Title: Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK-831 in Healthy Adult Asian Subjects

NCT Number: NCT03687684

Protocol Approve Date: 26-Feb-2019

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TAKEDA PHARMACEUTICALS

PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK-831 in Healthy Adult Asian Subjects

Phase 1 Study of TAK-831 in Healthy Adult Asian Subjects

Study Identifier: TAK-831-1002

Compound: TAK-831

Date: 26 February 2019

Version/Amendment Number: Amendment 3

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals	**Compound:** TAK-831
Study Identifier: TAK-831-1002	**Phase:** 1
Title of Study: Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK 831 in Healthy Adult Asian Subjects	
Trial Design: This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of TAK-831 in healthy adult Asian subjects. This study will include up to 5 cohorts of healthy adult Japanese or Chinese subjects. In Cohort 1, a single dose of TAK-831 will be administered under a 3 sequential dose escalation design, and the safety, PK and PD will be assessed. Eight healthy adult Japanese subjects will be randomized in dosing orders of A (100 mg→300 mg), B (100 mg→placebo), and C (placebo→300 mg) at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Day 1 and Day 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge. Cohort 2 will include 8 healthy adult Japanese subjects. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge. Cohorts 3 to 5 will be optional, in which a single dose will be administered followed by multiple doses, and Cohorts 3 and 4 may be studied based on emerging data from Cohorts 1 and 2. Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 and 5 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.	
Trial Primary Objective: To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects. **Secondary Objectives:** To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.	
Target: Healthy adult Asian subjects	
Planned Number of Subjects: Cohort 1: 8 subjects Cohorts 2 to 5: 8 subjects per cohort	**Planned Number of Sites:** 1 site
Dose Levels: <Cohort 1> Single dose at 100 mg on Day 1 (Part 1) and 300 mg on Day 9 (Part 2) (fasted) <Cohort 2> Single dose at 600 mg on Day 1. Multiple doses	**Route of Administration:** Oral

(once-daily) at 600 mg on Days 4 to 17 (fasted) <Cohort 3> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted) <Cohort 4> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted) <Cohort 5> Single dose at 50 mg on Day 1. Multiple doses (once-daily) at 50 mg on Days 4 to 17 (fasted)	
Duration of Treatment: <Cohort 1> Part 1: Single dose on Day 1 Part 2: Single dose on Day 9 <Cohorts 2 to 5> Single dose on Day 1 and once-daily multiple doses on Days 4 to 17, for 14 days, in each Cohort	**Planned Trial Duration:** <Cohort 1> Screening period: Day -28 to -1 Treatment period: Days 1 to 12 Follow-up period: Day 23 <Cohorts 2 to 5> Screening period: Day -28 to -1 Treatment period: Days 1 to 19 Follow-up period: Day 31

Inclusion Criteria:

Subject eligibility will be determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) $\geq$18.5 kg/m^2 and $\leq$25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the birth control requirements.

Exclusion Criteria:

The subject must be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or

diseases.

2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the trial procedure in the previous trial to the Screening Visit of the current trial.
3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).
5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms at the Screening Visit or Check-in.

Main Criteria for Evaluation and Analyses:

Primary Endpoint

Safety: Adverse event, laboratory tests, vital signs, weight, 12-lead electrocardiogram

Secondary Endpoints

Pharmacokinetics: The following parameters will be calculated.

C_{max} (Cohort 1, Day 1 of Cohorts 2 to 5)

$C_{max,ss}$ (Day 17 of Cohorts 2 to 5)

t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 5)

AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 5)

AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 5)

AUC_{τ} (Days 1 and 17 of Cohorts 2 to 5)

Statistical Considerations:

Pharmacokinetics:

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2, 4 and 5 as well as Cohort 3.

Concentrations of TAK-831 in plasma and cerebrospinal fluid will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time of TAK-831 will be presented. Plasma PK

parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Days 1 and 9 for Cohort 1 and Day 1 for Cohorts 2 to 5. Additional analyses on dose linearity will be included if appropriate.

Pharmacodynamics:

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2, 4 and 5 as well as Cohort 3. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

Safety:

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2, 4 and 5, and for Cohort 3.

A treatment-emergent adverse event (TEAE) refers to an adverse event that occurs after the start of study treatment. The frequency of all TEAEs, drug-related TEAEs , all TEAEs by intensity, drug-related TEAEs by intensity, TEAEs leading to study drug discontinuation, and serious TEAEs will be summarized. TEAEs will be coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

For continuous values of laboratory findings, vital signs and other safety parameters, summary statistics will be provieded for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

Sample Size Justification:

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, PK and PD of each cohort. This is not based on any statistical rationale.

2.0 STUDY SCHEMATIC

Figure 2.a shows the schematic of the trial design.

Figure 2.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - - Hospitalization - - - - -►		◄- - - - Hospitalization - - - -►			

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion

Sequence of administration	Part 1	Washout interval	Part 2
	Day 1 to 4	Day 5 to 8	Day 9 to 12
A	TAK-831 100 mg	Washout	TAK-831 300 mg
B	TAK-831 100 mg		Placebo
C	Placebo		TAK-831 300 mg

<Cohorts 2 to 5>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening (c)	Hospitalization (c)	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- - - - - - - - - - - - - - - - - - Hospitalization - - - - - - - - - - - - - - - - - - -►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion.
(c) After Cohort 3, Screening will be on Days -28 to -3, hospitalization will be on Day -2 and an examination at hospitalization will be on Day -1.

3.0 SCHEDULE OF STUDY PROCEDURES

<Cohort 1>

	Screening period		Treatment period										Early Termination	Follow-up visit
	Screening	Hospitalization	Part 1				Washout interval		Part 2					
Day	-28 to -2	-1	1	2	3	4	5 to 7	8	9	10	11	12		23 (±2)
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Demographics, medical history	X													
Prior medications	X													
Physical examination	X	X	X			X		X				X	X	X (l)
Vital signs (a)	X	X	X	X	X	X		X	X	X	X	X	X	X (l)
Weight, height, BMI (b)	X	X				X		X				X	X	X (l)
12-lead electrocardiogram (ECG) (c)	X	X	X			X		X	X			X	X	X (l)
Laboratory tests (d)	X	X				X		X				X	X	X (l)
Immunological test, alcohol tests	X													
FSH (e)	X													
Urinary drug tests	X	X						X						
C-SSRS (f)	X	X				X		X				X	X	
Sample collection for pharmacogenomic (PGx) Measurements (g)			X											
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X			X	X	X	X	X(k)	
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X	X	X			X	X	X	X		
Urine sample (for future tests) (j)		X		X						X			X	
Study drug administration			X						X					
Adverse events	X	X	X----------continuous monitoring----------X											
Concomitant medications	X	X	X----------continuous monitoring----------X											
Hospitalization		X	X----------X					X	X----------X					

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 1, on Day 8, predose on Day 9, and 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 9.

(b) Height will be measured at Screening only. Weight will be measured at Screening visit, Day -1, 72 hours postdose on Day 1, Day 8, 72 hours postdose on Day 9.

(c) 12-lead ECG will be measured at Screening, Day -1, predose, 2 and 72 hours postdose on Day 1, Day 8, predose on Day 9, 2 and 72 hours postdose on Day 9.

(d) Laboratory tests will be performed at Screening, on Day -1, 72 hours postdose on Day 1, on Day 8, and at 72 hours postdose on Day 9.

(e) FSH will be measured in postmenopause women only.

(f) C-SSRS will be investigate at Screening, Day -1, Day 4, Day 8, and Day 12.
(g) Samples for PGx measurements will be collected predose on Day 1.
(h) Samples for PK assessment will be collected predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 9, and 0.5, 1. 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(i) Samples for PD assessment will be collected on Day -1 (at 20, 16, 12 hours predose on Day 1), predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(j) Urine samples will be collected on Day -1, 24 hours postdose on Day 1, and 24 hours postdose on Day 9.
(k) Samples for PK assessment at discontinuation will be collected if it is possible.
(l) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

<Cohorts 2 to 5>

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening (n)	Hospitalization (n)	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Demographics, medical history	X																					
Prior medications	X																					
Physical examination	X	X	X																		X	X (m)
Vital signs (a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (m)
Weight, height, BMI (b)	X	X																			X	X (m)
12-lead electrocardiogram (ECG) (c)	X	X	X			X							X						X		X	X (m)
Holter ECG (c)		X																				
Laboratory tests (d)	X	X											X								X	X (m)
Immunological test, alcohol tests	X																					
FSH (e)	X																					
Urinary drug tests	X	X																				
C-SSRS (f)	X	X																			X	X
Sample collection for pharmacogenomic (PGx) Measurements (g)			X																			
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X							X			X			X	X		X (l)
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X									X			X			X	X		
Cerebrospinal fluid sample collection for pharmacodynamic (PD) assessment (j)		X																		X		

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening (n)	Hospitalization (n)	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Urine sample (for future tests) (k)		X		X																X		X	
Study drug administration			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Adverse events	X	X	X----------continuous monitoring----------X																			X	X
Concomitant medications	X	X	X----------continuous monitoring----------X																			X	X
Hospitalization		X	X----------X																				

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36 and 48 hours postdose on Day 1, predose on Days 4 to 16, predose on Day 17, and 1, 4, 12, 24, and 48 hours postdose on Day 17.

(b) Height will be measured at Screening only. Weight will be measured at Screening, on Day -1, and 48 hours postdose on Day 17.

(c) 12-lead ECG will be measured at Screening, Day -1, presdose and 2 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose, 2 and 48 hours postdose on Day 17.
Holter ECG will be measured from -23 hours predose to 24 hours post dose on Day 1 (after Cohort 3). Data will be extracted at -23, -22, -20, -16 and -12 predose, predose and 1, 2, 4, 8, 12 and 24 hours postdose on Day 1.

(d) Laboratory tests will be performed at Screening, Day -1, predose on Day 11, and at 48 hours postdose on Day 17.

(e) FSH will be measured in postmenopause women only.

(f) C-SSRS will be investigate at Screening Visit, Day -1, and Day 19.

(g) Samples for PGx measurements will be collected predose on Day 1.

(h) Samples for PK assessment will be collected predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose on Day 14, predose, 0.25, 0.5, 1. 1.5, 2, 4, 8, 12, 16, and 24 hours postdose on Day 17.

(i) Samples for PD assessment will be collected at 20, 16, and 12 hours predose on Day 1, predose, 1, 4, 8, 12, and 24 hours postdose on Day 1, predose on Day 11, predose on Day 14, predose, 1, 4, 8, 12, and 24 hours postdose on Day 17.

(j) Samples for PD assessment will be collected on Day -1 and 24 hours postdose on Day 17 (if it is performed). Samples will be also used to measure concentration of TAK-831 cerebrospinal fluid.

(k) Urine samples will be collected on Day -1, at 24 hours postdose on Day 1, and 24 hours postdose on Day 17.

(l) Samples for PK assessment at discontinuation will be collected if it is possible.

(m) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

(n) After Cohort 3, Screening will be on Days -28 to -3, hospitalization will be on Day -2 and an examination at hospitalization will be on Day -1.

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. Schizophrenia usually develops at late adolescence or early adulthood and manifests in maximum 1% of the population. For those who have relatives of first degree with schizophrenia, the incidence rate is higher by 10% (the concordance rate for schizophrenia in identical twins is 40% to 65%) [1][2][3]. Symptoms of schizophrenia can be subdivided into 3 broad classes: positive, negative, and cognitive symptoms [4]. Positive symptoms include hallucinations, delusions, and disordered thought and speech, and can be summarized as psychosis. Negative symptoms include reduced emotion, reduced ability to experience pleasure (anhedonia), lack of motivation, and reduced social interaction. Finally, cognitive symptoms include poor information processing, impaired ability to focus on objectives, and abnormalities of working memory and learning [4]. Currently available antipsychotics are broadly effective for the treatment of positive symptoms. However, the negative symptoms and cognitive impairment of schizophrenia are the known particular aspects that cause dysfunction, for which no therapy has been approved. There still are significant unmet medical needs.

Hypofunction of N-methyl-D-aspartic acid (NMDA) receptor is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain [5]. D-amino acid oxidase (DAAO) contributes to the metabolism of D-serine in the brain and is highly expressed in the cerebellum. Changes in the D-serine levels or D-serine to total serine ratios have been reported in the plasma of patients with schizophrenia both naive and under drug treatment [6]-[9]. 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 DAAO resides [10]. Therefore, inhibition of DAAO is considered to be a promising target in treatment of schizophrenia.

TAK-831 is a highly selective and potent inhibitor of DAAO. TAK-831 increased D-serine levels in the cerebellum of normal mice and showed efficacy in a mouse model of Friedreich ataxia (FRDA) mouse models. It also demonstrated a positive effect on cognition and social interaction in rodent cognition and behavioral models.

As stated above, TAK-831 is expected to provide a therapeutic effect on FRDA and cognitive impairment as well as negative symptoms associated with schizophrenia.

4.2 Rationale for the Proposed Study

TAK-831 is currently under development for the treatment of FRDA and cognitive impairment as well as negative symptoms of schizophrenia. Three overseas phase 1 studies in healthy adults (single and multiple dose study [TAK-831-1001], positron emission tomography [PET] study to determine DAAO brain enzyme occupancy [TAK-831-1003], and a study to evaluate the food effect [TAK-831-1004]) have been conducted so far, in which TAK-831 was well-tolerated.

In addition, two phase 1 studies in healthy adults (study with single and multiple doses at high dose level [TAK-831-1005] and relative bioavailability and food effect study [TAK-831-1006]) are being conducted or planned. Two phase 2 studies in patients with schizophrenia (small-scale crossover study to examine the cerebellar functions [TAK-831-2001], and a study to evaluate the efficacy and safety for negative symptoms of schizophrenia [TAK-831-2002]) are also underway. Besides, a phase 2 proof-of-concept (POC) study in patients with schizophrenia is being planned in China. Based on the result of these phase 2 studies, a phase 3 global study (long-term study) has been planned.

In parallel with these development plans, TAK-831 is also being developed in Japan for the treatment of cognitive impairment and negative symptoms associated with schizophrenia. In respect of FRDA, a genetic disease, since there has been no confirmed report as of June 2018 that clearly indicates the existence of Japanese patients, no development plan has been made for FRDA in Japan.

Enrollment of Japanese patients into the phase 3 global study and the phase 2 POC study in China has been considered. This study was planned to examine the safety and pharmacokinetic (PK) of TAK-831 in Japanese as well as to evaluate the safety and PK in Asian healthy subjects for the aforementioned studies.

4.3 Benefit/Risk Profile

Because this study will be conducted in healthy adults, there is no benefit to subjects.

The following risk mitigation measures will be implemented in this study. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, and the phase 1 studies (4 studies, including preliminary data of TAK-831-1005). Procedures may be added during the study as necessary based on evaluation of any additional clinical or nonclinical data.

The safety of TAK-831 has been studied in a prior single dose (up to 750 mg in suspension and 100 mg T1 tablet formulation) and multiple dose (up to 400 mg once daily [QD] in suspension) study in healthy Western subjects (TAK-831-1001), a single dose (up to 500 mg in suspension) PET study to investigate DAAO occupancy in the brain (TAK-831-1003) and a single dose food effect (400 mg T2 tablet formulation) study (TAK-831-1004). These studies have not resulted in a safety signal that would prevent additional studies. Additionally, TAK-831 given as single and 14 days multiple doses (up to 1200 mg in suspension and 600 mg T2 tablet formulation) is currently being studied in healthy adult subjects (TAK-831-1005). TAK-831 has been safe and well tolerated to date (provisional data as of end-April 2018).

- 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 pharmacodynamics (PD) monitoring (venipuncture may cause bruising),

and the placement of ECG pads (which may cause some local redness and/or erythema/itching).

- In case of serious adverse events (SAE), 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 Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered to monitor emergent suicidality.

The Investigator's Brochure should be referred for more detailed safety of TAK-831.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed on the basis of the following hypothesis.

- TAK-831 given as single or multiple doses shows no safety issue and is well tolerated.
- The PK of TAK-831 given as single or multiple doses to Asian subjects is equivalent to that in Western subjects.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.2 Trial Secondary Objective

To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.3 Trial Exploratory Objective

To assess the effect of TAK-831 on the concentrations of D-serine and L-serine in plasma (and concentrations of D-serine and L-serine in cerebrospinal fluid as necessary) after TAK-831 administration to healthy Asian subjects.

5.3 Endpoints

5.3.1 Primary Endpoint

Safety: Adverse events (AEs), laboratory tests, vital signs, weight, 12-lead electrocardiogram (ECG)

5.3.2 Secondary Endpoints

PK: The following parameters will be calculated.

- C_{max} (Cohort 1, Day 1 of Cohorts 2 to 5)
- $C_{max,ss}$ (Day 17 of Cohorts 2 to 5)
- t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 5)
- AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 5)
- AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 5)
- AUC_{τ} (Days 1 and 17 of Cohorts 2 to 5)

5.3.3 Exploratory Endpoints

- PK: $R_{ac\ (Cmax)}$ and $R_{ac(AUC)}$ on Days 1 and 17 (Cohorts 2 to 5), $t_{1/2z}$, CL/F, V_z/F
- Concentration of TAK-831 cerebrospinal fluid (if collected cerebrospinal fluid samples for PD)
- PD: Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (Days -1 and 18) (may be assessed in Cohort 2 or thereafter based on PD in plasma)

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, PK and PD of TAK-831 in healthy adult Asian subjects. This study will include up to 5 cohorts of healthy adult Japanese or Chinese subjects.

In Cohort 1, a single dose of TAK-831 will be administered at each dose level under a 3-sequential dose escalation design. Eight healthy adult Japanese subjects will be randomized to the sequence of administration A, B, and C at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Days 1 and 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge.

In Cohort 2, a single dose of study drug will be administered to healthy adult Japanese subjects, followed by multiple doses. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Cohorts 3 to 5 will be optional, in which a single dose of study drug will be administered followed by multiple doses, and Cohorts 3 and 4 may be studied based on emerging data from Cohorts 1 and 2.

Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 and 5 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Table 6.a shows the summary of cohorts, and Figure 6.a shows the schematic of the trial design.

Table 6.a Summary of Cohorts

Cohort	Subject	Dose	Remarks
1	Japanese 8 subjects	Part 1: 100 mg (4×25 mg T3 tablet formulation) Fasted, single dose	Wash out period between part 1 and 2 will be 8 days.
		Part 2: 300 mg (1×300 mg T3 tablet formulation) Fasted, single dose	
2	Japanese 8 subjects	600 mg (2×300 mg T3 tablet formulation) Fasted, single dose + multiple dose (once daily)	
3	Chinese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 3 may be run if emerging data from Cohorts 1 and 2 suggest ethnic-related differences in the tolerability and/or PK profile. Dose level will be determined based on the results from Cohorts 1 and 2.
4	Japanese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 4 may be run based on the emerging data from Cohorts 1 and 2 in Asian subjects.
5	Japanese 8 subjects	50 mg (2×25 mg T3 tablet formulation) Fasted, single dose + multiple dose (once daily)	

TBD: To be decided

Figure 6.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - - Hospitalization - - - - - ►			◄- - - - - Hospitalization - - - - ►		

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion

<Cohorts 2 to 5>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening (c)	Hospitalization (c)	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- - - - - - - - - - - - - - - - - - - Hospitalization - - - - - - - - - - - - - - - - - - -►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion.
(c) After Cohort 3, Screening will be on Days -28 to -3, hospitalization will be on Day -2 and an examination at hospitalization will be on Day -1.

6.2 Cohort transition/Dose Escalation

In Cohort 1, TAK-831 100 mg or placebo will be administered on Day 1 (Part 1) followed by confirmation of the safety and tolerability (AEs, physical examination, vital signs, weight, laboratory tests and 12-lead ECG) up to 72 hours postdose, and then TAK-831 300 mg or placebo will be administered on Day 9 (Part 2) followed by confirmation of the safety, tolerability and PK up to 72 hours postdose.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohort 1 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether the subsequent cohort should be run.

In Cohort 2, TAK-831 600 mg or placebo will be administered on Day 1, followed by confirmation of the safety and tolerability up to 72 hours postdose. Then, multiple doses of TAK-831 600 mg or placebo will be administered on Days 4 to 17. The data on safety and tolerability up to 48 hours postdose and PK up to 24 hours postdose will be examined.

The dose in Cohort 2 will be adjusted based on the safety and tolerability as well as PK and PD in Cohort 1.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohorts 1 and 2 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether Cohorts 3 and 4 should be run.

If Cohorts 3 and 4 are conducted, TAK-831 or placebo will be administered on Day 1, followed by confirmation of the safety and tolerability up to 72 hours postdose. Then, multiple doses of TAK-831 or placebo will be administered on Days 4 to 17. In Cohorts 3 and 4, the dose will be adjusted within 600 mg based on data from prior cohorts. If the dose is escalated, the dose escalation will be discontinued according to the following discontinuation criteria.

Discontinuation criteria for dose escalation:

- Exposures in any cohort exceed those observed at the highest dose tested in monkey (C_{max} of 3680 ng/mL, AUC_{24} of 35700 hr*ng/mL)

- 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 changes 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.

In Cohort 5, TAK-831 50 mg or placebo will be administered on Day 1, and multiple dose of TAK-831 50 mg or placebo will be administered on Days 4 to 17.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale for Study Population

The subject of this study is Japanese or Chinese with a purpose to support the future conduct of studies in Asian subjects. The study will be conducted in healthy adult subjects without any disease including circulatory or cerebrovascular diseases to appropriately assess the safety and tolerability as well as PK and PD of TAK-831.

6.3.2 Rationale of Trial Design

With a purpose to assess the safety and tolerability as well as the PK and PD profiles of TAK-831 when administered to Asian subject for the first time, this study employed a design with both single and multiple doses.

6.3.3 Rationale for Dose

To this date, the highest dose of TAK-831 tested in healthy Western subjects is 1200 mg (suspension formulation) once daily in the study TAK-831-1005. Based on the preliminary results, there were no significant adverse effects reported at this dose level, and as shown in Table 6.b, the mean steady-state exposure was C_{max} of 3015 ng/mL and AUC_{24} of 10501 h*ng/mL. The dose regimen of 600 mg given once daily (T2 tablet formulation) was also well tolerated and safe in healthy Western subjects. As for the mean steady-state exposures, C_{max} was 1494 ng/mL and AUC_{24} was 5090 h*ng/mL. This exposure at 600 mg was similar to that of monkeys at 100 mg/kg/day, the no-observed-adverse-effect-level (NOAEL).

In the study TAK-831-1005, the PK and PD of TAK-831 given as multiple doses at 100 and 600 mg (per day) to non-Japanese subjects was examined. The dose of 300 mg will be further examined in the study.

