catheter is being used on Day 1 and Day 16 (confinement from Day -1 to Day 19); and 21 days in CSF cohorts where CSF is collected through a single predose lumbar puncture on Day -1 prior to the start of** CCI [redacted] **measurements and through an indwelling catheter on Day 16 (confinement from Day -2 to Day 19).** Follow-up assessments will occur on Day 30 (±2) for all cohorts. An exception to these minimum confinement periods will be made if a determination is made to evaluate QT/QTc intervals for additional single doses of TAK-831 in non-CSF cohorts based on the established tolerated dose range.

The following sections also contain this change:

Title Page

1.0 STUDY SUMMARY

2.0 STUDY SCHEMATIC

3.0 SCHEDULE OF STUDY PROCEDURES

5.1.3 Trial Exploratory Objectives #4

5.2.3 Exploratory Endpoints #3, 4, 5, and 6

6.2 Dose Escalation

Table 6.a Proposed Doses and Cohort Dose Escalation

6.3.1 Rationale of Trial Design

6.3.3.3 Exploratory Endpoints

7.1 Inclusion Criteria

7.2 Exclusion Criteria

7.2.1 Additional Exclusion Criteria for Cohort(s) With CSF Collection

7.4.1 Diet and Fluid

9.2.1 Full Physical Examination

9.2.5.2 CCI [redacted]

9.2.7 Study Drug Administration

9.3.2.1 PD Sample Collection

9.3.2 PD Measurements

9.3.5 Confinement

11.1 Statistical and Analytical Plans

11.2 Interim Analysis and Criteria for Early Termination

Rationale for Change: Allow combination of CSF measurements at baseline and CCI monitoring, clarifications, and corrections/editorial changes.

Change 2: Updated clinical study material management.

The primary change occurs in Section 8.0 CLINICAL STUDY MATERIAL MANAGEMENT.

Initial wording:

8.1 Clinical Study Drug

Clinical study drug will be packaged to support enrollment.

8.1.1 Clinical Study Drug Labeling

Clinical study drug will be affixed with a clinical label in accordance with regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

Clinical study drug must be stored in a secure, limited-access location under the storage conditions specified on the label. Inventory (receipt and dispensing) of study drug must be recorded by an authorized person at the study site.

8.1.3 Clinical Study Drug Blinding

This is an investigator and subject blinded, sponsor unblinded study. The study drug blind is maintained through a randomization schedule held by the randomization personnel. Investigational drug will be dispensed in a manner so as to minimize the possibility of identification of different doses and placebo through appearance. Further details will be provided in the Pharmacy Manual.

8.1.4 Randomization Code Creation and Storage

Takeda Analytical Sciences Department or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

….

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical

treatment of the subject. All study assessments and causality should be performed, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor or designee should be contacted before the investigational drug blind is broken to discuss the need for unblinding. The sponsor must be notified as soon as possible if the investigational drug blind is broken.

Individual code break envelopes will be provided for all subjects by the sponsor or designee. Each sealed envelope containing the randomization code and treatment will be kept in a medication storage room, which is locked with restricted access. If opened, the name of the person who opened it, the date and time of opening and the reason for opening must be written on the envelope. A similar mechanism may be substituted for envelopes (eg, scratch-off cards).

Amended or new wording:

….

8.1 Clinical Study Drug

Details regarding the active drug and placebo in tablet dosage form and the extemporaneous preparation can be found in the IB and compounding manual respectively. Clinical study drug will be packaged to support enrollment **and replacement subjects as required. When a replacement subject is required, the sponsor needs to be contacted prior to dosing.**

8.1.1 Clinical Study Drug Labeling

Clinical study drug will be affixed with a clinical label in accordance with regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

Clinical study drug must be stored in a secure, limited-access location ~~under~~**and remained in** the **original container until dispensed. The** storage ~~conditions specified on~~**condition and temperature excursion information can be found in the** ~~label. Inventory (receipt~~**compounding manual. Receipt** and dispensing of study drug must be recorded by ~~an~~authorized ~~person~~**personnel** at the ~~study~~**trial** site.

8.1.3 Clinical Study Drug Blinding

This is an investigator and subject blinded, sponsor-**open study. The investigator and subjects are blinded to treatment assignment. The** unblinded study~~. The study~~ drug **supply will be provided to an unblinded pharmacist or other qualified trial site personnel who will** blind ~~is maintained through a~~**the trial supplies. Treatment identity (name and strength or potency) will be included on the study drug container label;** randomization ~~schedule held by the randomization personnel. Investigational drug will be dispensed in a manner so~~**code/disclosure envelopes or lists will be provided** as ~~to minimize the possibility of identification of different doses and placebo through appearance.~~

~~Further details will be provided in the Pharmacy Manual~~**per site procedure**.

8.1.4 Randomization Code Creation and Storage

~~Takeda Analytical Sciences Department~~**Randomization personnel of the sponsor** or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

….

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. ~~All~~**The investigator should perform all** study assessments and causality ~~should be performed~~**evaluation**, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor or designee should be contacted before the investigational drug blind is broken to discuss the need for unblinding. The sponsor must be notified as soon as possible if the investigational drug blind is broken.

Individual code break envelopes will be provided for all subjects **to the investigator or designee** by the sponsor or designee. Each sealed envelope containing the randomization code and treatment will be kept in a medication storage room, which is locked with restricted access. If opened, the name of the person who opened it, the date and time of opening and the reason for opening must be written on the envelope. A similar mechanism may be substituted for envelopes (eg, scratch-off cards).

….

Rationale for Change: Clarification of procedure.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	21-Mar-2018 01:14 UTC
	Biostatistics Approval	21-Mar-2018 02:10 UTC
	Clinical VP Approval	21-Mar-2018 16:18 UTC
	Clinical Pharmacology Approval	21-Mar-2018 18:28 UTC