Based on the above, the doses of 100, 300 and 600 mg were selected for this study in consideration to the safety in humans as well as the comparability of PK and PD between non-Japanese and Japanese subjects.

In addition, the doses used in a relative bioavailability between T2 and T3 tablets and food effect study (TAK-831-1006), which is planned overseas, are decided as 50 and 600 mg after the start of this study. Data of PK on T3 tablet 50 and 600 mg used in this study will be available from TAK-831-1006 study. Therefore, the dose of 50 mg was selected additionally considering the comparison of PK and PD between non-Japanese and Japanese with lower dose of T3 tablet.

In the 13-week repeat dose toxicity study in monkeys that are considered the more sensitive species than rats, adverse effects (vomiting, diarrhea, and loose stool) were noted at 600 mg/kg/day. The NOAEL was 100 mg/kg/day for both sexes.

TAK-831 has been administered at doses up to 1200 mg to non-Japanese, and no SAE has been reported with exposures exceeding the NOAEL. Besides, the adverse effects (vomiting, diarrhea, and loose stool) noted at a dose of 600 mg/kg/day in the 13-week repeat dose toxicity study in monkeys will be easily monitored in clinical trials.

Therefore, it is considered possible to administer doses exceeding the NOAEL exposure by carefully examining the safety and PK in each Cohort in this study. However, We have no information on toxicity at the level exceeding the exposure at 600 mg/kg/day in the 13-week repeated dose toxicity study in monkeys. Dose escalation will be stopped if exposures exceed that at 600 mg/kg/day in monkeys.

Table 6.b PK Parameters in 13-week Repeated Dose Toxicity Study in Monkeys and TAK-831 Given as Multiple Doses to Healthy Adult Subjects

Animal species-Study	Dose (mg/kg/day or mg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
Monkey 13-week (Day 91)	100 mg/kg/day (NOAEL)	1340 (male) 1270 (female)	7490 (male) 9190 (female)
	600 (300 BID) mg/kg/day	4650 (male) 2710 (female)	45500 (male) 25900 (female)
Human MRD (Day 16)	1200 mg QD (suspension formulation)	3015	10501
Human MRD (Day 16)	600 mg QD (T2 tablet formulation)	1494	5090

BID, twice daily; MRD, multiple repeated dose; NOAEL, no-observed-adverse-effect-level; QD, once daily

6.3.4 Rationale for Endpoints

6.3.4.1 Safety Endpoint

The safety endpoints in this study were defined to determine the safety and tolerability following a single dose and multiple dose of TAK-831. These are standard endpoints in the Phase 1 studies in healthy subjects.

Since TAK-831 involves effects on the central nervous system, the C-SSRS will be administered to assess the influence on suicidal ideation or suicidal behavior.

6.3.4.2 Pharmacokinetic Endpoint

Concentrations of TAK-831 in plasma will be examined to assess the PK of TAK-831 given as a single dose or multiple doses to healthy adult Asian subjects, and then the following PK parameters will be calculated.

- PK parameters: C_{max}, $C_{max,ss}$ (Cohorts 2 to 5), t_{max}, AUC_{last}, AUC_{∞}, AUC_{τ} (Cohorts 2 to 5), $R_{ac(Cmax)}$ (Cohorts 2 to 5), $R_{ac(AUC)}$ (Cohorts 2 to 5), $t_{1/2}$, CL/F, V_z/F
  Concentration of TAK-831 cerebrospinal fluid will be examined as needed.

6.3.4.3 Pharmacodynamic Endpoint

Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max} following TAK-831 doses will be examined to assess the PD of TAK-831 in healthy adult Asian subjects. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid may be assessed as necessary.

6.3.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

The objective of this section is to specify the sequence of procedures in the cases where the timing of each procedure overlaps.

- Safety evaluation will be conducted within the predetermined allowance window as far as possible.
- Blood samples for PK assessment will be collected at time points as close to the specified time as possible.
- Other procedures must be completed at time points as close to the specified or planned hours as possible irrespective of before or after the specified times.
- If the timing of blood sampling and ECG or vital signs measurement overlap, blood sampling should be prioritized. ECG or vital signs measurement may be performed within an acceptable time window (Appendix C).
- The priority may be changed upon agreement between the investigator and the sponsor based on discussion.
- Any test and procedure necessary to immediately assess safety concerns at the time of AEs must be prioritized over other regular predetermined procedures.
- The safety of subjects in the follow-up period may be confirmed by telephone unless abnormal, clinically significant findings are observed upon discharge.

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

The entire study will start when the first subject signs the informed consent form to participate in this study.

6.4.2 Definition of End of the Trial

The study will end when the last subject completes the last planned visit or follow-up visit (or last communication [may be via telephone] relating to the planned visit) or is withdrawn from the study or lost to follow up (the status that the subject cannot be reached by the investigator).

6.4.3 Definition of Trial Discontinuation

The study may be discontinued for reasons other than safety such as the followings:

- A finding (eg, PK, pharmacodynamics, efficacy, biologic targets) from the other nonclinical or clinical studies results with the study drug in the study discontinuation for non-safety related reasons.
- Data from drugs classified in the same class as the study drug, or methodologies used in this study become available and results in the study being stopped for a non-safety related reason.
- Study discontinuation due to non-scientific and non-safety-related reasons, such as slow enrollment.

Discontinuation of the clinical study for safety reasons:

- The study is prematurely terminated because other clinical or non-clinical trials where TAK-831 or other drugs of the same class are administered have confirmed unexpected safety concerns based on the methodology used in this study

6.4.4 Criteria for Premature Termination or Suspension of the Trial

6.4.4.1 Criteria for Premature Termination or Suspension of the Trial

The study will be completed as planned unless 1 or more of the following criteria are met that require temporary suspension or early termination of the study.

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

6.4.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the Sponsor, an institutional review board (IRB), or a regulatory authority elects to terminate or suspend the study, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

6.4.5 Criteria for Premature Termination or Suspension of a Study Site

6.4.5.1 Criteria for Premature Termination or Suspension of a Study Site

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

6.4.5.2 Procedure for Premature Termination or Suspension in a Study Site

In the event that the Sponsor, an IRB, or a regulatory authority elects to terminate or suspend of the study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) ≥18.5 kg/m^2 and ≤25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the following birth control requirements:
    - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug. No restrictions will be required for a vasectomized male subject provided the subject is at least 1 year post bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
    - Is a male subject who agrees to not donate sperm from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug.
    - Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
        a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or ≥6 months of spontaneous amenorrhea in females aged >45 years with

serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels should be required.

b) Hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

c) Had a tubal ligation with appropriate documentation of surgical procedure.

d) Congenital conditions such as uterine aplasia etc.

[Rationale for the inclusion criteria]

Inclusion criteria 1, 2, 5, 8 and 9:

These are standard criteria for clinical pharmacology studies in healthy adult subjects and defined in consideration to the safety of subjects.

Inclusion Criterion 3:

This is a standard criterion for clinical pharmacology studies in healthy adult subjects for sex. This is a standard criterion for clinical pharmacology studies in healthy adult subjects for age.

Inclusion Criterion 4:

This is the range of normal weight in the diagnosis criteria for obesity and obesity disease [11] proposed by the Japan Society for the Study of Obesity.

Inclusion Criterion 6:

This is set to appropriately assess the safety and PK in Chinese.

Inclusion Criterion 7:

This is set to eliminate the influence by dietary habits on the PK.

7.2 Exclusion Criteria

The subject will be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or diseases.
2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the trial procedure in the previous trial to the Screening Visit of the current trial.
3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).

5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec at the Screening Visit or Check-in.

[Rationale for the exclusion criteria]

Exclusion Criteria 1, 15:

This is set to eliminate the influence on safety evaluation for TAK-831.

Exclusion Criterion 2:

This is a minimum duration in which the previous clinical trial is considered to have no influence in reference to "General Considerations for Clinical Trials" [12] in order to ensure the safety of subjects.

Exclusion Criteria 3, 4, 6, 7, 12, 13, 14:

These are standard criteria for clinical pharmacology studies and defined in consideration to the safety of subjects.

Exclusion Criterion 5:

This is defined in consideration to the safety of subjects.

Exclusion Criteria 8, 9, 11:

This is defined in consideration to the safety of subjects. This is also defined for potential influence on PK and PD assessment.

Exclusion Criterion 10:

This is set to exclude subjects who have a known hypersensitivity to any component of the formulation of TAK-831 or related compounds in consideration of the safety of subjects.

7.3 Excluded Medications Supplements, Dietary Products

Table 7.a shows excluded medications, supplements, and dietary products.

Use of the drugs listed on Table 7.a (prescribed drugs and over-the-counter [OTC] drugs), vitamins, supplements, and dietary products will be excluded from a specified time point to until discharge given the effect on the safety and PK. Use of prohibited concomitant drugs will be allowed when the investigator or sub-investigator deems it necessary to use any of the concomitant drugs for reasons including treatment of an AE.

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

Table 7.a Excluded Medications, Supplements, Dietary Products

From 28 days before admission (Day -1) to the last discharge	7 days before admission (Day -1) to the last discharge	72 hours before admission (Day -1) to the last discharge
• Prescription drugs	• OTC drugs (including aspirin or aspirin-containing drugs) (a)	• Caffeine or xanthine containing products
• Supplements (St. John's wort, ginseng, kava kava, ginkgoes, chinese herbal medicine, and melatonin)	• Vitamins	
• Vaccination/vaccine (b)	• Beverages containing grapefruit (fruit juice, flesh), star fruits (fruit juice, flesh), citrus aurantiums (high acidity), orange (seville oranges), or marmalade	
	• Apple, orange or pineapple juice	
	• Brassicaceae vegetables (kale, cress, collard greens, kohlrabi, brussels sprouts, and mustard).	
	• Meat cocked over the charcoal	
• Nicotine-containing products	• Alcohol containing products	
• CYP 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1 and 2A6 inhibitors/inducers OTC drugs (c)		

CYP: cytochrome P-450, OTC drugs: over-the-counter drugs
Note: Excludes the drug needs to be administered to treat an AE and if the investigator or sub-investigator considers necessary to use the drug
(a) Use of paracetamol (≤1 g/daily) will be allowed.
(b) Includes H1N1 and other influenza vaccines, however, not limited to these medications.
(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Diet and fluid (except water) must be ingested at least10 hours before clinical laboratory tests.

On the day before clinical laboratory tests, evening meal must be ingested by 21:00.

During hospitalization, pre-specified diets must be ingested, and other diets will be prohibited. After discharge, excessive drinking and eating must be avoided until completion of follow-up period.

Subjects will be instructed to fast for at least 10 hours before study drug administration.

Subjects in Cohort 2 to 5 will be instructed to fast for an additional 4 hours on Days 1, 4 and 17 and 2 hours for all other study drug administration days.

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

Subjects should be prohibited from drinking any liquid from 1 hour before to 1 hours after study drug administration, with the exception of water (150 mL) taken with the study drug.

7.4.2 Activity

Smoking is prohibited during the study.

Excessive exercise is prohibited during the study.

Blood donation is prohibited for at least 12 weeks (84 days) from completion of the last test.

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the visit in advance whenever possible, and should be reported the circumstances and therapy after visit. The investigator or sub-investigator should communicate that medical institution about the subject's participation in the study.

7.5 Documentation of Subject Failure

The investigator or sub-investigator must account for all subjects who sign informed consent. If a subject discontinues the study before the first study drug administration, the investigator or sub-investigator should complete the electronic case report form (eCRF).

The primary reason for subject failure is to be recorded in the eCRF using the following categories:

- Death
- AE
- Screening failure (failed inclusion criteria or did meet exclusion criteria) <specify the reasons>
- Protocol deviation
- Lost to follow up
- Withdrawal by subject <specify the reasons>
- Study terminated by the Sponsor
- Pregnancy
- Sample size sufficient
- Other <specify the reasons>

Any subject identification number, once assigned to a subject, should not be reused if the assigned subject discontinues the study prior to the first study drug administration. Nevertheless, if a reserve subject is enrolled in the other cohort, the same subject identification number may be used.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

Primary reasons for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF using the following categories. For the subject who is withdrawn from the study before the first study drug administration in Period 1, refer to Section 7.5.

1. Death
   The subject died on study.

   Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). Refer to Section 10.2.9.3 for reporting procedures.

2. 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.

   The study drug will be immediately discontinued if a condition meets any following criteria during the treatment, and appropriate follow-up will be performed (clinical laboratory tests will be repeatedly performed until the clinical laboratory test profiles have normalized or returned to baseline, refer to Section 9.2.10.1):

   - Liver Function Test (LFT) Abnormalities
     - ALT or AST >8×the upper limit of normal (ULN), or
     - ALT or AST >5×ULN and persists for more than 2 weeks, or
     - ALT or AST >3×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (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%)
   - Prolonged QT/QTcF intervals

     If at least one remarkable prolonged QT interval was observed on 12-lead ECG (eg, absolute value of QTcF intervals >500 msec or an increase >60 msec from baseline), and the investigator or sub-investigator considered inappropriate to continue the study.

3. Protocol deviation
   The discovery after the start of the first study drug administration 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.

4. 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 in the subject's source documentation.

5. Pregnancy
   If a subject was found to be pregnant.

   Note: Participation in the study is immediately discontinued for any pregnancy. Refer to Appendix B for the procedures.

6. Voluntary withdrawal
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

7. Study terminated by the Sponsor
   The Sponsor terminates the study.

8. Other

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

7.7 Procedures for Discontinuation or Withdrawal of a Subject

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

7.8 Subject Replacement

The Part 1 in Cohort 1 and Cohorts 2 to 5 can have a few reserve subjects considered eligible for participation in the study based on screening test. If a subject has not received the study drug as scheduled during the study owing to any reason occurring before the study drug administration, a reserve subject will be allowed to participate in the study.

If a subject withdraws from the study after initiation of the study drug, the subject will not be replaced with a reserve subject.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

[Drug product]

Code name: TAK-831

Dosage form and strength:

TAK-831 tablet is a yellowish-red film-coated tablet containing 25 or 300 mg of TAK-831.

TAK-831 placebo tablet contains no TAK-831 and has same appearance as TAK-831 tablet.

8.1.1 Clinical Study Drug Labeling

Study drug labeling will show name of the study drug, quantity and storage condition of the study drug, manufacture number, expiration date, protocol number, name and address of the Sponsor, and statement the drug is for clinical trial use only.

8.1.2 Clinical Study Drug Inventory and Storage

TAK-831 is stored at a room temperature (1°C to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used, or returned to the Sponsor or its designee. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Randomization Code Creation and Storage

The personnel responsible for randomization (the Sponsor's designee) will prepare the randomization table/schedule prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.4 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigator must store the emergency key until the time of an emergency blind break or the end of the trial.

Since maintenance of the blind may be compromised because of results from drug concentrations and PD assessments, such results should not be disclosed prior to blind breaking. In the event that results must be reported to the investigator prior to breaking the blind, all efforts should be made to maintain the blind (eg, by changing a medication identification number in order to avoid identification of subjects by laboratory site personnel). Detailed procedures for measuring subject drug concentration levels and PD assessments will be provided in the separately created procedure for directions on the handling of biological samples for measuring drug concentrations and PD assessments.

To unblind a subject, the study drug blind can be obtained by opening a sealed envelope.

The Sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded in the eCRF.

If the investigator or sub-investigator breaks the blinding of the study drug, study drug must be stopped immediately and that subject must be withdrawn from the study.

No change should be made to any subject assessment after unblinding (except cases where the investigator or sub-investigator is not informed of unblinding information [unblinding for open-label analysis for the Sponsor]).

8.1.5 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (a site designee) will receive the pharmacy manual created by the Sponsor, and follow the procedures for managing the Sponsor-supplied drug supplies. A copy of these procedures will be provided to the investigator as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the Sponsor-supplied drug. The manual will also describe procedures for the collection of unused medications from the subject and their return to the Sponsor, or the destruction of any unused supplies.

The on-site pharmacist (a site designee) will immediately return any unused study drugs in a sealed package to the Sponsor after the study is closed at the investigational site.

9.0 STUDY PROCEDURES

The investigator or sub-investigator should collect data according to the procedures described in the following sections. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site designee whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the initiation of any study procedures. The requirements of informed consent are described in Section 13.2.

A separate informed consent form pertaining to the collection, storage, and analysis of samples must be obtained prior to collecting any blood sample for pharmacogenomic research for this study.

9.1.1.1 Assignment of Subject Identification Number

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

9.1.1.2 Study Drug Assignment

In Cohorts 1-2 and Cohort 5, and Cohorts 3 and 4 (if added), the subjects will be assigned in the order of medication identification number by Cohort according to the randomization code. The medication identification number will be a 4-digit number, starting with the following number:

Cohort 1: 1001, Cohort 2: 2001, Cohort 3: 3001, Cohort 4: 4001, Cohort 5: 5001

The assigned medication identification number will be used to identify the samples for PK by the study site and the only number to identity a subject during blood sampling for PK. The number will be always shown on the sample vials, which are sent to the laboratory to evaluate the PK. The laboratory will report the results using this number. The number will be used for only the purpose described in this section and cannot be replaced with the 7-digit subject identification number, which is assigned at the time of informed consent procedure and used in all other procedures during the clinical study period to identify a subject. In case of subject replacement, the study drug with a medication identification number for the withdrawn subject will be used by the replacing subject.

9.1.2 Inclusion and Exclusion

Each subject will be assessed according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Demographic information to be obtained will include date of birth, sex, height, weight, caffeine use, alcohol use, and smoking status of the subject.

Medical history to be obtained will include determining whether the subject has any clinically significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions. Medication history information to be obtained will include any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Subjects will be asked whether they have taken any medication other than the study drug (used from the signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC drugs, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication names, route of administrations, start and end dates, and reasons for use.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

9.2.2 Height and Weight

Each subject should have a height and weight measured. Height will be recorded in centimeters without decimal places (rounding off the first decimal place). Weight will be collected in kilograms (kg) with the first decimal place (rounding off the second decimal place).

9.2.3 BMI

BMI is calculated using the formula provided below.

Metric: BMI=weight (kg)/height $(m)^2$

The values should be calculated to the first decimal place (rounding off the second decimal place). When the BMI is used as entry criteria, then this determination must be made after rounding.

9.2.4 Vital Signs

Vital signs will include body temperature (axilla measurement), sitting blood pressure (systolic and diastolic, after resting more than 5 minutes), and pulse (beats per minute).

9.2.5 12-Lead ECG

A standard 12-lead ECG will be recorded. Subjects should be resting in a recumbent position for at least 5 minutes before each ECG measurement.

The investigator or sub-investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: normal or abnormal. If an ECG is abnormal, the investigator or sub-investigator (or a qualified observer at the investigational site) will judge clinical significance of the abnormality. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTcF.

9.2.6 Holter ECG

After Cohort 3, continuous (Holter) ECG will be measured from -23 hours predose to 24 hours postdose on Day 1 as needed. Procedures regarding Holter ECG will be provided in the separately created manual.

ECG obtained from 24 hours Holter measurement will not be analyzed as safety endpoints.

9.2.7 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be performed at the study procedures-specified time point. The investigator or sub-investigator will evaluate suicide risks based on the information obtained from C-SSRS. For any suicidal ideation and suicidal behavior will be documented as an adverse event.

9.2.8 Study Drug Administration

In Cohort 1, a single dose of TAK-831 T3 tablet 25 mg×4 tablets or placebo will be orally administered on Day 1 (Part 1), and a single dose of TAK-831 T3 tablet 300 mg×1 tablet or placebo will be orally administered on Day 9 (Part 2).

In Cohort 2, a single dose of TAK-831 T3 tablet 300 mg×2 tablets or placebo will be orally administered on Day 1, followed by multiple doses of TAK-831 T3 tablet 300 mg×2 tablets (once daily) or placebo on Days 4-17.

In Cohort 5, a single dose of TAK-831 T3 tablet 25 mg×2 or placebo will be orally administered on Day 1, followed by multiple doses of TAK-831 T3 tablet 25 mg×2 (once daily) or placebo on Days 4 to 17.

The study drug will be orally administered with 150 mL of water at a fasted state (fasted at least 10 hours before administration).

In Cohorts 3 and 4, the dose of the study drug will be determined based on the data obtained from Cohorts 1 and 2.

9.2.9 AE Monitoring

AE monitoring will begin after the signing of informed consent. A complete description of AE collections and procedures is provided in Section 10.2.

9.2.10 Laboratory Procedures and Assessments

Laboratory samples will be taken following a minimum 10 hour overnight fast on the days stipulated in the Schedule of Study Procedures (Section 3.0). Refer to Appendix C for the amount of blood samples.

The investigator or sub-investigator will take responsibility for evaluation of the clinical laboratory test results and storage. The investigator will maintain a copy of the reference ranges for the laboratory used.

9.2.10.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Red blood cell count	White blood cell count and differential leukocytes (lymphocytes, neutrophils, eosinophils, basophils, and monocytes)
Hemoglobin	Hematocrit
Platelet count	PT
APTT	

Chemistry

Chemistry evaluations will consist of the following chemistry tests:

Albumin	Creatinine
ALP	Glucose
ALT	Sodium
AST	Calcium
γ-GTP	Creatine kinase
Total bilirubin	Potassium
Direct bilirubin	Chloride
Total protein	Urea nitrogen

Urinalysis

Urinalysis will consist of the following tests:

pH	Specific gravity
Qualitative (protein, glucose, occult blood, and nitrite)	Urinary sediment (erythrocytes, leukocytes, and cylinder) (a)

(a) Will be performed for any abnormal urinalysis parameter.

Other

Immunological tests HIV antibody and antigen tests, hepatitis tests (HBs antigen and HCV antibody)
Alcohol tests (urinalysis or breath test)
Urinary drug tests
FSH (postmenopausal female subjects only)

HIV: human immunodeficiency virus, HBs: hepatitis B surface antigen, HCV: hepatitis C virus, FSH: follicle-stimulating hormone
Note: The investigator or sub-investigator will report the results of immunology, urine drug tests, and alcohol tests directly to subjects. The Sponsor will confirm the overall test results (as "Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug.

If subjects experience an ALT or AST of >3×ULN (except the tests at Screening), follow-up laboratory tests (at a minimum, serum alkaline phosphatase [ALP], ALT, AST, total bilirubin, gamma-glutamyl transferase [γ-GTP], and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Refer to Section 7.6 and Section 10.2.9.4 for the discontinuation or withdrawal criteria of a subject and the appropriate guidance on reporting abnormal LFTs as SAEs, respectively.

9.2.10.2 Urine sample for Future Tests

Urine samples for future tests will be collected according to the Schedule of Study Procedures (Section 3.0).

If acute renal failure is suspected, urinary biomarkers such as KIM-1, NGAL, and cystatin C may be measured using the collected sample.

The result of future urine test will not be analyzed as safety endpoints.

9.3 Biomarker, PK, PD, and PGx Samples

Samples for PK, PD, and PGx will be collected according to the schedule of study procedures (Section 3.0). Separated procedures describe the details of sampling, handling, and transferring to central laboratory. The actual sampling time for PK and PD analyses will be documented in the subject's source documents and eCRF.

Table 9.a shows primary specimen collections.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	PK Analysis	Mandatory
Plasma sample for PD	Blood	Plasma	PD analysis	Mandatory
Cerebrospinal fluid sample for PD	Cerebrospinal fluid	Cerebrospinal fluid	PK Analysis PD analysis	Optional
Blood sample for DNA PGx	Blood	DNA	PGx analysis	Optional

9.3.1 PK Measurements

The following PK parameters will be calculated from plasma concentrations of TAK-831, unless otherwise specified.

Mark/Term	Definition
Plasma	
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to time of infinity
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
C_{max}	Maximum observed plasma concentration (measured value)
$C_{max, ss}$	Maximum observed steady-state plasma concentration during a dosing interval (measured value)
t_{max}	Time of first occurrence of C_{max}
$t_{1/2z}$	Terminal disposition phase half-life
λ_z	Terminal disposition phase rate constant
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration
CL/F	Apparent clearance after extravascular administration
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}
$R_{ac(AUC)}$	Accumulation ratio based on AUC

9.3.1.1 Plasma for PK Measurements

Blood samples for plasma TAK-831 concentration will be collected (Table 9.b). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.b Blood Sample Collection for PK Analysis

Dose Levels:	Date of administration	Sampling time
Single dose	1	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
	9	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	1	Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, and 48 hours postdose
	4, 11, 14	Predose
	17	Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16, and 24 hours postdose

9.3.1.2 Cerebrospinal fluid samples for PK Measurements

Concentration of TAK-831 cerebrospinal fluid will be measured using cerebrospinal fluid samples collected for PD measurements (Section 9.3.2.2).

9.3.2 PD Analysis

The following PD parameters will be calculated from plasma concentrations of D-serine and L-serine, unless otherwise specified

Mark/Term	Definition
Plasma	
$AUEC_{24}$	Area under the effect-time curve from time 0 to 24 hours postdose
E_{max}	Maximum effect
time to E_{max}	Time to reach maximum PD effect

9.3.2.1 Plasma Samples for PD Analysis

Blood samples will be collected to measure plasma D-serine and L-serine concentrations (Table 9.c). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.c Blood Sample Collection for PD Analysis

Dose Levels:	Specimen	Date of administration	Sampling time
Single dose	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
		9	Predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, and 24 hours postdose
		11, 14	Predose
		17	Predose, 1, 4, 8, 12, and 24 hours postdose

9.3.2.2 Cerebrospinal fluid samples for PD Analysis

Cerebrospinal fluid will be collected to measure D-serine and L-serine concentrations (3.0 mL per scheduled time). The cerebrospinal fluid sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples. Cerebrospinal fluid samples for PD analysis will be also used to measure concentration of TAK-831 cerebrospinal fluid. After Cohort 2, collection of cerebrospinal fluid in the next Cohorts will be determined based on the results of plasma D-serine and L-serine concentrations obtained from the previous Cohorts.

9.3.3 PGx Measurements

9.3.3.1 Blood Sample for DNA PGx Measurements

When sampling of whole blood for pharmacogenomic analysis occurs, the subject must sign informed consent/be consented separately for PGx sampling, storage and analysis. PGx measurement is a part of the study, but participation of a subject is optional.

One 6-mL of whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected prior to the single dosing on Day 1 from each consenting subject in the study.

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. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification by the Sponsor. "Stored samples" are defined as samples that are 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 the study drug or related drug.

The sampling of whole blood for PGx and genotyping analysis is mandatory. Every subject must sign informed consent separately for PGx sampling. DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms.

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 exploratory research with the samples for PGx measurements.

9.3.4 Confinement

Cohort 1:

Subjects will be hospitalized from Day -1 to Day 4 and Day 8 to Day 12 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Days 4 and 12.

Cohorts 2:

Subjects will be hospitalized from Day -1 to Day 19 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Day 19.

Cohorts 3 to 5:

Subjects will be hospitalized from Day -2 to Day 19 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Day 19.

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 clinical study; it does not necessarily have to have a causal relationship with the the treatment (including the study drug) or study participation.

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered 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 or sub-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 may be considered as AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring for an abnormal value are not considered as an intervention. In addition, repeated or additional non-invasive tests for verification and evaluation of abnormality or monitoring purpose will not be considered as 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 conditions and should NOT be recorded as an AE. The observations or evaluations of first examination at baseline (eg, laboratory test, ECG, X-ray,

etc) should NOT be recorded as AEs 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). The investigator or sub-investigator 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. The investigator or sub-investigator should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a pre-existing chronic 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. The investigator or sub-investigator 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 drug or after any change in study drug, the worsening or complication should be recorded as a new AE. The investigator or sub-investigator should ensure that the event term reported captures the change in adverse event (eg, "worsening of…").

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to the signing of informed consent are not considered AEs. However, if a preplanned procedure is performed earlier (eg, as an emergency) due to a worsening of a 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 study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the sub-investigator to decide whether a dose is to be considered as overdose, in consultation with the Sponsor.

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.9.
- 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 Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

Severity/Intensity of AEs will be classified or defined as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying disease, 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 the underlying disease, complications, concomitant medications and concurrent treatments.

10.2.3 Assigning Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

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

10.2.4 Start Date

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

10.2.5 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.

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken with Study Treatment

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

10.2.8 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/signs/symptoms have almost disappeared; the abnormal laboratory values improved, but have 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 values on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.9 Collection and Reporting of AEs, SAEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent and continue until the follow-up visit or phone call.

10.2.9.2 Reporting AEs

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

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator or sub-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 Adverse Event (Frequency)
- Severity/Intensity.
- The Investigator's or sub-investigator's opinion of the causal relationship between the event and administration of study drug(s). (Related/Not related)
- Action taken with the study drug
- Outcome of the event.
- Seriousness.
- Timing of occurrence (after administration of the study drug)

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator or sub-investigator to the Sponsor within 1 business day of the first onset or notification of the SAE, along with any relevant information. The

investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. 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 or sub-investigator's name.
- Name of the study drug(s).
- Causality assessment.

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

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator or sub-investigator should complete the follow-up SAE form or provide other written documentation immediately to the Sponsor. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory values, discharge summary, postmortem results) in the institution should be submitted to the Sponsor, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.2.9.4 Reporting of Abnormal LFTs

If a subject experiences 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 10.2.9.3. The investigator or sub-investigator will contact the monitor for discussion and investigation of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease, medical history/ongoing disease. Follow-up laboratory tests as described in Section 9.2.10 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs and Regulatory Authorities

The Sponsor will report all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs and the head of the study site. 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 the study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definitions of analysis variables, and analysis methodologies to address all study objectives.

11.1.1 Analysis Sets

In this study, 3 analysis sets are defined: the Safety Analysis Set, the PK Analysis Set, and the PD analysis Set. The definition of each analysis set will be described in the SAP.

The Sponsor will verify the validity of the definitions of the analysis sets and the rules for handling data in consultation with a medical expert, as needed, prior to unblinding the study drug assignment. The Sponsor will address all remaining uncertainties not specified at planning, and will finalize the SAP prior to unblinding of subject's treatment assignment.

11.1.1.1 Safety Analysis Set

The Safety Analysis Set will be defined as all subjects who received at least one dose of study drug.

11.1.1.2 PK Analysis Set

The PK Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PK parameter.

11.1.1.3 PD Analysis Set

The PD Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PD parameter.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the Safety Analysis Set.

11.1.3 PK Analysis

Endpoints and its analytical method

[Endpoints]

Secondary endpoints: C_{max} (Cohort 1, Day 1 in Cohorts 2 to 5), $C_{max,ss}$ (Day 17 in Cohorts 2 to 5), t_{max} (Cohort 1, Days 1 and 17 in Cohort 2 to 5), AUC_{last} (Cohort 1, Day 1 in Cohorts 2 to 5), AUC_{∞} (Cohort 1, Day 1 in Cohorts 2 to 5), AUC_{τ} (Days 1 and 17 in Cohorts 2 to 5)

Exploratory endpoints: $R_{ac(Cmax)}$ and $R_{ac(AUC)}$ (Cohort 2 to 5) on Days 1 and 17, $t_{1/2z}$, CL/F, V_z/F, concentration of TAK-831 cerebrospinal fluid (Cohort 2 to 5)

[Analytical method]

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2, 4 and 5 as well as Cohort 3.

Concentrations of TAK-831 in plasma and cerebrospinal fluid will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time of TAK-831 will be presented. Plasma PK parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Day 1 and Day 9 for Cohort 1 and Day 1 for Cohorts 2 to 5. Additional analyses on dose linearity will be included if appropriate.

11.1.4 PD Analysis

Endpoints and its analytical method

[Endpoints]

- Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (on Days -1 and 18) (if available)

[Analytical method]

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2, 4 and 5 as well as Cohort 3.

Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent the change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

11.1.5 Safety Analysis

Endpoints and its analytical method

[Endpoints]

AEs, laboratory findings, vital signs, weight, 12-lead ECG

[Analytical method]

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2, 4 and 5, and for Cohort 3.

11.1.5.1 AEs

A treatment-emergent adverse event (TEAE) is defined as an AE whose date of onset occurs on or after the start of study drug.

The followings will be analyzed for TEAEs. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

- Frequency of all TEAEs
- Frequency of drug-related TEAEs
- Frequency of all TEAEs by intensity
- Frequency of drug-related TEAEs by intensity
- Frequency of TEAEs leading to study drug discontinuation
- Frequency of serious TEAEs

11.1.5.2 Clinical Laboratory Evaluation

Summary statistics will be provided for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

11.1.5.3 Vital Signs

Summary statistics will be provided for the observed values at each evaluation time point and changes from baseline.

11.1.5.4 Other Safety Parameters

The ECG parameters will be summarized as follows. Summary statistics will be calculated for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables. The analysis methods for other endpoints will be specified in detail in the SAP.

11.2 Determination of Sample Size

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, and PK of each cohort. This is not based on any statistical rationale.

11.3 Interim Analysis and Criteria for Early Termination

In order to support a development plan of TAK-831, an interim analysis of the safety and tolerability following a single dose and multiple dose of TAK-831 may be conducted after the completion of Cohort 4. Details will be provided in SAP. It should be noted that continuation or discontinuation of this study will not be judged by the interim analysis.

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.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, and informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, sub-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 or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the Sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the Sponsor and the head of the study site of the deviation or changes as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the Sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

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 study 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 [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency [MHRA], and the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory authority, the Sponsor should be notified immediately. The investigator and the head of the institution guarantee 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 Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for GCP. The investigator will conduct the study according to applicable local or regional regulatory requirements in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

The IRB must be constituted according to the applicable local requirements of each participating region. The Sponsor or the designee will require documentation noting all names and titles of the members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. The Sponsor or the designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the written informed consent form, and, if applicable, subject recruitment materials and/or advertisements, if applicable, and other documents required by all applicable laws and regulations, must be submitted to the IRB for approval. The IRB's written approval of the protocol and subject written informed consent must be obtained and submitted to the Sponsor or the designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, written informed consent form) reviewed; and state the approval date. The Sponsor will notify the study site that the Sponsor has confirmed the adequacy of the study site regulatory documentation. Until the study site receives a notification, no protocol activities, including screening, may occur.

The study site must adhere to all requirements stipulated by its respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the written 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, and submission of the investigator's final status report to IRB. All IRB 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 and the 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 written informed consent form describes 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 further explains 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 approval of the written informed consent form. The written informed consent form must be approved by both the IRB and the Sponsor prior to use.

The informed consent form must be described in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines he or she will participate in the clinical study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed by the investigator or sub-investigator to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form will be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects 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 prior to analysis. Notify the 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 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, MHRA, and PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents),

including 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 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. The investigator or sub-investigator needs to obtain a prior written approval from the Sponsor to publish any information from the study externally, such as to a professional association.

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 the facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

13.5 Clinical Trial Results Disclosure

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

13.6 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study 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 or sub-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

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.2 Investigator Agreement

A separate agreement will be provided to the study site.

14.1.3 Study-Related Responsibilities

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.4 List of Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUEC	area under the effect-time curve
BMI	body mass index
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DAAO	D-amino acid oxidase
DNA	deoxyribonucleic acid
E_{max}	maximum effect
FDA	Food and Drug Administration
FRDA	Friedreich ataxia
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
γ-GTP	gamma-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requrements for Pharmaceuticals for Human Use
INR	international normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency

Term	Definition
NMDA	*N*-methyl-D-aspartate
NOAEL	no observed adverse effect level
PET	positron emission tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
POC	proof-of-concept
R_{ac}	accumulation ratio
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occrurrence of C_{max}
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration

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 eCRFs

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

The Sponsor or its designee will supply the study sites with access to eCRFs. The Sponsor will provide training opportunities for the 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 the Sponsor (or the designee) and will be answered by the study 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.

The 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.

The following data will not be recorded in the eCRFs.

- PGx analysis results
- Clinical laboratory test results
- Drug concentration measurement results
- PD measurement results
- Holter ECG measurement date, time and results
- Future urinalysis measurement results

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 or sub-investigator with use of change and modification records of the eCRFs. The investigator must review the data change for completeness and accuracy, and must e-sign.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the Sponsor or its designee. 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 or the head of the study site agree to keep the records stipulated in Section 15.1 and those documents that include (but not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated 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.

The investigator and the head of the study site are required to retain essential documents until the day specified as 1 or 2 below, whichever comes later. However, if the Sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the Sponsor.

1. The day on which marketing approval for the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion for the study.

In addition, the investigator and the head of the study site should retain the relevant essential documents until the receipt of a Sponsor-issued notification that states the retention is no longer required.

16.0 REFERENCES

[1] Sham PC, Gottesman, II, MacLean CJ, Kendler KS. Schizophrenia: sex and familial morbidity. Psychiatry Res 1994;52(2):125-34.

[2] Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999;56(2):162-8.

[3] Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo UH, Bassett AS, Cornblatt BA, Kestenbaum CJ, et al. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch Gen Psychiatry 1995;52(10):857-65.

[4] van Os J, Kapur S. Schizophrenia. Lancet 2009;374(9690):635-45.

[5] Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 2003;169(3-4):215-33.

[6] Calcia MA, Madeira C, Alheira FV, Silva TC, Tannos FM, Vargas-Lopes C, et al. Plasma levels of D-serine in Brazilian individuals with schizophrenia. Schizophr Res 2012;142(1-3):83-7.

[7] Ohnuma T, Sakai Y, Maeshima H, Hatano T, Hanzawa R, Abe S, et al. Changes in plasma glycine, L-serine, and D-serine levels in patients with schizophrenia as their clinical symptoms improve: results from the Juntendo University Schizophrenia Projects (JUSP). Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):1905-12.

[8] Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, et al. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the N-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch Gen Psychiatry 2003;60(6):572-6.

[9] Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(5):767-9.

[10] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511(7510):421-7.

[11] Japan Sciety for the Study of Obesity. Diagnostic Criteria for Obesity 2011. Journal of Japan Society for the Study of Obesity, 2011 Oct; additional edition.

[12] General Considerations for Clinical Trials (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998).

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to a sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study site in advance to get them accepted.
3. Prepare a written informed consent form and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the study site that sufficient medical care for all clinically significant AEs related to the study are provided to subjects throughout and beyond the period when subjects participate in the study, upon obtaining consent from the subject.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study site and the Sponsor in writing.
11. Determine the need of emergency key code unblinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the Sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the Sponsor with electronic signature.
14. Discuss any proposal from the Sponsor including update of the protocol.
15. Notify the head of the study site of the end of the study in writing.

Appendix B Pregnancy and Contraception

Male Subjects and Their Female Partners

From the signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, any nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use adequate contraception. In addition, they must be advised not to donate sperm during this period or subjects should refrain from having sexual intercourse from 1 month prior to the first study drug administration throughout the study period and until 35 days after the last study drug administration. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the table on containing adequate contraception below.

Female Subjects and Their Male Partners

Female subjects of childbearing potential* will be excluded from this study.

* Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation), or who are postmenopausal (eg, defined as at least 2 years since last regular menses with an FSH of >40 IU/L).

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documented absence of sperm in the ejaculate, or have had a bilateral orchidectomy.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate.

Barrier methods (each time the subject has intercourse)	Intrauterine device (IUD)	Hormonal contraceptives
Male condoms with a spermicide	Copper T PLUS condom Progesterone T PLUS condom	Combined pill

Subjects will be provided with information on acceptable methods of contraception for 95 days after last dose of study drug, as part of their informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy in partners and of sperm donations for 95 days after their last dose of study drug.

Pregnancy

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

If the pregnancy in the partner of a male subject occurs during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of his right to receive treatment information. If the subject chooses to receive unblinded treatment information, that individual's blind should be broken by the investigator or sub-investigator. Any subjects randomized to placebo need not be followed.

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

All female subjects and the female partners of male subjects who became pregnant will be followed to final outcome, using the pregnancy form, with the consent of the female subjects or the female partners of those male subjects. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after any birth of a child will also be conducted.

Appendix C Acceptable Time Window for Study Procedure

<Cohort 1>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
	Follow-up period	Day 23	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Study treatment period (Part 1)	Day 1 72 hours postdose	Day 4 from awakening to discharge
	Washout period	Day 8	Not applicable
	Study treatment period (Part 2)	Day 9 72 hours postdose	Day 12 from awakening to discharge
	Follow-up period	Day 23	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 2 and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Urinary drug tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Washout period	Day 8	Not applicable
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
Samples for PGx measurements	Treatment period (Part 1)	Day 1 predose	Not applicable
Blood samples for PK	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 1 hour postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 24 hours postdose	Within ± 2 hours
	Treatment period (Part 2)	Day 9 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, and FSH

<Cohorts 2 to 5>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Days 5-10 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Days 12-13 predose	From awakening to immediately prior to dose
		Day 14 predose	From awakening to immediately prior to dose
		Days 15-16 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 1, 4, 12, 24, and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 48 hours postdose	Day 19 from awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 2 and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
Holter ECG (b) (if performed)	Hospitalization	Day 1 -23, -22, -20, -16 and -12 hours predose	Within ± 15 minutes
	Treatment period (Single dose part)	Day 1 predose	Within ± 15 minutes predose
		Day 1 1, 2, 4, 8, 12 and 24 hours postdose	Within ± 15 minutes
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 11 predose	From awakening to immediately prior to dose
		Day 17 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
Samples for PGx measurements	Treatment period (Single dose part)	Day 1 predose	Not applicable

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PK	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 0.25, 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	Within 15 minutes predose
		Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 0.25, 0.5, 1, 1.5, and 2 hours postdose	Within ± 5 minutes
		Day 17 4, 8, 12, 16 and 24 hours postdose	Within ± 15 minutes
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 1 hour postdose	Within ± 15 minutes
		Day 17 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
Cerebrospinal fluid samples for PD (If performed)	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 3 hours
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 24 hours postdose	Within ± 2 hours
	Treatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, FSH, and urinary drug tests
(b) After Cohort 3, Holter ECG will be performed as needed.

Total blood sampling volumes for an individual subject is shown below:

<Cohort 1>

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)
		Screening	Day -1	Days 1-4	Day 8	Days 9-12	
Clinical Laboratory Tests	20	1	1	1	1	1	100
Blood samples for PK	4	-	-	12	-	12	96
Blood samples for PD	6	-	3	9	-	9	126
Samples for PGx Measurements	6	-	-	1	-	-	6
						Total Blood Sampling Volume	**328**

-: No blood collection

<Cohorts 2 to 5>

Sample Type	Sample Volume (mL)	Number of Samples									Total Volume (mL)
		Screening	Day -1	Day 1	Day 2	Day 3	Day 4	Day 11	Day 14	Days 17-18	Day 19	
Clinical Laboratory Tests	20	1	1	-	-	-	-	1	-	-	1	80
Blood samples for PK	4	-	-	9	2	1	1	1	1	11	-	104
Blood samples for PD	6	-	3	5	1	-	-	1	1	6	-	102
Samples for PGx Measurements	6	-	-	1	-	-	-	-	-	-	-	6
										Total Blood Sampling Volume		**292**

-: No blood collection

TAKEDA PHARMACEUTICALS

PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK-831 in Healthy Adult Asian Subjects

Phase 1 Study of TAK-831 in Healthy Adult Asian Subjects

Study Identifier: TAK-831-1002

Compound: TAK-831

Date: 28 November 2018

Version/Amendment Number: Amendment 2

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals	**Compound:** TAK-831
Study Identifier: TAK-831-1002	**Phase:** 1
Title of Study: Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK 831 in Healthy Adult Asian Subjects	
Trial Design: This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of TAK-831 in healthy adult Asian subjects. This study will include up to 4 cohorts of healthy adult Japanese or Chinese subjects. In Cohort 1, a single dose of TAK-831 will be administered under a 3 sequential dose escalation design, and the safety, PK and PD will be assessed. Eight healthy adult Japanese subjects will be randomized in dosing orders of A (100 mg→300 mg), B (100 mg→placebo), and C (placebo→300 mg) at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Day 1 and Day 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge. Cohort 2 will include 8 healthy adult Japanese subjects. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge. Cohorts 3 and 4 will be optional, in which a single dose will be administered followed by multiple doses, and may be studied based on emerging data from the prior cohorts. Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.	
Trial Primary Objective: To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects. **Secondary Objectives:** To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.	
Target: Healthy adult Asian subjects	
Planned Number of Subjects: Cohort 1: 8 subjects Cohorts 2 to 4: 8 subjects per cohort	**Planned Number of Sites:** 1 site
Dose Levels: <Cohort 1> Single dose at 100 mg on Day 1 (Part 1) and 300 mg on Day 9 (Part 2) (fasted) <Cohort 2> Single dose at 600 mg on Day 1. Multiple doses	**Route of Administration:** Oral

(once-daily) at 600 mg on Days 4 to 17 (fasted) <Cohort 3> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted) <Cohort 4> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted)	
Duration of Treatment: <Cohort 1> Part 1: Single dose on Day 1 Part 2: Single dose on Day 9 <Cohorts 2 to 4> Single dose on Day 1 and once-daily multiple doses on Days 4 to 17, for 14 days, in each Cohort	**Planned Trial Duration:** <Cohort 1> Screening period: Day -28 to -1 Treatment period: Days 1 to 12 Follow-up period: Day 23 <Cohorts 2 to 4> Screening period: Day -28 to -1 Treatment period: Days 1 to 19 Follow-up period: Day 31

Inclusion Criteria:

Subject eligibility will be determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) $\geq$18.5 kg/m^2 and $\leq$25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the birth control requirements.

Exclusion Criteria:

The subject must be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or diseases.
2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the

trial procedure in the previous trial to the Screening Visit of the current trial.

3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).
5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms at the Screening Visit or Check-in.

Main Criteria for Evaluation and Analyses:

Primary Endpoint

Safety: Adverse event, laboratory tests, vital signs, weight, 12-lead electrocardiogram

Secondary Endpoints

Pharmacokinetics: The following parameters will be calculated.

C_{max} (Cohort 1, Day 1 of Cohorts 2 to 4)

$C_{max,ss}$ (Day 17 of Cohorts 2 to 4)

t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 4)

AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 4)

AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 4)

AUC_{τ} (Days 1 and 17 of Cohorts 2 to 4)

Statistical Considerations:

Pharmacokinetics:

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of TAK-831 in plasma will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time will be presented. Plasma PK parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Days 1

and 9 for Cohort 1 and Day 1 for Cohorts 2 to 4. Additional analyses on dose linearity will be included if appropriate.

Pharmacodynamics:

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2 and 4, as well as Cohort 3. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

Safety:

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2 and 4, and for Cohort 3.

A treatment-emergent adverse event (TEAE) refers to an adverse event that occurs after the start of study treatment. The frequency of all TEAEs, drug-related TEAEs , all TEAEs by intensity, drug-related TEAEs by intensity, TEAEs leading to study drug discontinuation, and serious TEAEs will be summarized. TEAEs will be coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

For continuous values of laboratory findings, vital signs and other safety parameters, summary statistics will be provieded for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

Sample Size Justification:

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, PK and PD of each cohort. This is not based on any statistical rationale.

2.0 STUDY SCHEMATIC

Figure 2.a shows the schematic of the trial design.

Figure 2.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - - Hospitalization - - - - - ►		◄- - - - Hospitalization - - - ►			

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion

Sequence of administration	Part 1	Washout interval	Part 2
	Day 1 to 4	Day 5 to 8	Day 9 to 12
A	TAK-831 100 mg	Washout	TAK-831 300 mg
B	TAK-831 100 mg		Placebo
C	Placebo		TAK-831 300 mg

<Cohorts 2 to 4>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening	Hospitalization	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- Hospitalization - ►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion

3.0 SCHEDULE OF STUDY PROCEDURES

<Cohort 1>

	Screening period		Treatment period										Early Termination	Follow-up visit
	Screening	Hospitalization	Part 1				Washout interval		Part 2					
Day	-28 to -2	-1	1	2	3	4	5 to 7	8	9	10	11	12		23 (±2)
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Demographics, medical history	X													
Prior medications	X													
Physical examination	X	X	X			X		X				X	X	X (l)
Vital signs (a)	X	X	X	X	X	X		X	X	X	X	X	X	X (l)
Weight, height, BMI (b)	X	X				X		X				X	X	X (l)
12-lead electrocardiogram (ECG) (c)	X	X	X			X		X	X			X	X	X (l)
Laboratory tests (d)	X	X				X		X				X	X	X (l)
Immunological test, alcohol tests	X													
FSH (e)	X													
Urinary drug tests	X	X						X						
C-SSRS (f)	X	X				X		X				X	X	
Sample collection for pharmacogenomic (PGx) Measurements (g)			X											
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X			X	X	X	X	X(k)	
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X	X	X			X	X	X	X		
Urine sample (for future tests) (j)		X		X						X			X	
Study drug administration			X						X					
Adverse events	X	X	X----------continuous monitoring----------X											
Concomitant medications	X	X	X----------continuous monitoring----------X											
Hospitalization		X	X----------X					X	X----------X					

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 1, on Day 8, predose on Day 9, and 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 9.

(b) Height will be measured at Screening only. Weight will be measured at Screening visit, Day -1, 72 hours postdose on Day 1, Day 8, 72 hours postdose on Day 9.

(c) 12-lead ECG will be measured at Screening, Day -1, predose, 2 and 72 hours postdose on Day 1, Day 8, predose on Day 9, 2 and 72 hours postdose on Day 9.

(d) Laboratory tests will be performed at Screening, on Day -1, 72 hours postdose on Day 1, on Day 8, and at 72 hours postdose on Day 9.

(e) FSH will be measured in postmenopause women only.

(f) C-SSRS will be investigate at Screening, Day -1, Day 4, Day 8, and Day 12.
(g) Samples for PGx measurements will be collected predose on Day 1.
(h) Samples for PK assessment will be collected predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 9, and 0.5, 1. 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(i) Samples for PD assessment will be collected on Day -1 (at 20, 16, 12 hours predose on Day 1), predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(j) Urine samples will be collected on Day -1, 24 hours postdose on Day 1, and 24 hours postdose on Day 9.
(k) Samples for PK assessment at discontinuation will be collected if it is possible.
(l) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

<Cohorts 2 to 4>

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening	Hospitalization	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Demographics, medical history	X																					
Prior medications	X																					
Physical examination	X	X	X																		X	X (m)
Vital signs (a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (m)
Weight, height, BMI (b)	X	X																			X	X (m)
12-lead electrocardiogram (ECG) (c)	X	X	X			X							X						X		X	X (m)
Laboratory tests (d)	X	X											X								X	X (m)
Immunological test, alcohol tests	X																					
FSH (e)	X																					
Urinary drug tests	X	X																				
C-SSRS (f)	X	X																			X	X
Sample collection for pharmacogenomic (PGx) Measurements (g)			X																			
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X							X			X			X	X		X (l)
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X									X			X			X	X		
Cerebrospinal fluid sample collection for pharmacodynamic (PD) assessment (j)		X																		X		
Urine sample (for future tests) (k)		X		X																X		X	

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening	Hospitalization	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Study drug administration			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events	X	X	X----------continuous monitoring----------X																			X	X
Concomitant medications	X	X	X----------continuous monitoring----------X																			X	X
Hospitalization		X	X----------X																				

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36 and 48 hours postdose on Day 1, predose on Days 4 to 16, predose on Day 17, and 1, 4, 12, 24, and 48 hours postdose on Day 17.
(b) Height will be measured at Screening only. Weight will be measured at Screening, on Day -1, and 48 hours postdose on Day 17.
(c) 12-lead ECG will be measured at Screening, Day -1,presdose and 2 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose, 2 and 48 hours postdose on Day 17.
(d) Laboratory tests will be performed at Screening, Day -1, predose on Day 11, and at 48 hours postdose on Day 17.
(e) FSH will be measured in postmenopause women only.
(f) C-SSRS will be investigate at Screening Visit, Day -1, and Day 19.
(g) Samples for PGx measurements will be collected predose on Day 1.
(h) Samples for PK assessment will be collected predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose on Day 14, predose, 0.25, 0.5, 1. 1.5, 2, 4, 8, 12, 16, and 24 hours postdose on Day 17.
(i) Samples for PD assessment will be collected at 20, 16, and 12 hours predose on Day 1, predose, 1, 4, 8, 12, and 24 hours postdose on Day 1, predose on Day 11, predose on Day 14, predose, 1, 4, 8, 12, and 24 hours postdose on Day 17.
(j) Samples for PD assessment will be collected on Day -1 and 24 hours postdose on Day 17 (if it is performed).
(k) Urine samples will be collected on Day -1, at 24 hours postdose on Day 1, and 24 hours postdose on Day 17.
(l) Samples for PK assessment at discontinuation will be collected if it is possible.
(m) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. Schizophrenia usually develops at late adolescence or early adulthood and manifests in maximum 1% of the population. For those who have relatives of first degree with schizophrenia, the incidence rate is higher by 10% (the concordance rate for schizophrenia in identical twins is 40% to 65%) [1][2][3]. Symptoms of schizophrenia can be subdivided into 3 broad classes: positive, negative, and cognitive symptoms [4]. Positive symptoms include hallucinations, delusions, and disordered thought and speech, and can be summarized as psychosis. Negative symptoms include reduced emotion, reduced ability to experience pleasure (anhedonia), lack of motivation, and reduced social interaction. Finally, cognitive symptoms include poor information processing, impaired ability to focus on objectives, and abnormalities of working memory and learning [4]. Currently available antipsychotics are broadly effective for the treatment of positive symptoms. However, the negative symptoms and cognitive impairment of schizophrenia are the known particular aspects that cause dysfunction, for which no therapy has been approved. There still are significant unmet medical needs.

Hypofunction of N-methyl-D-aspartic acid (NMDA) receptor is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain [5]. D-amino acid oxidase (DAAO) contributes to the metabolism of D-serine in the brain and is highly expressed in the cerebellum. Changes in the D-serine levels or D-serine to total serine ratios have been reported in the plasma of patients with schizophrenia both naive and under drug treatment [6]-[9]. 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 DAAO resides [10]. Therefore, inhibition of DAAO is considered to be a promising target in treatment of schizophrenia.

TAK-831 is a highly selective and potent inhibitor of DAAO. TAK-831 increased D-serine levels in the cerebellum of normal mice and showed efficacy in a mouse model of Friedreich ataxia (FRDA) mouse models. It also demonstrated a positive effect on cognition and social interaction in rodent cognition and behavioral models.

As stated above, TAK-831 is expected to provide a therapeutic effect on FRDA and cognitive impairment as well as negative symptoms associated with schizophrenia.

4.2 Rationale for the Proposed Study

TAK-831 is currently under development for the treatment of FRDA and cognitive impairment as well as negative symptoms of schizophrenia. Three overseas phase 1 studies in healthy adults (single and multiple dose study [TAK-831-1001], positron emission tomography [PET] study to determine DAAO brain enzyme occupancy [TAK-831-1003], and a study to evaluate the food effect [TAK-831-1004]) have been conducted so far, in which TAK-831 was well-tolerated.

In addition, two phase 1 studies in healthy adults (study with single and multiple doses at high dose level [TAK-831-1005] and bioequivalence study [TAK-831-1006]) are being conducted or planned. Two phase 2 studies in patients with schizophrenia (small-scale crossover study to examine the cerebellar functions [TAK-831-2001], and a study to evaluate the efficacy and safety for negative symptoms of schizophrenia [TAK-831-2002]) are also underway. Besides, a phase 2 proof-of-concept (POC) study in patients with schizophrenia is being planned in China. Based on the result of these phase 2 studies, a phase 3 global study (long-term study) has been planned.

In parallel with these development plans, TAK-831 is also being developed in Japan for the treatment of cognitive impairment and negative symptoms associated with schizophrenia. In respect of FRDA, a genetic disease, since there has been no confirmed report as of June 2018 that clearly indicates the existence of Japanese patients, no development plan has been made for FRDA in Japan.

Enrollment of Japanese patients into the phase 3 global study and the phase 2 POC study in China has been considered. This study was planned to examine the safety and pharmacokinetic (PK) of TAK-831 in Japanese as well as to evaluate the safety and PK in Asian healthy subjects for the aforementioned studies.

4.3 Benefit/Risk Profile

Because this study will be conducted in healthy adults, there is no benefit to subjects.

The following risk mitigation measures will be implemented in this study. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, and the phase 1 studies (4 studies, including preliminary data of TAK-831-1005). Procedures may be added during the study as necessary based on evaluation of any additional clinical or nonclinical data.

The safety of TAK-831 has been studied in a prior single dose (up to 750 mg in suspension and 100 mg T1 tablet formulation) and multiple dose (up to 400 mg once daily [QD] in suspension) study in healthy Western subjects (TAK-831-1001), a single dose (up to 500 mg in suspension) PET study to investigate DAAO occupancy in the brain (TAK-831-1003) and a single dose food effect (400 mg T2 tablet formulation) study (TAK-831-1004). These studies have not resulted in a safety signal that would prevent additional studies. Additionally, TAK-831 given as single and 14 days multiple doses (up to 1200 mg in suspension and 600 mg T2 tablet formulation) is currently being studied in healthy adult subjects (TAK-831-1005). TAK-831 has been safe and well tolerated to date (provisional data as of end-April 2018).

- 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 pharmacodynamics (PD) monitoring (venipuncture may cause bruising), and the placement of ECG pads (which may cause some local redness and/or erythema/itching).

- In case of serious adverse events (SAE), 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 Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered to monitor emergent suicidality.

The Investigator's Brochure should be referred for more detailed safety of TAK-831.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed on the basis of the following hypothesis.

- TAK-831 given as single or multiple doses shows no safety issue and is well tolerated.
- The PK of TAK-831 given as single or multiple doses to Asian subjects is equivalent to that in Western subjects.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.2 Trial Secondary Objective

To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.3 Trial Exploratory Objective

To assess the effect of TAK-831 on the concentrations of D-serine and L-serine in plasma (and concentrations of D-serine and L-serine in cerebrospinal fluid as necessary) after TAK-831 administration to healthy Asian subjects.

5.3 Endpoints

5.3.1 Primary Endpoint

Safety: Adverse events (AEs), laboratory tests, vital signs, weight, 12-lead electrocardiogram (ECG)

5.3.2 Secondary Endpoints

PK: The following parameters will be calculated.

- C_{max} (Cohort 1, Day 1 of Cohorts 2 to 4)
- $C_{max,ss}$ (Day 17 of Cohorts 2 to 4)
- t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 4)
- AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 4)
- AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 4)
- AUC_{τ} (Days 1 and 17 of Cohorts 2 to 4)

5.3.3 Exploratory Endpoints

- PK: $R_{ac\ (Cmax)}$ and $R_{ac(AUC)}$ on Days 1 and 17 (Cohorts 2 to 4), $t_{1/2z}$, CL/F, V_z/F
- PD: Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (Days -1 and 18) (may be assessed in Cohort 2 or thereafter based on PD in plasma)

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, PK and PD of TAK-831 in healthy adult Asian subjects. This study will include up to 4 cohorts of healthy adult Japanese or Chinese subjects.

In Cohort 1, a single dose of TAK-831 will be administered at each dose level under a 3-sequential dose escalation design. Eight healthy adult Japanese subjects will be randomized to the sequence of administration A, B, and C at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Days 1 and 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge.

In Cohort 2, a single dose of study drug will be administered to healthy adult Japanese subjects, followed by multiple doses. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Cohorts 3 and 4 will be optional, in which a single dose of study drug will be administered followed by multiple doses, and may be studied based on emerging data from Cohorts 1 and 2.

Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Table 6.a shows the summary of cohorts, and Figure 6.a shows the schematic of the trial design.

Table 6.a Summary of Cohorts

Cohort	Subject	Dose	Remarks
1	Japanese 8 subjects	Part 1: 100 mg (4×25 mg T3 tablet formulation) Fasted, single dose	Wash out period between part 1 and 2 will be 8 days.
		Part 2: 300 mg (1×300 mg T3 tablet formulation) Fasted, single dose	
2	Japanese 8 subjects	600 mg (2×300 mg T3 tablet formulation) Fasted, single dose + multiple dose (once daily)	
3	Chinese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 3 may be run if emerging data from Cohorts 1 and 2 suggest ethnic-related differences in the tolerability and/or PK profile. Dose level will be determined based on the results from Cohorts 1 and 2.
4	Japanese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 4 may be run based on the emerging data from Cohorts 1 and 2 in Asian subjects.

TBD: To be decided

Figure 6.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - -Hospitalization- - - - -►			◄- - - - -Hospitalization- - - -►		

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion.

<Cohorts 2 to 4>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening	Hospitalization	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- - - - - - - - - - - - - - - - - - -Hospitalization- - - - - - - - - - - - - - - - - - -►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion

6.2 Cohort transition/Dose Escalation

In Cohort 1, TAK-831 100 mg or placebo will be administered on Day 1 (Part 1) followed by confirmation of the safety and tolerability (AEs, physical examination, vital signs, weight, laboratory tests and 12-lead ECG) up to 72 hours postdose, and then TAK-831 300 mg or placebo will be administered on Day 9 (Part 2) followed by confirmation of the safety, tolerability and PK up to 72 hours postdose.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohort 1 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether the subsequent cohort should be run.

In Cohort 2, TAK-831 600 mg or placebo will be administered on Day 1, followed by confirmation of the safety and tolerability up to 72 hours postdose. Then, multiple doses of TAK-831 600 mg or placebo will be administered on Days 4 to 17. The data on safety and tolerability up to 48 hours postdose and PK up to 24 hours postdose will be examined.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohorts 1 and 2 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether Cohorts 3 and 4 should be run.

In Cohort 2 and onwards, the dose will be escalated but the dose escalation will be discontinued according to the following discontinuation criteria. The dose in Cohort 2 will be adjusted based on the safety and tolerability as well as PK and PD in Cohort 1.

Discontinuation criteria for dose escalation:

- Exposures in any cohort exceed those observed at the highest dose tested in monkey (C_{max} of 3680 ng/mL, AUC_{24} of 35700 hr*ng/mL)
- 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 changes 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 for Study Population

The subject of this study is Japanese or Chinese with a purpose to support the future conduct of studies in Asian subjects. The study will be conducted in healthy adult subjects without any

disease including circulatory or cerebrovascular diseases to appropriately assess the safety and tolerability as well as PK and PD of TAK-831.

6.3.2 Rationale of Trial Design

With a purpose to assess the safety and tolerability as well as the PK and PD profiles of TAK-831 when administered to Asian subject for the first time, this study employed a design with both single and multiple doses.

6.3.3 Rationale for Dose

To this date, the highest dose of TAK-831 tested in healthy Western subjects is 1200 mg (suspension formulation) once daily in the study TAK-831-1005. Based on the preliminary results, there were no significant adverse effects reported at this dose level, and as shown in Table 6.b, the mean steady-state exposure was C_{max} of 3015 ng/mL and AUC_{24} of 10501 h*ng/mL. The dose regimen of 600 mg given once daily (T2 tablet formulation) was also well tolerated and safe in healthy Western subjects. As for the mean steady-state exposures, C_{max} was 1494 ng/mL and AUC_{24} was 5090 h*ng/mL. This exposure at 600 mg was similar to that of monkeys at 100 mg/kg/day, the no-observed-adverse-effect-level (NOAEL).

In the study TAK-831-1005, the PK and PD of TAK-831 given as multiple doses at 100 and 600 mg (per day) to non-Japanese subjects was examined. The dose of 300 mg will be further examined in the study.

Based on the above, the doses of 100, 300 and 600 mg were selected for this study in consideration to the safety in humans as well as the comparability of PK and PD between non-Japanese and Japanese subjects.

In the 13-week repeat dose toxicity study in monkeys that are considered the more sensitive species than rats, adverse effects (vomiting, diarrhea, and loose stool) were noted at 600 mg/kg/day. The NOAEL was 100 mg/kg/day for both sexes.

TAK-831 has been administered at doses up to 1200 mg to non-Japanese, and no SAE has been reported with exposures exceeding the NOAEL. Besides, the adverse effects (vomiting, diarrhea, and loose stool) noted at a dose of 600 mg/kg/day in the 13-week repeat dose toxicity study in monkeys will be easily monitored in clinical trials.

Therefore, it is considered possible to administer doses exceeding the NOAEL exposure by carefully examining the safety and PK in each Cohort in this study. However, We have no information on toxicity at the level exceeding the exposure at 600 mg/kg/day in the 13-week repeated dose toxicity study in monkeys. Dose escalation will be stopped if exposures exceed that at 600 mg/kg/day in monkeys.

Table 6.b PK Parameters in 13-week Repeated Dose Toxicity Study in Monkeys and TAK-831 Given as Multiple Doses to Healthy Adult Subjects

Animal species-Study	Dose (mg/kg/day or mg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
Monkey 13-week (Day 91)	100 mg/kg/day (NOAEL)	1340 (male) 1270 (female)	7490 (male) 9190 (female)
	600 (300 BID) mg/kg/day	4650 (male) 2710 (female)	45500 (male) 25900 (female)
Human MRD (Day 16)	1200 mg QD (suspension formulation)	3015	10501
Human MRD (Day 16)	600 mg QD (T2 tablet formulation)	1494	5090

BID, twice daily; MRD, multiple repeated dose; NOAEL, no-observed-adverse-effect-level; QD, once daily

6.3.4 Rationale for Endpoints

6.3.4.1 Safety Endpoint

The safety endpoints in this study were defined to determine the safety and tolerability following a single dose and multiple dose of TAK-831. These are standard endpoints in the Phase 1 studies in healthy subjects.

Since TAK-831 involves effects on the central nervous system, the C-SSRS will be administered to assess the influence on suicidal ideation or suicidal behavior.

6.3.4.2 Pharmacokinetic Endpoint

Concentrations of TAK-831 in plasma will be examined to assess the PK of TAK-831 given as a single dose or multiple doses to healthy adult Asian subjects, and then the following PK parameters will be calculated.

- PK parameters: C_{max}, $C_{max,ss}$ (Cohorts 2 to 4), t_{max}, AUC_{last}, AUC_{∞}, AUC_{τ} (Cohorts 2 to 4), $R_{ac(Cmax)}$ (Cohorts 2 to 4), $R_{ac(AUC)}$ (Cohorts 2 to 4), $t_{1/2}$, CL/F, V_z/F

6.3.4.3 Pharmacodynamic Endpoint

Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max} following TAK-831 doses will be examined to assess the PD of TAK-831 in healthy adult Asian subjects. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid may be assessed as necessary.

6.3.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

The objective of this section is to specify the sequence of procedures in the cases where the timing of each procedure overlaps.

- Safety evaluation will be conducted within the predetermined allowance window as far as possible.
- Blood samples for PK assessment will be collected at time points as close to the specified time as possible.
- Other procedures must be completed at time points as close to the specified or planned hours as possible irrespective of before or after the specified times.
- If the timing of blood sampling and ECG or vital signs measurement overlap, blood sampling should be prioritized. ECG or vital signs measurement may be performed within an acceptable time window (Appendix C).
- The priority may be changed upon agreement between the investigator and the sponsor based on discussion.
- Any test and procedure necessary to immediately assess safety concerns at the time of AEs must be prioritized over other regular predetermined procedures.
- The safety of subjects in the follow-up period may be confirmed by telephone unless abnormal, clinically significant findings are observed upon discharge.

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

The entire study will start when the first subject signs the informed consent form to participate in this study.

6.4.2 Definition of End of the Trial

The study will end when the last subject completes the last planned visit or follow-up visit (or last communication [may be via telephone] relating to the planned visit) or is withdrawn from the study or lost to follow up (the status that the subject cannot be reached by the investigator).

6.4.3 Definition of Trial Discontinuation

The study may be discontinued for reasons other than safety such as the followings:

- A finding (eg, PK, pharmacodynamics, efficacy, biologic targets) from the other nonclinical or clinical studies results with the study drug in the study discontinuation for non-safety related reasons.
- Data from drugs classified in the same class as the study drug, or methodologies used in this study become available and results in the study being stopped for a non-safety related reason.
- Study discontinuation due to non-scientific and non-safety-related reasons, such as slow enrollment.

Discontinuation of the clinical study for safety reasons:

- The study is prematurely terminated because other clinical or non-clinical trials where TAK-831 or other drugs of the same class are administered have confirmed unexpected safety concerns based on the methodology used in this study

6.4.4 Criteria for Premature Termination or Suspension of the Trial

6.4.4.1 Criteria for Premature Termination or Suspension of the Trial

The study will be completed as planned unless 1 or more of the following criteria are met that require temporary suspension or early termination of the study.

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

6.4.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the Sponsor, an institutional review board (IRB), or a regulatory authority elects to terminate or suspend the study, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

6.4.5 Criteria for Premature Termination or Suspension of a Study Site

6.4.5.1 Criteria for Premature Termination or Suspension of a Study Site

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

6.4.5.2 Procedure for Premature Termination or Suspension in a Study Site

In the event that the Sponsor, an IRB, or a regulatory authority elects to terminate or suspend of the study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) ≥18.5 kg/m^2 and ≤25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the following birth control requirements:
    - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug. No restrictions will be required for a vasectomized male subject provided the subject is at least 1 year post bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
    - Is a male subject who agrees to not donate sperm from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug.
    - Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
        a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or ≥6 months of spontaneous amenorrhea in females aged >45 years with

serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels should be required.

b) Hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

c) Had a tubal ligation with appropriate documentation of surgical procedure.

d) Congenital conditions such as uterine aplasia etc.

[Rationale for the inclusion criteria]

Inclusion criteria 1, 2, 5, 8 and 9:

These are standard criteria for clinical pharmacology studies in healthy adult subjects and defined in consideration to the safety of subjects.

Inclusion Criterion 3:

This is a standard criterion for clinical pharmacology studies in healthy adult subjects for sex. This is a standard criterion for clinical pharmacology studies in healthy adult subjects for age.

Inclusion Criterion 4:

This is the range of normal weight in the diagnosis criteria for obesity and obesity disease [11] proposed by the Japan Society for the Study of Obesity.

Inclusion Criterion 6:

This is set to appropriately assess the safety and PK in Chinese.

Inclusion Criterion 7:

This is set to eliminate the influence by dietary habits on the PK.

7.2 Exclusion Criteria

The subject will be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or diseases.
2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the trial procedure in the previous trial to the Screening Visit of the current trial.
3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).

5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec at the Screening Visit or Check-in.

[Rationale for the exclusion criteria]

Exclusion Criteria 1, 15:

This is set to eliminate the influence on safety evaluation for TAK-831.

Exclusion Criterion 2:

This is a minimum duration in which the previous clinical trial is considered to have no influence in reference to "General Considerations for Clinical Trials" [12] in order to ensure the safety of subjects.

Exclusion Criteria 3, 4, 6, 7, 12, 13, 14:

These are standard criteria for clinical pharmacology studies and defined in consideration to the safety of subjects.

Exclusion Criterion 5:

This is defined in consideration to the safety of subjects.

Exclusion Criteria 8, 9, 11:

This is defined in consideration to the safety of subjects. This is also defined for potential influence on PK and PD assessment.

Exclusion Criterion 10:

This is set to exclude subjects who have a known hypersensitivity to any component of the formulation of TAK-831 or related compounds in consideration of the safety of subjects.

7.3 Excluded Medications Supplements, Dietary Products

Table 7.a shows excluded medications, supplements, and dietary products.

Use of the drugs listed on Table 7.a (prescribed drugs and over-the-counter [OTC] drugs), vitamins, supplements, and dietary products will be excluded from a specified time point to until discharge given the effect on the safety and PK. Use of prohibited concomitant drugs will be allowed when the investigator or sub-investigator deems it necessary to use any of the concomitant drugs for reasons including treatment of an AE.

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

Table 7.a Excluded Medications, Supplements, Dietary Products

From 28 days before admission (Day -1) to the last discharge	7 days before admission (Day -1) to the last discharge	72 hours before admission (Day -1) to the last discharge
• Prescription drugs • Supplements (St. John's wort, ginseng, kava kava, ginkgoes, chinese herbal medicine, and melatonin) • Vaccination/vaccine (b) • Nicotine-containing products • CYP 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1 and 2A6 inhibitors/inducers OTC drugs (c)	• OTC drugs (including aspirin or aspirin-containing drugs) (a) • Vitamins • Beverages containing grapefruit (fruit juice, flesh), star fruits (fruit juice, flesh), citrus aurantiums (high acidity), orange (seville oranges), or marmalade • Apple, orange or pineapple juice • Brassicaceae vegetables (kale, cress, collard greens, kohlrabi, brussels sprouts, and mustard). • Meat cocked over the charcoal • Alcohol containing products	• Caffeine or xanthine containing products

CYP: cytochrome P-450, OTC drugs: over-the-counter drugs
Note: Excludes the drug needs to be administered to treat an AE and if the investigator or sub-investigator considers necessary to use the drug
(a) Use of paracetamol (≤1 g/daily) will be allowed.
(b) Includes H1N1 and other influenza vaccines, however, not limited to these medications.
(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Diet and fluid (except water) must be ingested at least10 hours before clinical laboratory tests.

On the day before clinical laboratory tests, evening meal must be ingested by 21:00.

During hospitalization, pre-specified diets must be ingested, and other diets will be prohibited. After discharge, excessive drinking and eating must be avoided until completion of follow-up period.

Subjects will be instructed to fast for at least 10 hours before study drug administration.

Subjects in Cohort 2-4 will be instructed to fast for an additional 4 hours on Days 1, 4 and 17 and 2 hours for all other study drug administration days.

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

Subjects should be prohibited from drinking any liquid from 1 hour before to 1 hours after study drug administration, with the exception of water (150 mL) taken with the study drug.

7.4.2 Activity

Smoking is prohibited during the study.

Excessive exercise is prohibited during the study.

Blood donation is prohibited for at least 12 weeks (84 days) from completion of the last test.

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the visit in advance whenever possible, and should be reported the circumstances and therapy after visit. The investigator or sub-investigator should communicate that medical institution about the subject's participation in the study.

7.5 Documentation of Subject Failure

The investigator or sub-investigator must account for all subjects who sign informed consent. If a subject discontinues the study before the first study drug administration, the investigator or sub-investigator should complete the electronic case report form (eCRF).

The primary reason for subject failure is to be recorded in the eCRF using the following categories:

- Death
- AE
- Screening failure (failed inclusion criteria or did meet exclusion criteria) <specify the reasons>
- Protocol deviation
- Lost to follow up
- Withdrawal by subject <specify the reasons>
- Study terminated by the Sponsor
- Pregnancy
- Sample size sufficient
- Other <specify the reasons>

Any subject identification number, once assigned to a subject, should not be reused if the assigned subject discontinues the study prior to the first study drug administration. Nevertheless, if a reserve subject is enrolled in the other cohort, the same subject identification number may be used.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

Primary reasons for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF using the following categories. For the subject who is withdrawn from the study before the first study drug administration in Period 1, refer to Section 7.5.

1. Death
   The subject died on study.

   Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). Refer to Section 10.2.9.3 for reporting procedures.

2. 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.

   The study drug will be immediately discontinued if a condition meets any following criteria during the treatment, and appropriate follow-up will be performed (clinical laboratory tests will be repeatedly performed until the clinical laboratory test profiles have normalized or returned to baseline, refer to Section 9.2.9.1):

   - Liver Function Test (LFT) Abnormalities
     - ALT or AST >8×the upper limit of normal (ULN), or
     - ALT or AST >5×ULN and persists for more than 2 weeks, or
     - ALT or AST >3×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (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%)
   - Prolonged QT/QTcF intervals

     If at least one remarkable prolonged QT interval was observed on 12-lead ECG (eg, absolute value of QTcF intervals >500 msec or an increase >60 msec from baseline), and the investigator or sub-investigator considered inappropriate to continue the study.

3. Protocol deviation
   The discovery after the start of the first study drug administration 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.

4. 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 in the subject's source documentation.

5. Pregnancy
   If a subject was found to be pregnant.

   Note: Participation in the study is immediately discontinued for any pregnancy. Refer to Appendix B for the procedures.

6. Voluntary withdrawal
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

7. Study terminated by the Sponsor
   The Sponsor terminates the study.

8. Other

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

7.7 Procedures for Discontinuation or Withdrawal of a Subject

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

7.8 Subject Replacement

The Part 1 in Cohort 1 and Cohorts 2-4 can have a few reserve subjects considered eligible for participation in the study based on screening test. If a subject has not received the study drug as scheduled during the study owing to any reason occurring before the study drug administration, a reserve subject will be allowed to participate in the study.

If a subject withdraws from the study after initiation of the study drug, the subject will not be replaced with a reserve subject.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

[Drug product]

Code name: TAK-831

Dosage form and strength:

TAK-831 tablet is a yellowish-red film-coated tablet containing 25 or 300 mg of TAK-831.

TAK-831 placebo tablet contains no TAK-831 and has same appearance as TAK-831 tablet.

8.1.1 Clinical Study Drug Labeling

Study drug labeling will show name of the study drug, quantity and storage condition of the study drug, manufacture number, expiration date, protocol number, name and address of the Sponsor, and statement the drug is for clinical trial use only.

8.1.2 Clinical Study Drug Inventory and Storage

TAK-831 is stored at a room temperature (1°C to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used, or returned to the Sponsor or its designee. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Randomization Code Creation and Storage

The personnel responsible for randomization (the Sponsor's designee) will prepare the randomization table/schedule prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.4 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigator must store the emergency key until the time of an emergency blind break or the end of the trial.

Since maintenance of the blind may be compromised because of results from drug concentrations and PD assessments, such results should not be disclosed prior to blind breaking. In the event that results must be reported to the investigator prior to breaking the blind, all efforts should be made to maintain the blind (eg, by changing a medication identification number in order to avoid identification of subjects by laboratory site personnel). Detailed procedures for measuring subject drug concentration levels and PD assessments will be provided in the separately created procedure for directions on the handling of biological samples for measuring drug concentrations and PD assessments.

To unblind a subject, the study drug blind can be obtained by opening a sealed envelope.

The Sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded in the eCRF.

If the investigator or sub-investigator breaks the blinding of the study drug, study drug must be stopped immediately and that subject must be withdrawn from the study.

No change should be made to any subject assessment after unblinding (except cases where the investigator or sub-investigator is not informed of unblinding information [unblinding for open-label analysis for the Sponsor]).

8.1.5 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (a site designee) will receive the pharmacy manual created by the Sponsor, and follow the procedures for managing the Sponsor-supplied drug supplies. A copy of these procedures will be provided to the investigator as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the Sponsor-supplied drug. The manual will also describe procedures for the collection of unused medications from the subject and their return to the Sponsor, or the destruction of any unused supplies.

The on-site pharmacist (a site designee) will immediately return any unused study drugs in a sealed package to the Sponsor after the study is closed at the investigational site.

9.0 STUDY PROCEDURES

The investigator or sub-investigator should collect data according to the procedures described in the following sections. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site designee whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the initiation of any study procedures. The requirements of informed consent are described in Section 13.2.

A separate informed consent form pertaining to the collection, storage, and analysis of samples must be obtained prior to collecting any blood sample for pharmacogenomic research for this study.

9.1.1.1 Assignment of Subject Identification Number

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

9.1.1.2 Study Drug Assignment

In Cohorts 1-2 and Cohorts 3-4 (if added), the subjects will be assigned in the order of medication identification number by Cohort according to the randomization code. The medication identification number will be a 4-digit number, starting with the following number:

Cohort 1: 1001, Cohort 2: 2001, Cohort 3: 3001, Cohort 4: 4001

The assigned medication identification number will be used to identify the samples for PK by the study site and the only number to identity a subject during blood sampling for PK. The number will be always shown on the sample vials, which are sent to the laboratory to evaluate the PK. The laboratory will report the results using this number. The number will be used for only the purpose described in this section and cannot be replaced with the 7-digit subject identification number, which is assigned at the time of informed consent procedure and used in all other procedures during the clinical study period to identify a subject. In case of subject replacement, the study drug with a medication identification number for the withdrawn subject will be used by the replacing subject.

9.1.2 Inclusion and Exclusion

Each subject will be assessed according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Demographic information to be obtained will include date of birth, sex, height, weight, caffeine use, alcohol use, and smoking status of the subject.

Medical history to be obtained will include determining whether the subject has any clinically significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions. Medication history information to be obtained will include any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Subjects will be asked whether they have taken any medication other than the study drug (used from the signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC drugs, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication names, route of administrations, start and end dates, and reasons for use.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

9.2.2 Height and Weight

Each subject should have a height and weight measured. Height will be recorded in centimeters without decimal places (rounding off the first decimal place). Weight will be collected in kilograms (kg) with the first decimal place (rounding off the second decimal place).

9.2.3 BMI

BMI is calculated using the formula provided below.

Metric: BMI=weight (kg)/height $(m)^2$

The values should be calculated to the first decimal place (rounding off the second decimal place). When the BMI is used as entry criteria, then this determination must be made after rounding.

9.2.4 Vital Signs

Vital signs will include body temperature (axilla measurement), sitting blood pressure (systolic and diastolic, after resting more than 5 minutes), and pulse (beats per minute).

9.2.5 12-Lead ECG

A standard 12-lead ECG will be recorded. Subjects should be resting in a recumbent position for at least 5 minutes before each ECG measurement.

The investigator or sub-investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: normal or abnormal. If an ECG is abnormal, the investigator or sub-investigator (or a qualified observer at the investigational site) will judge clinical significance of the abnormality. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTcF.

9.2.6 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be performed at the study procedures-specified time point. The investigator or sub-investigator will evaluate suicide risks based on the information obtained from C-SSRS. For any suicidal ideation and suicidal behavior will be documented as an adverse event.

9.2.7 Study Drug Administration

In Cohort 1, a single dose of TAK-831 T3 tablet 25 mg×4 tablets or placebo will be orally administered on Day 1 (Part 1), and a single dose of TAK-831 T3 tablet 300 mg×1 tablet or placebo will be orally administered on Day 9 (Part 2).

In Cohort 2, a single dose of TAK-831 T3 tablet 300 mg×2 tablets or placebo will be orally administered on Day 1, followed by multiple doses of TAK-831 T3 tablet 300 mg×2 tablets (once daily) or placebo on Days 4-17.

The study drug will be orally administered with 150 mL of water at a fasted state (fasted at least 10 hours before administration).

In Cohorts 3 and 4, the dose of the study drug will be determined based on the data obtained from Cohorts 1 and 2.

9.2.8 AE Monitoring

AE monitoring will begin after the signing of informed consent. A complete description of AE collections and procedures is provided in Section 10.2.

9.2.9 Laboratory Procedures and Assessments

Laboratory samples will be taken following a minimum 10 hour overnight fast on the days stipulated in the Schedule of Study Procedures (Section 3.0). Refer to Appendix C for the amount of blood samples.

The investigator or sub-investigator will take responsibility for evaluation of the clinical laboratory test results and storage. The investigator will maintain a copy of the reference ranges for the laboratory used.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Red blood cell count	White blood cell count and differential leukocytes (lymphocytes, neutrophils, eosinophils, basophils, and monocytes)
Hemoglobin	Hematocrit
Platelet count	

Chemistry

Chemistry evaluations will consist of the following chemistry tests:

Albumin	Creatinine
ALP	Glucose
ALT	Sodium
AST	Calcium
γ-GTP	Creatine kinase
Total bilirubin	Potassium
Direct bilirubin	Chloride
Total protein	PT
Urea nitrogen	APTT

Urinalysis

Urinalysis will consist of the following tests:

pH	Specific gravity
Qualitative (protein, glucose, occult blood, and nitrite)	Urinary sediment (erythrocytes, leukocytes, and cylinder) (a)

(a) Will be performed for any abnormal urinalysis parameter.

Other

Immunological tests HIV antibody and antigen tests, hepatitis tests (HBs antigen and HCV antibody)
Alcohol tests (urinalysis or breath test)
Urinary drug tests
FSH (postmenopausal female subjects only)

HIV: human immunodeficiency virus, HBs: hepatitis B surface antigen, HCV: hepatitis C virus, FSH: follicle-stimulating hormone

Note: The investigator or sub-investigator will report the results of immunology, urine drug tests, and alcohol tests directly to subjects. The Sponsor will confirm the overall test results (as "Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug.

If subjects experience an ALT or AST of >3×ULN (except the tests at Screening), follow-up laboratory tests (at a minimum, serum alkaline phosphatase [ALP], ALT, AST, total bilirubin,

gamma-glutamyl transferase [γ-GTP], and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Refer to Section 7.6 and Section 10.2.9.4 for the discontinuation or withdrawal criteria of a subject and the appropriate guidance on reporting abnormal LFTs as SAEs, respectively.

9.2.9.2 Urine sample for Future Tests

Urine samples for future tests will be collected according to the Schedule of Study Procedures (Section 3.0).

If acute renal failure is suspected, urinary biomarkers such as KIM-1, NGAL, and cystatin C may be measured using the collected sample.

9.3 Biomarker, PK, PD, and PGx Samples

Samples for PK, PD, and PGx will be collected according to the schedule of study procedures (Section 3.0). Separated procedures describe the details of sampling, handling, and transferring to central laboratory. The actual sampling time for PK and PD analyses will be documented in the subject's source documents and eCRF.

Table 9.a shows primary specimen collections.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	PK Analysis	Mandatory
Plasma sample for PD	Blood	Plasma	PD analysis	Mandatory
Cerebrospinal fluid sample for PD	Cerebrospinal fluid	Cerebrospinal fluid	PD analysis	Optional
Blood sample for DNA PGx	Blood	DNA	PGx analysis	Optional

9.3.1 PK Measurements

The following PK parameters will be calculated from plasma concentrations of TAK-831, unless otherwise specified.

Mark/Term	Definition
Plasma	
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to time of infinity
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
C_{max}	Maximum observed plasma concentration (measured value)
$C_{max, ss}$	Maximum observed steady-state plasma concentration during a dosing interval (measured value)
t_{max}	Time of first occurrence of C_{max}
$t_{1/2z}$	Terminal disposition phase half-life
λ_z	Terminal disposition phase rate constant
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration
CL/F	Apparent clearance after extravascular administration
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}
$R_{ac(AUC)}$	Accumulation ratio based on AUC

9.3.1.1 Plasma for PK Measurements

Blood samples for plasma TAK-831 concentration will be collected (Table 9.b). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.b Blood Sample Collection for PK Analysis

Dose Levels:	Date of administration	Sampling time
Single dose	1	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
	9	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	1	Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, and 48 hours postdose
	4, 11, 14	Predose
	17	Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16, and 24 hours postdose

9.3.2 PD Analysis

The following PD parameters will be calculated from plasma concentrations of D-serine and L-serine, unless otherwise specified

Mark/Term	Definition
Plasma	
$AUEC_{24}$	Area under the effect-time curve from time 0 to 24 hours postdose
E_{max}	Maximum effect
time to E_{max}	Time to reach maximum PD effect

9.3.2.1 Plasma Samples for PD Analysis

Blood samples will be collected to measure plasma D-serine and L-serine concentrations (Table 9.c). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.c Blood Sample Collection for PD Analysis

Dose Levels:	Specimen	Date of administration	Sampling time
Single dose	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
		9	Predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, and 24 hours postdose
		11, 14	Predose
		17	Predose, 1, 4, 8, 12, and 24 hours postdose

9.3.2.2 Cerebrospinal fluid samples for PD Analysis

Cerebrospinal fluid will be collected to measure D-serine and L-serine concentrations (3.0 mL per scheduled time). The cerebrospinal fluid sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples. After Cohort 2, collection of cerebrospinal fluid in the next Cohorts will be determined based on the results of plasma D-serine and L-serine concentrations obtained from the previous Cohorts.

9.3.3 PGx Measurements

9.3.3.1 Blood Sample for DNA PGx Measurements

When sampling of whole blood for pharmacogenomic analysis occurs, the subject must sign informed consent/be consented separately for PGx sampling, storage and analysis. PGx measurement is a part of the study, but participation of a subject is optional.

One 6-mL of whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected prior to the single dosing on Day 1 from each consenting subject in the study.

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. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification by the Sponsor. “Stored samples” are defined as samples that are 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 the study drug or related drug.

The sampling of whole blood for PGx and genotyping analysis is mandatory. Every subject must sign informed consent separately for PGx sampling. DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms.

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 exploratory research with the samples for PGx measurements.

9.3.4 Confinement

Cohort 1:

Subjects will be hospitalized from Day -1 to Day 4 and Day 8 to Day 12 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Days 4 and 12.

Cohorts 2-4:

Subjects will be hospitalized from Day -1 to Day 19 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Day 19.

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 clinical study; it does not necessarily have to have a causal relationship with the the treatment (including the study drug) or study participation.

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered 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 or sub-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 may be considered as AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring for an abnormal value are not considered as an intervention. In addition, repeated or additional non-invasive tests for verification and evaluation of abnormality or monitoring purpose will not be considered as 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 conditions and should NOT be recorded as an AE. The observations or evaluations of first examination at baseline (eg, laboratory test, ECG, X-ray,

etc) should NOT be recorded as AEs 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). The investigator or sub-investigator 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. The investigator or sub-investigator should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a pre-existing chronic 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. The investigator or sub-investigator 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 drug or after any change in study drug, the worsening or complication should be recorded as a new AE. The investigator or sub-investigator should ensure that the event term reported captures the change in adverse event (eg, "worsening of…").

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to the signing of informed consent are not considered AEs. However, if a preplanned procedure is performed earlier (eg, as an emergency) due to a worsening of a 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 study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the sub-investigator to decide whether a dose is to be considered as overdose, in consultation with the Sponsor.

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.9.
- 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 Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

Severity/Intensity of AEs will be classified or defined as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying disease, 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 the underlying disease, complications, concomitant medications and concurrent treatments.

10.2.3 Assigning Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

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

10.2.4 Start Date

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

10.2.5 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.

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken with Study Treatment

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

10.2.8 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/signs/symptoms have almost disappeared; the abnormal laboratory values improved, but have 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 values on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.9 Collection and Reporting of AEs, SAEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent and continue until the follow-up visit or phone call.

10.2.9.2 Reporting AEs

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

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator or sub-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 Adverse Event (Frequency)
- Severity/Intensity.
- The Investigator's or sub-investigator's opinion of the causal relationship between the event and administration of study drug(s). (Related/Not related)
- Action taken with the study drug
- Outcome of the event.
- Seriousness.
- Timing of occurrence (after administration of the study drug)

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator or sub-investigator to the Sponsor within 1 business day of the first onset or notification of the SAE, along with any relevant information. The

investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. 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 or sub-investigator's name.
- Name of the study drug(s).
- Causality assessment.

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

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator or sub-investigator should complete the follow-up SAE form or provide other written documentation immediately to the Sponsor. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory values, discharge summary, postmortem results) in the institution should be submitted to the Sponsor, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.2.9.4 Reporting of Abnormal LFTs

If a subject experiences 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 10.2.9.3. The investigator or sub-investigator will contact the monitor for discussion and investigation of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease, medical history/ongoing disease. Follow-up laboratory tests as described in Section 9.2.9 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs and Regulatory Authorities

The Sponsor will report all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs and the head of the study site. 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 the study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definitions of analysis variables, and analysis methodologies to address all study objectives.

11.1.1 Analysis Sets

In this study, 3 analysis sets are defined: the Safety Analysis Set, the PK Analysis Set, and the PD analysis Set. The definition of each analysis set will be described in the SAP.

The Sponsor will verify the validity of the definitions of the analysis sets and the rules for handling data in consultation with a medical expert, as needed, prior to unblinding the study drug assignment. The Sponsor will address all remaining uncertainties not specified at planning, and will finalize the SAP prior to unblinding of subject's treatment assignment.

11.1.1.1 Safety Analysis Set

The Safety Analysis Set will be defined as all subjects who received at least one dose of study drug.

11.1.1.2 PK Analysis Set

The PK Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PK parameter.

11.1.1.3 PD Analysis Set

The PD Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PD parameter.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the Safety Analysis Set.

11.1.3 PK Analysis

Endpoints and its analytical method

[Endpoints]

Secondary endpoints: C_{max} (Cohort 1, Day 1 in Cohorts 2 to 4), $C_{max,ss}$ (Day 17 in Cohorts 2 to 4), t_{max} (Cohort 1, Days 1 and 17 in Cohort 2 to 4), AUC_{last} (Cohort 1, Day 1 in Cohorts 2 to 4), AUC_{∞} (Cohort 1, Day 1 in Cohorts 2 to 4), AUC_{τ} (Days 1 and 17 in Cohorts 2 to 4)

Exploratory endpoints: $R_{ac(Cmax)}$ and $R_{ac(AUC)}$ (Cohort 2 to 4) on Days 1 and 17, $t_{1/2z}$, CL/F, V_z/F

[Analytical method]

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of TAK-831 in plasma will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time will be presented. Plasma PK parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Day 1 and Day 9 for Cohort 1 and Day 1 for Cohorts 2 to 4. Additional analyses on dose linearity will be included if appropriate.

11.1.4 PD Analysis

Endpoints and its analytical method

[Endpoints]

- Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (on Days -1 and 18) (if available)

[Analytical method]

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent the change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

11.1.5 Safety Analysis

Endpoints and its analytical method

[Endpoints]

AEs, laboratory findings, vital signs, weight, 12-lead ECG

[Analytical method]

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2 and 4, and for Cohort 3.

11.1.5.1 AEs

A treatment-emergent adverse event (TEAE) is defined as an AE whose date of onset occurs on or after the start of study drug.

The followings will be analyzed for TEAEs. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

- Frequency of all TEAEs
- Frequency of drug-related TEAEs
- Frequency of all TEAEs by intensity
- Frequency of drug-related TEAEs by intensity
- Frequency of TEAEs leading to study drug discontinuation
- Frequency of serious TEAEs

11.1.5.2 Clinical Laboratory Evaluation

Summary statistics will be provided for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

11.1.5.3 Vital Signs

Summary statistics will be provided for the observed values at each evaluation time point and changes from baseline.

11.1.5.4 Other Safety Parameters

The ECG parameters will be summarized as follows. Summary statistics will be calculated for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables. The analysis methods for other endpoints will be specified in detail in the SAP.

11.2 Determination of Sample Size

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, and PK of each cohort. This is not based on any statistical rationale.

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.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, and informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, sub-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 or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the Sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the Sponsor and the head of the study site of the deviation or changes as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the Sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

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 study 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 [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency [MHRA], and the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory authority, the Sponsor should be notified immediately. The investigator and the head of the institution guarantee 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 Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for GCP. The investigator will conduct the study according to applicable local or regional regulatory requirements in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

The IRB must be constituted according to the applicable local requirements of each participating region. The Sponsor or the designee will require documentation noting all names and titles of the members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. The Sponsor or the designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the written informed consent form, and, if applicable, subject recruitment materials and/or advertisements, if applicable, and other documents required by all applicable laws and regulations, must be submitted to the IRB for approval. The IRB's written approval of the protocol and subject written informed consent must be obtained and submitted to the Sponsor or the designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, written informed consent form) reviewed; and state the approval date. The Sponsor will notify the study site that the Sponsor has confirmed the adequacy of the study site regulatory documentation. Until the study site receives a notification, no protocol activities, including screening, may occur.

The study site must adhere to all requirements stipulated by its respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the written 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, and submission of the investigator's final status report to IRB. All IRB 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 and the 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 written informed consent form describes 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 further explains 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 approval of the written informed consent form. The written informed consent form must be approved by both the IRB and the Sponsor prior to use.

The informed consent form must be described in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines he or she will participate in the clinical study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed by the investigator or sub-investigator to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form will be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects 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 prior to analysis. Notify the 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 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, MHRA, and PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents),

including 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 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. The investigator or sub-investigator needs to obtain a prior written approval from the Sponsor to publish any information from the study externally, such as to a professional association.

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 the facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

13.5 Clinical Trial Results Disclosure

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

13.6 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study 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 or sub-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

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.2 Investigator Agreement

A separate agreement will be provided to the study site.

14.1.3 Study-Related Responsibilities

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.4 List of Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUEC	area under the effect-time curve
BMI	body mass index
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DAAO	D-amino acid oxidase
DNA	deoxyribonucleic acid
E_{max}	maximum effect
FDA	Food and Drug Administration
FRDA	Friedreich ataxia
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
γ-GTP	gamma-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requrements for Pharmaceuticals for Human Use
INR	international normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency

Term	Definition
NMDA	*N*-methyl-D-aspartate
NOAEL	no observed adverse effect level
PET	positron emission tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
POC	proof-of-concept
R_{ac}	accumulation ratio
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occrurrence of C_{max}
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration

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 eCRFs

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

The Sponsor or its designee will supply the study sites with access to eCRFs. The Sponsor will provide training opportunities for the 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 the Sponsor (or the designee) and will be answered by the study 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.

The 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.

The following data will not be recorded in the eCRFs.

- PGx analysis results
- Clinical laboratory test results
- Drug concentration measurement results
- PD measurement results

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 or sub-investigator with use of change and modification records of the eCRFs. The investigator must review the data change for completeness and accuracy, and must e-sign.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the Sponsor or its designee. 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 or the head of the study site agree to keep the records stipulated in Section 15.1 and those documents that include (but not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated 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.

The investigator and the head of the study site are required to retain essential documents until the day specified as 1 or 2 below, whichever comes later. However, if the Sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the Sponsor.

1. The day on which marketing approval for the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion for the study.

In addition, the investigator and the head of the study site should retain the relevant essential documents until the receipt of a Sponsor-issued notification that states the retention is no longer required.

16.0 REFERENCES

[1] Sham PC, Gottesman, II, MacLean CJ, Kendler KS. Schizophrenia: sex and familial morbidity. Psychiatry Res 1994;52(2):125-34.

[2] Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999;56(2):162-8.

[3] Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo UH, Bassett AS, Cornblatt BA, Kestenbaum CJ, et al. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch Gen Psychiatry 1995;52(10):857-65.

[4] van Os J, Kapur S. Schizophrenia. Lancet 2009;374(9690):635-45.

[5] Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 2003;169(3-4):215-33.

[6] Calcia MA, Madeira C, Alheira FV, Silva TC, Tannos FM, Vargas-Lopes C, et al. Plasma levels of D-serine in Brazilian individuals with schizophrenia. Schizophr Res 2012;142(1-3):83-7.

[7] Ohnuma T, Sakai Y, Maeshima H, Hatano T, Hanzawa R, Abe S, et al. Changes in plasma glycine, L-serine, and D-serine levels in patients with schizophrenia as their clinical symptoms improve: results from the Juntendo University Schizophrenia Projects (JUSP). Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):1905-12.

[8] Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, et al. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the N-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch Gen Psychiatry 2003;60(6):572-6.

[9] Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(5):767-9.

[10] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511(7510):421-7.

[11] Japan Sciety for the Study of Obesity. Diagnostic Criteria for Obesity 2011. Journal of Japan Society for the Study of Obesity, 2011 Oct; additional edition.

[12] General Considerations for Clinical Trials (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998).

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to a sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study site in advance to get them accepted.
3. Prepare a written informed consent form and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the study site that sufficient medical care for all clinically significant AEs related to the study are provided to subjects throughout and beyond the period when subjects participate in the study, upon obtaining consent from the subject.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study site and the Sponsor in writing.
11. Determine the need of emergency key code unblinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the Sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the Sponsor with electronic signature.
14. Discuss any proposal from the Sponsor including update of the protocol.
15. Notify the head of the study site of the end of the study in writing.

Appendix B Pregnancy and Contraception

Male Subjects and Their Female Partners

From the signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, any nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use adequate contraception. In addition, they must be advised not to donate sperm during this period or subjects should refrain from having sexual intercourse from 1 month prior to the first study drug administration throughout the study period and until 35 days after the last study drug administration. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the table on containing adequate contraception below.

Female Subjects and Their Male Partners

Female subjects of childbearing potential* will be excluded from this study.

* Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation), or who are postmenopausal (eg, defined as at least 2 years since last regular menses with an FSH of >40 IU/L).

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documented absence of sperm in the ejaculate, or have had a bilateral orchidectomy.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate.

Barrier methods (each time the subject has intercourse)	Intrauterine device (IUD)	Hormonal contraceptives
Male condoms with a spermicide	Copper T PLUS condom Progesterone T PLUS condom	Combined pill

Subjects will be provided with information on acceptable methods of contraception for 95 days after last dose of study drug, as part of their informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy in partners and of sperm donations for 95 days after their last dose of study drug.

Pregnancy

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

If the pregnancy in the partner of a male subject occurs during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of his right to receive treatment information. If the subject chooses to receive unblinded treatment information, that individual's blind should be broken by the investigator or sub-investigator. Any subjects randomized to placebo need not be followed.

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

All female subjects and the the female partners of male subjects who became pregnant will be followed to final outcome, using the pregnancy form, with the consent of the female subjects or the female partners of those male subjects. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after any birth of a child will also be conducted.

Appendix C Acceptable Time Window for Study Procedure

<Cohort 1>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
	Follow-up period	Day 23	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Study treatment period (Part 1)	Day 1 72 hours postdose	Day 4 from awakening to discharge
	Washout period	Day 8	Not applicable
	Study treatment period (Part 2)	Day 9 72 hours postdose	Day 12 from awakening to discharge
	Follow-up period	Day 23	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 2 and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicabled
	Treatment period (Part 1)	Day 1 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Urinary drug tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Washout period	Day 8	Not applicable
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
Samples for PGx measurements	Treatment period (Part 1)	Day 1 predose	Not applicable
Blood samples for PK	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 1 hour postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 24 hours postdose	Within ± 2 hours
	Treatment period (Part 2)	Day 9 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, and FSH

<Cohorts 2-4>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Days 5-10 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Days 12-13 predose	From awakening to immediately prior to dose
		Day 14 predose	From awakening to immediately prior to dose
		Days 15-16 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 1, 4, 12, 24, and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 48 hours postdose	Day 19 from awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 2 and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 11 predose	From awakening to immediately prior to dose
		Day 17 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
Samples for PGx measurements	Treatment period (Single dose part)	Day 1 predose	Not applicable

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PK	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 0.25, 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	Within 15 minutes predose
		Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 0.25, 0.5, 1, 1.5, and 2 hours postdose	Within ± 5 minutes
		Day 17 4, 8, 12, 16 and 24 hours postdose	Within ± 15 minutes
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 1 hour postdose	Within ± 15 minutes
		Day 17 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
Cerebrospinal fluid samples for PD (If performed)	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 3 hours
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 24 hours postdose	Within ± 2 hours
	Teatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, FSH, and urinary drug tests

Total blood sampling volumes for an individual subject is shown below:

<Cohort 1>

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)
		Screening	Day -1	Days 1-4	Day 8	Days 9-12	
Clinical Laboratory Tests	20	1	1	1	1	1	100
Blood sampls for PK	4	-	-	12	-	12	96
Blood sampls for PD	6	-	3	9	-	9	126
Samples for PGx Measurements	6	-	-	1	-	-	6
						Total Blood Sampling Volume	**328**

-: No blood collection

<Cohorts 2-4>

Sample Type	Sample Volume (mL)	Number of Samples										Total Volume (mL)
		Screening	Day -1	Day 1	Day 2	Day 3	Day 4	Day 11	Day 14	Days 17-18	Day 19	
Clinical Laboratory Tests	20	1	1	-	-	-	-	1	-	-	1	80
Blood sampls for PK	4	-	-	9	2	1	1	1	1	11	-	104
Blood sampls for PD	6	-	3	5	1	-	-	1	1	6	-	102
Samples for PGx Measurements	6	-	-	1	-	-	-	-	-	-	-	6
											Total Blood Sampling Volume	**292**

-: No blood collection

TAKEDA PHARMACEUTICALS

PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK-831 in Healthy Adult Asian Subjects

Phase 1 Study of TAK-831 in Healthy Adult Asian Subjects

Study Identifier:	TAK-831-1002
Compound:	TAK-831
Date:	5 September 2018
Version/Amendment Number:	Amendment 1

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals	**Compound:** TAK-831
Study Identifier: TAK-831-1002	**Phase:** 1
Title of Study: Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK 831 in Healthy Adult Asian Subjects	
Trial Design: This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of TAK-831 in healthy adult Asian subjects. This study will include up to 4 cohorts of healthy adult Japanese or Chinese subjects. In Cohort 1, a single dose of TAK-831 will be administered under a 3 sequential dose escalation design, and the safety, PK and PD will be assessed. Eight healthy adult Japanese subjects will be randomized in dosing orders of A (100 mg→300 mg), B (100 mg→placebo), and C (placebo→300 mg) at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Day 1 and Day 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge. Cohort 2 will include 8 healthy adult Japanese subjects. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge. Cohorts 3 and 4 will be optional, in which a single dose will be administered followed by multiple doses, and may be studied based on emerging data from the prior cohorts. Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.	
Trial Primary Objective: To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects. **Secondary Objectives:** To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.	
Target: Healthy adult Asian subjects	
Planned Number of Subjects: Cohort 1: 8 subjects Cohorts 2 to 4: 8 subjects per cohort	**Planned Number of Sites:** 1 site
Dose Levels: <Cohort 1> Single dose at 100 mg on Day 1 (Part 1) and 300 mg on Day 9 (Part 2) (fasted) <Cohort 2> Single dose at 600 mg on Day 1. Multiple doses	**Route of Administration:** Oral

(once-daily) at 600 mg on Days 4 to 17 (fasted) <Cohort 3> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted) <Cohort 4> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted)	
Duration of Treatment: <Cohort 1> Part 1: Single dose on Day 1 Part 2: Single dose on Day 9 <Cohorts 2 to 4> Single dose on Day 1 and once-daily multiple doses on Days 4 to 17, for 14 days, in each Cohort	**Planned Trial Duration:** <Cohort 1> Screening period: Day -28 to -1 Treatment period: Days 1 to 12 Follow-up period: Day 23 <Cohorts 2 to 4> Screening period: Day -28 to -1 Treatment period: Days 1 to 19 Follow-up period: Day 31

Inclusion Criteria:

Subject eligibility will be determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) $\geq$18.5 kg/m^2 and $\leq$25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the birth control requirements.

Exclusion Criteria:

The subject must be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or diseases.
2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the

trial procedure in the previous trial to the Screening Visit of the current trial.

3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).
5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms at the Screening Visit or Check-in.

Main Criteria for Evaluation and Analyses:

Primary Endpoint

Safety: Adverse event, laboratory tests, vital signs, weight, 12-lead electrocardiogram

Secondary Endpoints

Pharmacokinetics: The following parameters will be calculated.

C_{max} (Cohort 1, Day 1 of Cohorts 2 to 4)

$C_{max,ss}$ (Day 17 of Cohorts 2 to 4)

t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 4)

AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 4)

AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 4)

AUC_{τ} (Days 1 and 17 of Cohorts 2 to 4)

Statistical Considerations:

Pharmacokinetics:

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of TAK-831 in plasma will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time will be presented. Plasma PK parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Days 1

and 9 for Cohort 1 and Day 1 for Cohorts 2 to 4. Additional analyses on dose linearity will be included if appropriate.

Pharmacodynamics:

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2 and 4, as well as Cohort 3. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

Safety:

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2 and 4, and for Cohort 3.

A treatment-emergent adverse event (TEAE) refers to an adverse event that occurs after the start of study treatment. The frequency of all TEAEs, drug-related TEAEs , all TEAEs by intensity, drug-related TEAEs by intensity, TEAEs leading to study drug discontinuation, and serious TEAEs will be summarized. TEAEs will be coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

For continuous values of laboratory findings, vital signs and other safety parameters, summary statistics will be provieded for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

Sample Size Justification:

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, PK and PD of each cohort. This is not based on any statistical rationale.

2.0 STUDY SCHEMATIC

Figure 2.a shows the schematic of the trial design.

Figure 2.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - - Hospitalization - - - - -►			◄- - - - Hospitalization - - - -►		

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion

Sequence of administration	Part 1	Washout interval	Part 2
	Day 1 to 4	Day 5 to 8	Day 9 to 12
A	TAK-831 100 mg	Washout	TAK-831 300 mg
B	TAK-831 100 mg		Placebo
C	Placebo		TAK-831 300 mg

<Cohorts 2 to 4>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening	Hospitalization	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- - - - - - - - - - - - - - - - - - Hospitalization - - - - - - - - - - - - - - - - - - -►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion

3.0 SCHEDULE OF STUDY PROCEDURES

<Cohort 1>

	Screening period		Treatment period										Early Termination	Follow-up visit
	Screening	Hospitalization	Part 1				Washout interval		Part 2					
Day	-28 to -2	-1	1	2	3	4	5 to 7	8	9	10	11	12		23 (±2)
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Demographics, medical history	X													
Prior medications	X													
Physical examination	X	X	X			X		X				X	X	X (l)
Vital signs (a)	X	X	X	X	X	X		X	X	X	X	X	X	X (l)
Weight, height, BMI (b)	X	X				X		X				X	X	X (l)
12-lead electrocardiogram (ECG) (c)	X	X	X			X		X	X			X	X	X (l)
Laboratory tests (d)	X	X				X		X				X	X	X (l)
Immunological test, alcohol tests	X													
FSH (e)	X													
Urinary drug tests	X	X						X						
C-SSRS (f)	X	X				X		X				X	X	
Sample collection for pharmacogenomic (PGx) Measurements (g)			X											
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X			X	X	X	X	X(k)	
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X	X	X			X	X	X	X		
Urine sample (for future tests) (j)		X		X						X			X	
Study drug administration			X						X					
Adverse events	X	X	X----------continuous monitoring----------X											
Concomitant medications	X	X	X----------continuous monitoring----------X											
Hospitalization		X	X----------X					X	X----------X					

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 1, on Day 8, predose on Day 9, and 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 9.

(b) Height will be measured at Screening only. Weight will be measured at Screening visit, Day -1, 72 hours postdose on Day 1, Day 8, 72 hours postdose on Day 9.

(c) 12-lead ECG will be measured at Screening, Day -1, predose, 2 and 72 hours postdose on Day 1, Day 8, predose on Day 9, 2 and 72 hours postdose on Day 9.

(d) Laboratory tests will be performed at Screening, on Day -1, 72 hours postdose on Day 1, on Day 8, and at 72 hours postdose on Day 9.

(e) FSH will be measured in postmenopause women only.

(f) C-SSRS will be investigate at Screening, Day -1, Day 4, Day 8, and Day 12.
(g) Samples for PGx measurements will be collected predose on Day 1.
(h) Samples for PK assessment will be collected predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 9, and 0.5, 1. 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(i) Samples for PD assessment will be collected on Day -1 (at 20, 16, 12 hours predose on Day 1), predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(j) Urine samples will be collected on Day -1, 24 hours postdose on Day 1, and 24 hours postdose on Day 9.
(k) Samples for PK assessment at discontinuation will be collected if it is possible.
(l) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

<Cohorts 2 to 4>

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening	Hospitalization	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Demographics, medical history	X																					
Prior medications	X																					
Physical examination	X	X	X																		X	X (m)
Vital signs (a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (m)
Weight, height, BMI (b)	X	X																			X	X (m)
12-lead electrocardiogram (ECG) (c)	X	X	X			X							X						X		X	X (m)
Laboratory tests (d)	X	X											X								X	X (m)
Immunological test, alcohol tests	X																					
FSH (e)	X																					
Urinary drug tests	X	X																				
C-SSRS (f)	X	X																			X	X
Sample collection for pharmacogenomic (PGx) Measurements (g)			X																			
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X							X			X			X	X		X (l)
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X									X			X			X	X		
Cerebrospinal fluid sample collection for pharmacodynamic (PD) assessment (j)		X																		X		
Urine sample (for future tests) (k)		X		X																X		X

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening	Hospitalization	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Study drug administration			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events	X	X	X----------continuous monitoring----------X																		X	X
Concomitant medications	X	X	X----------continuous monitoring----------X																		X	X
Hospitalization		X	X----------X																			

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone.

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36 and 48 hours postdose on Day 1, predose on Days 4 to 16, predose on Day 17, and 1, 4, 12, 24, and 48 hours postdose on Day 17.
(b) Height will be measured at Screening only. Weight will be measured at Screening, on Day -1, and 48 hours postdose on Day 17.
(c) 12-lead ECG will be measured at Screening, Day -1,presdose and 2 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose, 2 and 48 hours postdose on Day 17.
(d) Laboratory tests will be performed at Screening, Day -1, predose on Day 11, and at 48 hours postdose on Day 17.
(e) FSH will be measured in postmenopause women only.
(f) C-SSRS will be investigate at Screening Visit, Day -1, and Day 19.
(g) Samples for PGx measurements will be collected predose on Day 1.
(h) Samples for PK assessment will be collected predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose on Day 14, predose, 0.5, 1. 1.5, 2, 4, 8, 12, 16, and 24 hours postdose on Day 17.
(i) Samples for PD assessment will be collected at 20, 16, and 12 hours predose on Day 1, predose, 1, 4, 8, 12, and 24 hours postdose on Day 1, predose on Day 11, predose on Day 14, predose, 1, 4, 8, 12, and 24 hours postdose on Day 17.
(j) Samples for PD assessment will be collected on Day -1 and 24 hours postdose on Day 17 (if it is performed in Cohort 3 and thereafter).
(k) Urine samples will be collected on Day -1, at 24 hours postdose on Day 1, and 24 hours postdose on Day 17.
(l) Samples for PK assessment at discontinuation will be collected if it is possible.
(m) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. Schizophrenia usually develops at late adolescence or early adulthood and manifests in maximum 1% of the population. For those who have relatives of first degree with schizophrenia, the incidence rate is higher by 10% (the concordance rate for schizophrenia in identical twins is 40% to 65%) [1][2][3]. Symptoms of schizophrenia can be subdivided into 3 broad classes: positive, negative, and cognitive symptoms [4]. Positive symptoms include hallucinations, delusions, and disordered thought and speech, and can be summarized as psychosis. Negative symptoms include reduced emotion, reduced ability to experience pleasure (anhedonia), lack of motivation, and reduced social interaction. Finally, cognitive symptoms include poor information processing, impaired ability to focus on objectives, and abnormalities of working memory and learning [4]. Currently available antipsychotics are broadly effective for the treatment of positive symptoms. However, the negative symptoms and cognitive impairment of schizophrenia are the known particular aspects that cause dysfunction, for which no therapy has been approved. There still are significant unmet medical needs.

Hypofunction of N-methyl-D-aspartic acid (NMDA) receptor is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain [5]. D-amino acid oxidase (DAAO) contributes to the metabolism of D-serine in the brain and is highly expressed in the cerebellum. Changes in the D-serine levels or D-serine to total serine ratios have been reported in the plasma of patients with schizophrenia both naive and under drug treatment [6]-[9]. 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 DAAO resides [10]. Therefore, inhibition of DAAO is considered to be a promising target in treatment of schizophrenia.

TAK-831 is a highly selective and potent inhibitor of DAAO. TAK-831 increased D-serine levels in the cerebellum of normal mice and showed efficacy in a mouse model of Friedreich ataxia (FRDA) mouse models. It also demonstrated a positive effect on cognition and social interaction in rodent cognition and behavioral models.

As stated above, TAK-831 is expected to provide a therapeutic effect on FRDA and cognitive impairment as well as negative symptoms associated with schizophrenia.

4.2 Rationale for the Proposed Study

TAK-831 is currently under development for the treatment of FRDA and cognitive impairment as well as negative symptoms of schizophrenia. Three overseas phase 1 studies in healthy adults (single and multiple dose study [TAK-831-1001], positron emission tomography [PET] study to determine DAAO brain enzyme occupancy [TAK-831-1003], and a study to evaluate the food effect [TAK-831-1004]) have been conducted so far, in which TAK-831 was well-tolerated.

In addition, two phase 1 studies in healthy adults (study with single and multiple doses at high dose level [TAK-831-1005] and bioequivalence study [TAK-831-1006]) are being conducted or planned. Two phase 2 studies in patients with schizophrenia (small-scale crossover study to examine the cerebellar functions [TAK-831-2001], and a study to evaluate the efficacy and safety for negative symptoms of schizophrenia [TAK-831-2002]) are also underway. Besides, a phase 2 proof-of-concept (POC) study in patients with schizophrenia is being planned in China. Based on the result of these phase 2 studies, a phase 3 global study (long-term study) has been planned.

In parallel with these development plans, TAK-831 is also being developed in Japan for the treatment of cognitive impairment and negative symptoms associated with schizophrenia. In respect of FRDA, a genetic disease, since there has been no confirmed report as of June 2018 that clearly indicates the existence of Japanese patients, no development plan has been made for FRDA in Japan.

Enrollment of Japanese patients into the phase 3 global study and the phase 2 POC study in China has been considered. This study was planned to examine the safety and pharmacokinetic (PK) of TAK-831 in Japanese as well as to evaluate the safety and PK in Asian healthy subjects for the aforementioned studies.

4.3 Benefit/Risk Profile

Because this study will be conducted in healthy adults, there is no benefit to subjects.

The following risk mitigation measures will be implemented in this study. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, and the phase 1 studies (4 studies, including preliminary data of TAK-831-1005). Procedures may be added during the study as necessary based on evaluation of any additional clinical or nonclinical data.

The safety of TAK-831 has been studied in a prior single dose (up to 750 mg in suspension and 100 mg T1 tablet formulation) and multiple dose (up to 400 mg once daily [QD] in suspension) study in healthy Western subjects (TAK-831-1001), a single dose (up to 500 mg in suspension) PET study to investigate DAAO occupancy in the brain (TAK-831-1003) and a single dose food effect (400 mg T2 tablet formulation) study (TAK-831-1004). These studies have not resulted in a safety signal that would prevent additional studies. Additionally, TAK-831 given as single and 14 days multiple doses (up to 1200 mg in suspension and 600 mg T2 tablet formulation) is currently being studied in healthy adult subjects (TAK-831-1005). TAK-831 has been safe and well tolerated to date (provisional data as of end-April 2018).

- 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 pharmacodynamics (PD) monitoring (venipuncture may cause bruising), and the placement of ECG pads (which may cause some local redness and/or erythema/itching).

- In case of serious adverse events (SAE), 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 Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered to monitor emergent suicidality.

The Investigator's Brochure should be referred for more detailed safety of TAK-831.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed on the basis of the following hypothesis.

- TAK-831 given as single or multiple doses shows no safety issue and is well tolerated.
- The PK of TAK-831 given as single or multiple doses to Asian subjects is equivalent to that in Western subjects.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.2 Trial Secondary Objective

To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.3 Trial Exploratory Objective

To assess the effect of TAK-831 on the concentrations of D-serine and L-serine in plasma (and concentrations of D-serine and L-serine in cerebrospinal fluid as necessary) after TAK-831 administration to healthy Asian subjects.

5.3 Endpoints

5.3.1 Primary Endpoint

Safety: Adverse events (AEs), laboratory tests, vital signs, weight, 12-lead electrocardiogram (ECG)

5.3.2 Secondary Endpoints

PK: The following parameters will be calculated.

- C_{max} (Cohort 1, Day 1 of Cohorts 2 to 4)
- $C_{max,ss}$ (Day 17 of Cohorts 2 to 4)
- t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 4)
- AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 4)
- AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 4)
- AUC_{τ} (Days 1 and 17 of Cohorts 2 to 4)

5.3.3 Exploratory Endpoints

- PK: $R_{ac\ (Cmax)}$ and $R_{ac(AUC)}$ on Days 1 and 17 (Cohorts 2 to 4), $t_{1/2z}$, CL/F, V_z/F
- PD: Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (Days -1 and 18) (may be assessed in Cohort 3 or thereafter based on PD in plasma)

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, PK and PD of TAK-831 in healthy adult Asian subjects. This study will include up to 4 cohorts of healthy adult Japanese or Chinese subjects.

In Cohort 1, a single dose of TAK-831 will be administered at each dose level under a 3-sequential dose escalation design. Eight healthy adult Japanese subjects will be randomized to the sequence of administration A, B, and C at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Days 1 and 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge.

In Cohort 2, a single dose of study drug will be administered to healthy adult Japanese subjects, followed by multiple doses. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Cohorts 3 and 4 will be optional, in which a single dose of study drug will be administered followed by multiple doses, and may be studied based on emerging data from Cohorts 1 and 2.

Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Table 6.a shows the summary of cohorts, and Figure 6.a shows the schematic of the trial design.

Table 6.a Summary of Cohorts

Cohort	Subject	Dose	Remarks
1	Japanese 8 subjects	Part 1: 100 mg (4×25 mg T3 tablet formulation) Fasted, single dose	Wash out period between part 1 and 2 will be 8 days.
		Part 2: 300 mg (1×300 mg T3 tablet formulation) Fasted, single dose	
2	Japanese 8 subjects	600 mg (2×300 mg T3 tablet formulation) Fasted, single dose + multiple dose (once daily)	
3	Chinese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 3 may be run if emerging data from Cohorts 1 and 2 suggest ethnic-related differences in the tolerability and/or PK profile. Dose level will be determined based on the results from Cohorts 1 and 2.
4	Japanese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 4 may be run based on the emerging data from Cohorts 1 and 2 in Asian subjects.

TBD: To be decided

Figure 6.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - -Hospitalization- - - - -►			◄- - - - -Hospitalization - - - -►		

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion

<Cohorts 2 to 4>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening	Hospitalization	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- - - - - - - - - - - - - - - - - - -Hospitalization - - - - - - - - - - - - - - - - - - -►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion

6.2 Cohort transition/Dose Escalation

In Cohort 1, TAK-831 100 mg or placebo will be administered on Day 1 (Part 1) followed by confirmation of the safety and tolerability (AEs, physical examination, vital signs, weight, laboratory tests and 12-lead ECG) up to 72 hours postdose, and then TAK-831 300 mg or placebo will be administered on Day 9 (Part 2) followed by confirmation of the safety, tolerability and PK up to 72 hours postdose.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohort 1 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether the subsequent cohort should be run.

In Cohort 2, TAK-831 600 mg or placebo will be administered on Day 1, followed by confirmation of the safety and tolerability up to 72 hours postdose. Then, multiple doses of TAK-831 600 mg or placebo will be administered on Days 4 to 17. The data on safety and tolerability as well as PK up to 72 hours postdose will be examined.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohorts 1 and 2 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether Cohorts 3 and 4 should be run.

In Cohort 2 and onwards, the dose will be escalated but the dose escalation will be discontinued according to the following discontinuation criteria. The dose in Cohort 2 will be adjusted based on the safety and tolerability as well as PK and PD in Cohort 1.

Discontinuation criteria for dose escalation:

- Exposures in any cohort exceed those observed at the highest dose tested in monkey (C_{max} of 3680 ng/mL, AUC_{24} of 35700 hr*ng/mL)
- 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 changes 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 for Study Population

The subject of this study is Japanese or Chinese with a purpose to support the future conduct of studies in Asian subjects. The study will be conducted in healthy adult subjects without any

disease including circulatory or cerebrovascular diseases to appropriately assess the safety and tolerability as well as PK and PD of TAK-831.

6.3.2 Rationale of Trial Design

With a purpose to assess the safety and tolerability as well as the PK and PD profiles of TAK-831 when administered to Asian subject for the first time, this study employed a design with both single and multiple doses.

6.3.3 Rationale for Dose

To this date, the highest dose of TAK-831 tested in healthy Western subjects is 1200 mg (suspension formulation) once daily in the study TAK-831-1005. Based on the preliminary results, there were no significant adverse effects reported at this dose level, and as shown in Table 6.b, the mean steady-state exposure was C_{max} of 3015 ng/mL and AUC_{24} of 10501 h*ng/mL. The dose regimen of 600 mg given once daily (T2 tablet formulation) was also well tolerated and safe in healthy Western subjects. As for the mean steady-state exposures, C_{max} was 1494 ng/mL and AUC_{24} was 5090 h*ng/mL. This exposure at 600 mg was similar to that of monkeys at 100 mg/kg/day, the no-observed-adverse-effect-level (NOAEL).

In the study TAK-831-1005, the PK and PD of TAK-831 given as multiple doses at 100 and 600 mg (per day) to non-Japanese subjects was examined. The dose of 300 mg will be further examined in the study.

Based on the above, the doses of 100, 300 and 600 mg were selected for this study in consideration to the safety in humans as well as the comparability of PK and PD between non-Japanese and Japanese subjects.

In the 13-week repeat dose toxicity study in monkeys that are considered the more sensitive species than rats, adverse effects (vomiting, diarrhea, and loose stool) were noted at 600 mg/kg/day. The NOAEL was 100 mg/kg/day for both sexes.

TAK-831 has been administered at doses up to 1200 mg to non-Japanese, and no SAE has been reported with exposures exceeding the NOAEL. Besides, the adverse effects (vomiting, diarrhea, and loose stool) noted at a dose of 600 mg/kg/day in the 13-week repeat dose toxicity study in monkeys will be easily monitored in clinical trials.

Therefore, it is considered possible to administer doses exceeding the NOAEL exposure by carefully examining the safety and PK in each Cohort in this study. However, We have no information on toxicity at the level exceeding the exposure at 600 mg/kg/day in the 13-week repeated dose toxicity study in monkeys. Dose escalation will be stopped if exposures exceed that at 600 mg/kg/day in monkeys.

Table 6.b PK Parameters in 13-week Repeated Dose Toxicity Study in Monkeys and TAK-831 Given as Multiple Doses to Healthy Adult Subjects

Animal species-Study	Dose (mg/kg/day or mg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
Monkey 13-week (Day 91)	100 mg/kg/day (NOAEL)	1340 (male) 1270 (female)	7490 (male) 9190 (female)
	600 (300 BID) mg/kg/day	4650 (male) 2710 (female)	45500 (male) 25900 (female)
Human MRD (Day 16)	1200 mg QD (suspension formulation)	3015	10501
Human MRD (Day 16)	600 mg QD (T2 tablet formulation)	1494	5090

BID, twice daily; MRD, multiple repeated dose; NOAEL, no-observed-adverse-effect-level; QD, once daily

6.3.4 Rationale for Endpoints

6.3.4.1 Safety Endpoint

The safety endpoints in this study were defined to determine the safety and tolerability following a single dose and multiple dose of TAK-831. These are standard endpoints in the Phase 1 studies in healthy subjects.

Since TAK-831 involves effects on the central nervous system, the C-SSRS will be administered to assess the influence on suicidal ideation or suicidal behavior.

6.3.4.2 Pharmacokinetic Endpoint

Concentrations of TAK-831 in plasma will be examined to assess the PK of TAK-831 given as a single dose or multiple doses to healthy adult Asian subjects, and then the following PK parameters will be calculated.

- PK parameters: C_{max}, $C_{max,ss}$ (Cohorts 2 to 4), t_{max}, AUC_{last}, AUC_{∞}, AUC_{τ} (Cohorts 2 to 4), $R_{ac(Cmax)}$ (Cohorts 2 to 4), $R_{ac(AUC)}$ (Cohorts 2 to 4), $t_{1/2}$, CL/F, V_z/F

6.3.4.3 Pharmacodynamic Endpoint

Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max} following TAK-831 doses will be examined to assess the PD of TAK-831 in healthy adult Asian subjects. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid may be assessed as necessary.

6.3.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

The objective of this section is to specify the sequence of procedures in the cases where the timing of each procedure overlaps.

- Safety evaluation will be conducted within the predetermined allowance window as far as possible.
- Blood samples for PK assessment will be collected at time points as close to the specified time as possible.
- Other procedures must be completed at time points as close to the specified or planned hours as possible irrespective of before or after the specified times.
- If the timing of blood sampling and ECG or vital signs measurement overlap, blood sampling should be prioritized. ECG or vital signs measurement may be performed within an acceptable time window (Appendix C).
- The priority may be changed upon agreement between the investigator and the sponsor based on discussion.
- Any test and procedure necessary to immediately assess safety concerns at the time of AEs must be prioritized over other regular predetermined procedures.
- The safety of subjects in the follow-up period may be confirmed by telephone unless abnormal, clinically significant findings are observed upon discharge.

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

The entire study will start when the first subject signs the informed consent form to participate in this study.

6.4.2 Definition of End of the Trial

The study will end when the last subject completes the last planned visit or follow-up visit (or last communication [may be via telephone] relating to the planned visit) or is withdrawn from the study or lost to follow up (the status that the subject cannot be reached by the investigator).

6.4.3 Definition of Trial Discontinuation

The study may be discontinued for reasons other than safety such as the followings:

- A finding (eg, PK, pharmacodynamics, efficacy, biologic targets) from the other nonclinical or clinical studies results with the study drug in the study discontinuation for non-safety related reasons.
- Data from drugs classified in the same class as the study drug, or methodologies used in this study become available and results in the study being stopped for a non-safety related reason.
- Study discontinuation due to non-scientific and non-safety-related reasons, such as slow enrollment.

Discontinuation of the clinical study for safety reasons:

- The study is prematurely terminated because other clinical or non-clinical trials where TAK-831 or other drugs of the same class are administered have confirmed unexpected safety concerns based on the methodology used in this study

6.4.4 Criteria for Premature Termination or Suspension of the Trial

6.4.4.1 Criteria for Premature Termination or Suspension of the Trial

The study will be completed as planned unless 1 or more of the following criteria are met that require temporary suspension or early termination of the study.

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

6.4.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the Sponsor, an institutional review board (IRB), or a regulatory authority elects to terminate or suspend the study, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

6.4.5 Criteria for Premature Termination or Suspension of a Study Site

6.4.5.1 Criteria for Premature Termination or Suspension of a Study Site

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

6.4.5.2 Procedure for Premature Termination or Suspension in a Study Site

In the event that the Sponsor, an IRB, or a regulatory authority elects to terminate or suspend of the study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) ≥18.5 kg/m^2 and ≤25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the following birth control requirements:
    - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug. No restrictions will be required for a vasectomized male subject provided the subject is at least 1 year post bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
    - Is a male subject who agrees to not donate sperm from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug.
    - Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
        a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or ≥6 months of spontaneous amenorrhea in females aged >45 years with

serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels should be required.

b) Hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

c) Had a tubal ligation with appropriate documentation of surgical procedure.

d) Congenital conditions such as uterine aplasia etc.

[Rationale for the inclusion criteria]

Inclusion criteria 1, 2, 5, 8 and 9:

These are standard criteria for clinical pharmacology studies in healthy adult subjects and defined in consideration to the safety of subjects.

Inclusion Criterion 3:

This is a standard criterion for clinical pharmacology studies in healthy adult subjects for sex. This is a standard criterion for clinical pharmacology studies in healthy adult subjects for age.

Inclusion Criterion 4:

This is the range of normal weight in the diagnosis criteria for obesity and obesity disease [11] proposed by the Japan Society for the Study of Obesity.

Inclusion Criterion 6:

This is set to appropriately assess the safety and PK in Chinese.

Inclusion Criterion 7:

This is set to eliminate the influence by dietary habits on the PK.

7.2 Exclusion Criteria

The subject will be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or diseases.
2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the trial procedure in the previous trial to the Screening Visit of the current trial.
3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).

5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec at the Screening Visit or Check-in.

[Rationale for the exclusion criteria]

Exclusion Criteria 1, 15:

This is set to eliminate the influence on safety evaluation for TAK-831.

Exclusion Criterion 2:

This is a minimum duration in which the previous clinical trial is considered to have no influence in reference to "General Considerations for Clinical Trials" [12] in order to ensure the safety of subjects.

Exclusion Criteria 3, 4, 6, 7, 12, 13, 14:

These are standard criteria for clinical pharmacology studies and defined in consideration to the safety of subjects.

Exclusion Criterion 5:

This is defined in consideration to the safety of subjects.

Exclusion Criteria 8, 9, 11:

This is defined in consideration to the safety of subjects. This is also defined for potential influence on PK and PD assessment.

Exclusion Criterion 10:

This is set to exclude subjects who have a known hypersensitivity to any component of the formulation of TAK-831 or related compounds in consideration of the safety of subjects.

7.3 Excluded Medications Supplements, Dietary Products

Table 7.a shows excluded medications, supplements, and dietary products.

Use of the drugs listed on Table 7.a (prescribed drugs and over-the-counter [OTC] drugs), vitamins, supplements, and dietary products will be excluded from a specified time point to until discharge given the effect on the safety and PK. Use of prohibited concomitant drugs will be allowed when the investigator or sub-investigator deems it necessary to use any of the concomitant drugs for reasons including treatment of an AE.

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

Table 7.a Excluded Medications, Supplements, Dietary Products

From 28 days before admission (Day -1) to the last discharge	7 days before admission (Day -1) to the last discharge	72 hours before admission (Day -1) to the last discharge
• Prescription drugs • Supplements (St. John's wort, ginseng, kava kava, ginkgoes, chinese herbal medicine, and melatonin) • Vaccination/vaccine (b) • Nicotine-containing products • CYP 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1 and 2A6 inhibitors/inducers OTC drugs (c)	• OTC drugs (including aspirin or aspirin-containing drugs) (a) • Vitamins • Beverages containing grapefruit (fruit juice, flesh), star fruits (fruit juice, flesh), citrus aurantiums (high acidity), orange (seville oranges), or marmalade • Apple, orange or pineapple juice • Brassicaceae vegetables (kale, cress, collard greens, kohlrabi, brussels sprouts, and mustard). • Meat cocked over the charcoal • Alcohol containing products	• Caffeine or xanthine containing products

CYP: cytochrome P-450, OTC drugs: over-the-counter drugs
Note: Excludes the drug needs to be administered to treat an AE and if the investigator or sub-investigator considers necessary to use the drug
(a) Use of paracetamol (≤1 g/daily) will be allowed.
(b) Includes H1N1 and other influenza vaccines, however, not limited to these medications.
(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Diet and fluid (except water) must be ingested at least10 hours before clinical laboratory tests.

On the day before clinical laboratory tests, evening meal must be ingested by 21:00.

During hospitalization, pre-specified diets must be ingested, and other diets will be prohibited. After discharge, excessive drinking and eating must be avoided until completion of follow-up period.

7.4.2 Activity

Smoking is prohibited during the study.

Excessive exercise is prohibited during the study.

Blood donation is prohibited for at least 12 weeks (84 days) from completion of the last test.

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the visit in advance whenever possible, and should be reported the circumstances and therapy after visit. The investigator or sub-investigator should communicate that medical institution about the subject's participation in the study.

7.5 Documentation of Subject Failure

The investigator or sub-investigator must account for all subjects who sign informed consent. If a subject discontinues the study before the first study drug administration, the investigator or sub-investigator should complete the electronic case report form (eCRF).

The primary reason for subject failure is to be recorded in the eCRF using the following categories:

- Death
- AE
- Screening failure (failed inclusion criteria or did meet exclusion criteria) <specify the reasons>
- Protocol deviation
- Lost to follow up
- Withdrawal by subject <specify the reasons>
- Study terminated by the Sponsor
- Pregnancy
- Sample size sufficient
- Other <specify the reasons>

Any subject identification number, once assigned to a subject, should not be reused if the assigned subject discontinues the study prior to the first study drug administration. Nevertheless, if a reserve subject is enrolled in the other cohort, the same subject identification number may be used.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

Primary reasons for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF using the following categories. For the subject who is withdrawn from the study before the first study drug administration in Period 1, refer to Section 7.5.

1. Death
   The subject died on study.

   Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). Refer to Section 10.2.9.3 for reporting procedures.

2. 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.

The study drug will be immediately discontinued if a condition meets any following criteria during the treatment, and appropriate follow-up will be performed (clinical laboratory tests will be repeatedly performed until the clinical laboratory test profiles have normalized or returned to baseline, refer to Section 9.2.9.1):

- Liver Function Test (LFT) Abnormalities
  - ALT or AST >8×the upper limit of normal (ULN), or
  - ALT or AST >5×ULN and persists for more than 2 weeks, or
  - ALT or AST >3×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (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%)
- Prolonged QT/QTcF intervals

  If at least one remarkable prolonged QT interval was observed on 12-lead ECG (eg, absolute value of QTcF intervals >500 msec or an increase >60 msec from baseline), and the investigator or sub-investigator considered inappropriate to continue the study.

3. Protocol deviation
   The discovery after the start of the first study drug administration 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.
4. 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 in the subject's source documentation.
5. Pregnancy
   If a subject was found to be pregnant.

   Note: Participation in the study is immediately discontinued for any pregnancy. Refer to Appendix B for the procedures.
6. Voluntary withdrawal
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
7. Study terminated by the Sponsor
   The Sponsor terminates the study.

8. Other

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

7.7 Procedures for Discontinuation or Withdrawal of a Subject

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

7.8 Subject Replacement

The Part 1 in Cohort 1 and Cohorts 2-4 can have a few reserve subjects considered eligible for participation in the study based on screening test. If a subject has not received the study drug as scheduled during the study owing to any reason occurring before the study drug administration, a reserve subject will be allowed to participate in the study.

If a subject withdraws from the study after initiation of the study drug, the subject will not be replaced with a reserve subject.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

[Drug product]

Code name: TAK-831

Dosage form and strength:

TAK-831 tablet is a yellowish-red film-coated tablet containing 25 or 300 mg of TAK-831.

TAK-831 placebo tablet contains no TAK-831 and has same appearance as TAK-831 tablet.

8.1.1 Clinical Study Drug Labeling

Study drug labeling will show name of the study drug, quantity and storage condition of the study drug, manufacture number, expiration date, protocol number, name and address of the Sponsor, and statement the drug is for clinical trial use only.

8.1.2 Clinical Study Drug Inventory and Storage

TAK-831 is stored at a room temperature (1°C to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used, or returned to the Sponsor or its designee. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Randomization Code Creation and Storage

The personnel responsible for randomization (the Sponsor's designee) will prepare the randomization table/schedule prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.4 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigator must store the emergency key until the time of an emergency blind break or the end of the trial.

Since maintenance of the blind may be compromised because of results from drug concentrations and PD assessments, such results should not be disclosed prior to blind breaking. In the event that results must be reported to the investigator prior to breaking the blind, all efforts should be made to maintain the blind (eg, by changing a medication identification number in order to avoid identification of subjects by laboratory site personnel). Detailed procedures for measuring subject drug concentration levels and PD assessments will be provided in the separately created procedure for directions on the handling of biological samples for measuring drug concentrations and PD assessments.

To unblind a subject, the study drug blind can be obtained by opening a sealed envelope.

The Sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded in the eCRF.

If the investigator or sub-investigator breaks the blinding of the study drug, study drug must be stopped immediately and that subject must be withdrawn from the study.

No change should be made to any subject assessment after unblinding (except cases where the investigator or sub-investigator is not informed of unblinding information [unblinding for open-label analysis for the Sponsor]).

8.1.5 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (a site designee) will receive the pharmacy manual created by the Sponsor, and follow the procedures for managing the Sponsor-supplied drug supplies. A copy of these procedures will be provided to the investigator as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the Sponsor-supplied drug. The manual will also describe procedures for the collection of unused medications from the subject and their return to the Sponsor, or the destruction of any unused supplies.

The on-site pharmacist (a site designee) will immediately return any unused study drugs in a sealed package to the Sponsor after the study is closed at the investigational site.

9.0 STUDY PROCEDURES

The investigator or sub-investigator should collect data according to the procedures described in the following sections. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site designee whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the initiation of any study procedures. The requirements of informed consent are described in Section 13.2.

A separate informed consent form pertaining to the collection, storage, and analysis of samples must be obtained prior to collecting any blood sample for pharmacogenomic research for this study.

9.1.1.1 Assignment of Subject Identification Number

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

9.1.1.2 Study Drug Assignment

In Cohorts 1-2 and Cohorts 3-4 (if added), the subjects will be assigned in the order of medication identification number by Cohort according to the randomization code. The medication identification number will be a 4-digit number, starting with the following number:

Cohort 1: 1001, Cohort 2: 2001, Cohort 3: 3001, Cohort 4: 4001

The assigned medication identification number will be used to identify the samples for PK by the study site and the only number to identity a subject during blood sampling for PK. The number will be always shown on the sample vials, which are sent to the laboratory to evaluate the PK. The laboratory will report the results using this number. The number will be used for only the purpose described in this section and cannot be replaced with the 7-digit subject identification number, which is assigned at the time of informed consent procedure and used in all other procedures during the clinical study period to identify a subject. In case of subject replacement, the study drug with a medication identification number for the withdrawn subject will be used by the replacing subject.

9.1.2 Inclusion and Exclusion

Each subject will be assessed according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Demographic information to be obtained will include date of birth, sex, height, weight, caffeine use, alcohol use, and smoking status of the subject.

Medical history to be obtained will include determining whether the subject has any clinically significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions. Medication history information to be obtained will include any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Subjects will be asked whether they have taken any medication other than the study drug (used from the signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC drugs, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication names, route of administrations, start and end dates, and reasons for use.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

9.2.2 Height and Weight

Each subject should have a height and weight measured. Height will be recorded in centimeters without decimal places (rounding off the first decimal place). Weight will be collected in kilograms (kg) with the first decimal place (rounding off the second decimal place).

9.2.3 BMI

BMI is calculated using the formula provided below.

Metric: BMI=weight (kg)/height $(m)^2$

The values should be calculated to the first decimal place (rounding off the second decimal place). When the BMI is used as entry criteria, then this determination must be made after rounding.

9.2.4 Vital Signs

Vital signs will include body temperature (axilla measurement), sitting blood pressure (systolic and diastolic, after resting more than 5 minutes), and pulse (beats per minute).

9.2.5 12-Lead ECG

A standard 12-lead ECG will be recorded. Subjects should be resting in a recumbent position for at least 5 minutes before each ECG measurement.

The investigator or sub-investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: normal or abnormal. If an ECG is abnormal, the investigator or sub-investigator (or a qualified observer at the investigational site) will judge clinical significance of the abnormality. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTcF.

9.2.6 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be performed at the study procedures-specified time point. The investigator or sub-investigator will evaluate suicide risks based on the information obtained from C-SSRS. For any suicidal ideation and suicidal behavior will be documented as an adverse event.

9.2.7 Study Drug Administration

In Cohort 1, a single dose of TAK-831 T3 tablet 25 mg×4 tablets or placebo will be orally administered on Day 1 (Part 1), and a single dose of TAK-831 T3 tablet 300 mg×1 tablet or placebo will be orally administered on Day 9 (Part 2).

In Cohort 2, a single dose of TAK-831 T3 tablet 300 mg×2 tablets or placebo will be orally administered on Day 1, followed by multiple doses of TAK-831 T3 tablet 300 mg×2 tablets (once daily) or placebo on Days 4-17.

The study drug will be orally administered with 150 mL of water at a fasted state (fasted at least 10 hours before administration).

In Cohorts 3 and 4, the dose of the study drug will be determined based on the data obtained from Cohorts 1 and 2.

9.2.8 AE Monitoring

AE monitoring will begin after the signing of informed consent. A complete description of AE collections and procedures is provided in Section 10.2.

9.2.9 Laboratory Procedures and Assessments

Laboratory samples will be taken following a minimum 10 hour overnight fast on the days stipulated in the Schedule of Study Procedures (Section 3.0). Refer to Appendix C for the amount of blood samples.

The investigator or sub-investigator will take responsibility for evaluation of the clinical laboratory test results and storage. The investigator will maintain a copy of the reference ranges for the laboratory used.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Red blood cell count	White blood cell count and differential leukocytes (lymphocytes, neutrophils, eosinophils, basophils, and monocytes)
Hemoglobin	Hematocrit
Platelet count	

Chemistry

Chemistry evaluations will consist of the following chemistry tests:

Albumin	Creatinine
ALP	Glucose
ALT	Sodium
AST	Calcium
γ-GTP	Creatine kinase
Total bilirubin	Potassium
Direct bilirubin	Chloride
Total protein	PT
Urea nitrogen	APTT

Urinalysis

Urinalysis will consist of the following tests:

pH	Specific gravity
Qualitative (protein, glucose, occult blood, and nitrite)	Urinary sediment (erythrocytes, leukocytes, and cylinder) (a)

(a) Will be performed for any abnormal urinalysis parameter.

Other

Immunological tests HIV antibody and antigen tests, hepatitis tests (HBs antigen and HCV antibody)
Alcohol tests (urinalysis or breath test)
Urinary drug tests
FSH (postmenopausal female subjects only)

HIV: human immunodeficiency virus, HBs: hepatitis B surface antigen, HCV: hepatitis C virus, FSH: follicle-stimulating hormone

Note: The investigator or sub-investigator will report the results of immunology, urine drug tests, and alcohol tests directly to subjects. The Sponsor will confirm the overall test results (as "Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug.

If subjects experience an ALT or AST of >3×ULN (except the tests at Screening), follow-up laboratory tests (at a minimum, serum alkaline phosphatase [ALP], ALT, AST, total bilirubin,

gamma-glutamyl transferase [γ-GTP], and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Refer to Section 7.6 and Section 10.2.9.4 for the discontinuation or withdrawal criteria of a subject and the appropriate guidance on reporting abnormal LFTs as SAEs, respectively.

9.2.9.2 Urine sample for Future Tests

Urine samples for future tests will be collected according to the Schedule of Study Procedures (Section 3.0).

If acute renal failure is suspected, urinary biomarkers such as KIM-1, NGAL, and cyctatin C may be measured using the collected sample.

9.3 Biomarker, PK, PD, and PGx Samples

Samples for PK, PD, and PGx will be collected according to the schedule of study procedures (Section 3.0). Separated procedures describe the details of sampling, handling, and transferring to central laboratory. The actual sampling time for PK and PD analyses will be documented in the subject's source documents and eCRF.

Table 9.a shows primary specimen collections.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	PK Analysis	Mandatory
Plasma sample for PD	Blood	Plasma	PD analysis	Mandatory
Cerebrospinal fluid sample for PD	Cerebrospinal fluid	Cerebrospinal fluid	PD analysis	Optional
Blood sample for DNA PGx	Blood	DNA	PGx analysis	Optional

9.3.1 PK Measurements

The following PK parameters will be calculated from plasma concentrations of TAK-831, unless otherwise specified.

Mark/Term	Definition
Plasma	
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to time of infinity
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
C_{max}	Maximum observed plasma concentration (measured value)
$C_{max, ss}$	Maximum observed steady-state plasma concentration during a dosing interval (measured value)
t_{max}	Time of first occurrence of C_{max}
$t_{1/2z}$	Terminal disposition phase half-life
λ_z	Terminal disposition phase rate constant
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration
CL/F	Apparent clearance after extravascular administration
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}
$R_{ac(AUC)}$	Accumulation ratio based on AUC

9.3.1.1 Plasma for PK Measurements

Blood samples for plasma TAK-831 concentration will be collected (Table 9.b). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.b Blood Sample Collection for PK Analysis

Dose Levels:	Date of administration	Sampling time
Single dose	1	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
	9	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	1	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, and 48 hours postdose
	4, 11, 14	Predose
	17	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 16, and 24 hours postdose

9.3.2 PD Analysis

The following PD parameters will be calculated from plasma concentrations of D-serine and L-serine, unless otherwise specified

Mark/Term	Definition
Plasma	
$AUEC_{24}$	Area under the effect-time curve from time 0 to 24 hours postdose
E_{max}	Maximum effect
time to E_{max}	Time to reach maximum PD effect

9.3.2.1 Plasma Samples for PD Analysis

Blood samples will be collected to measure plasma D-serine and L-serine concentrations (Table 9.c). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.c Blood Sample Collection for PD Analysis

Dose Levels:	Specimen	Date of administration	Sampling time
Single dose	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
		9	Predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, and 24 hours postdose
		11, 14	Predose
		17	Predose, 1, 4, 8, 12, and 24 hours postdose

9.3.2.2 Cerebrospinal fluid samples for PD Analysis

Cerebrospinal fluid will be collected to measure D-serine and L-serine concentrations (3.0 mL per scheduled time). The cerebrospinal fluid sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples. After Cohort 3, collection of cerebrospinal fluid in the next Cohorts will be determined based on the results of plasma D-serine and L-serine concentrations obtained from the previous Cohorts.

9.3.3 PGx Measurements

9.3.3.1 Blood Sample for DNA PGx Measurements

When sampling of whole blood for pharmacogenomic analysis occurs, the subject must sign informed consent/be consented separately for PGx sampling, storage and analysis. PGx measurement is a part of the study, but participation of a subject is optional.

One 6-mL of whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected prior to the single dosing on Day 1 from each consenting subject in the study.

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. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification by the Sponsor. “Stored samples” are defined as samples that are 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 the study drug or related drug.

The sampling of whole blood for PGx and genotyping analysis is mandatory. Every subject must sign informed consent separately for PGx sampling. DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms.

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 exploratory research with the samples for PGx measurements.

9.3.4 Confinement

Cohort 1:

Subjects will be hospitalized from Day -1 to Day 4 and Day 8 to Day 12 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Days 4 and 12.

Cohorts 2-4:

Subjects will be hospitalized from Day -1 to Day 19 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Day 19.

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 clinical study; it does not necessarily have to have a causal relationship with the the treatment (including the study drug) or study participation.

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered 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 or sub-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 may be considered as AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring for an abnormal value are not considered as an intervention. In addition, repeated or additional non-invasive tests for verification and evaluation of abnormality or monitoring purpose will not be considered as 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 conditions and should NOT be recorded as an AE. The observations or evaluations of first examination at baseline (eg, laboratory test, ECG, X-ray,

etc) should NOT be recorded as AEs 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). The investigator or sub-investigator 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. The investigator or sub-investigator should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a pre-existing chronic 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. The investigator or sub-investigator 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 drug or after any change in study drug, the worsening or complication should be recorded as a new AE. The investigator or sub-investigator should ensure that the event term reported captures the change in adverse event (eg, "worsening of…").

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to the signing of informed consent are not considered AEs. However, if a preplanned procedure is performed earlier (eg, as an emergency) due to a worsening of a 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 study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the sub-investigator to decide whether a dose is to be considered as overdose, in consultation with the Sponsor.

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.9.
- 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 Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

Severity/Intensity of AEs will be classified or defined as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying disease, 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 the underlying disease, complications, concomitant medications and concurrent treatments.

10.2.3 Assigning Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

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

10.2.4 Start Date

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

10.2.5 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.

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken with Study Treatment

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

10.2.8 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/signs/symptoms have almost disappeared; the abnormal laboratory values improved, but have 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 values on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.9 Collection and Reporting of AEs, SAEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent and continue until the follow-up visit or phone call.

10.2.9.2 Reporting AEs

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

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator or sub-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 Adverse Event (Frequency)
- Severity/Intensity.
- The Investigator's or sub-investigator's opinion of the causal relationship between the event and administration of study drug(s). (Related/Not related)
- Action taken with the study drug
- Outcome of the event.
- Seriousness.
- Timing of occurrence (after administration of the study drug)

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator or sub-investigator to the Sponsor within 1 business day of the first onset or notification of the SAE, along with any relevant information. The

investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. 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 or sub-investigator's name.
- Name of the study drug(s).
- Causality assessment.

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

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator or sub-investigator should complete the follow-up SAE form or provide other written documentation immediately to the Sponsor. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory values, discharge summary, postmortem results) in the institution should be submitted to the Sponsor, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.2.9.4 Reporting of Abnormal LFTs

If a subject experiences 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 10.2.9.3. The investigator or sub-investigator will contact the monitor for discussion and investigation of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease, medical history/ongoing disease. Follow-up laboratory tests as described in Section 9.2.9 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs and Regulatory Authorities

The Sponsor will report all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs and the head of the study site. 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 the study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definitions of analysis variables, and analysis methodologies to address all study objectives.

11.1.1 Analysis Sets

In this study, 3 analysis sets are defined: the Safety Analysis Set, the PK Analysis Set, and the PD analysis Set. The definition of each analysis set will be described in the SAP.

The Sponsor will verify the validity of the definitions of the analysis sets and the rules for handling data in consultation with a medical expert, as needed, prior to unblinding the study drug assignment. The Sponsor will address all remaining uncertainties not specified at planning, and will finalize the SAP prior to unblinding of subject's treatment assignment.

11.1.1.1 Safety Analysis Set

The Safety Analysis Set will be defined as all subjects who received at least one dose of study drug.

11.1.1.2 PK Analysis Set

The PK Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PK parameter.

11.1.1.3 PD Analysis Set

The PD Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PD parameter.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the Safety Analysis Set.

11.1.3 PK Analysis

Endpoints and its analytical method

[Endpoints]

Secondary endpoints: C_{max} (Cohort 1, Day 1 in Cohorts 2 to 4), $C_{max,ss}$ (Day 17 in Cohorts 2 to 4), t_{max} (Cohort 1, Days 1 and 17 in Cohort 2 to 4), AUC_{last} (Cohort 1, Day 1 in Cohorts 2 to 4), AUC_{∞} (Cohort 1, Day 1 in Cohorts 2 to 4), AUC_{τ} (Days 1 and 17 in Cohorts 2 to 4)

Exploratory endpoints: $R_{ac(Cmax)}$ and $R_{ac(AUC)}$ (Cohort 2 to 4) on Days 1 and 17, $t_{1/2z}$, CL/F, V_z/F

[Analytical method]

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of TAK-831 in plasma will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time will be presented. Plasma PK parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Day 1 and Day 9 for Cohort 1 and Day 1 for Cohorts 2 to 4. Additional analyses on dose linearity will be included if appropriate.

11.1.4 PD Analysis

Endpoints and its analytical method

[Endpoints]

- Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (on Days -1 and 18) (if available)

[Analytical method]

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent the change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

11.1.5 Safety Analysis

Endpoints and its analytical method

[Endpoints]

AEs, laboratory findings, vital signs, weight, 12-lead ECG

[Analytical method]

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2 and 4, and for Cohort 3.

11.1.5.1 AEs

A treatment-emergent adverse event (TEAE) is defined as an AE whose date of onset occurs on or after the start of study drug.

The followings will be analyzed for TEAEs. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

- Frequency of all TEAEs
- Frequency of drug-related TEAEs
- Frequency of all TEAEs by intensity
- Frequency of drug-related TEAEs by intensity
- Frequency of TEAEs leading to study drug discontinuation
- Frequency of serious TEAEs

11.1.5.2 Clinical Laboratory Evaluation

Summary statistics will be provided for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

11.1.5.3 Vital Signs

Summary statistics will be provided for the observed values at each evaluation time point and changes from baseline.

11.1.5.4 Other Safety Parameters

The ECG parameters will be summarized as follows. Summary statistics will be calculated for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables. The analysis methods for other endpoints will be specified in detail in the SAP.

11.2 Determination of Sample Size

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, and PK of each cohort. This is not based on any statistical rationale.

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.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, and informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, sub-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 or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the Sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the Sponsor and the head of the study site of the deviation or changes as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the Sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

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 study 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 [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency [MHRA], and the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory authority, the Sponsor should be notified immediately. The investigator and the head of the institution guarantee 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 Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for GCP. The investigator will conduct the study according to applicable local or regional regulatory requirements in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

The IRB must be constituted according to the applicable local requirements of each participating region. The Sponsor or the designee will require documentation noting all names and titles of the members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. The Sponsor or the designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the written informed consent form, and, if applicable, subject recruitment materials and/or advertisements, if applicable, and other documents required by all applicable laws and regulations, must be submitted to the IRB for approval. The IRB's written approval of the protocol and subject written informed consent must be obtained and submitted to the Sponsor or the designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, written informed consent form) reviewed; and state the approval date. The Sponsor will notify the study site that the Sponsor has confirmed the adequacy of the study site regulatory documentation. Until the study site receives a notification, no protocol activities, including screening, may occur.

The study site must adhere to all requirements stipulated by its respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the written 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, and submission of the investigator's final status report to IRB. All IRB 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 and the 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 written informed consent form describes 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 further explains 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 approval of the written informed consent form. The written informed consent form must be approved by both the IRB and the Sponsor prior to use.

The informed consent form must be described in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines he or she will participate in the clinical study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed by the investigator or sub-investigator to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form will be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects 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 prior to analysis. Notify the 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 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, MHRA, and PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents),

including 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 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. The investigator or sub-investigator needs to obtain a prior written approval from the Sponsor to publish any information from the study externally, such as to a professional association.

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 the facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

13.5 Clinical Trial Results Disclosure

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

13.6 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study 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 or sub-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

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.2 Investigator Agreement

A separate agreement will be provided to the study site.

14.1.3 Study-Related Responsibilities

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.4 List of Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUEC	area under the effect-time curve
BMI	body mass index
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DAAO	D-amino acid oxidase
DNA	deoxyribonucleic acid
E_{max}	maximum effect
FDA	Food and Drug Administration
FRDA	Friedreich ataxia
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
γ-GTP	gamma-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requrements for Pharmaceuticals for Human Use
INR	international normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency

Term	Definition
NMDA	*N*-methyl-D-aspartate
NOAEL	no observed adverse effect level
PET	positron emission tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
POC	proof-of-concept
R_{ac}	accumulation ratio
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occrurrence of C_{max}
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration

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 eCRFs

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

The Sponsor or its designee will supply the study sites with access to eCRFs. The Sponsor will provide training opportunities for the 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 the Sponsor (or the designee) and will be answered by the study 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.

The 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.

The following data will not be recorded in the eCRFs.

- PGx analysis results
- Clinical laboratory test results
- Drug concentration measurement results
- PD measurement results

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 or sub-investigator with use of change and modification records of the eCRFs. The investigator must review the data change for completeness and accuracy, and must e-sign.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the Sponsor or its designee. 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 or the head of the study site agree to keep the records stipulated in Section 15.1 and those documents that include (but not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated 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.

The investigator and the head of the study site are required to retain essential documents until the day specified as 1 or 2 below, whichever comes later. However, if the Sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the Sponsor.

1. The day on which marketing approval for the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion for the study.

In addition, the investigator and the head of the study site should retain the relevant essential documents until the receipt of a Sponsor-issued notification that states the retention is no longer required.

16.0 REFERENCES

[1] Sham PC, Gottesman, II, MacLean CJ, Kendler KS. Schizophrenia: sex and familial morbidity. Psychiatry Res 1994;52(2):125-34.

[2] Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999;56(2):162-8.

[3] Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo UH, Bassett AS, Cornblatt BA, Kestenbaum CJ, et al. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch Gen Psychiatry 1995;52(10):857-65.

[4] van Os J, Kapur S. Schizophrenia. Lancet 2009;374(9690):635-45.

[5] Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 2003;169(3-4):215-33.

[6] Calcia MA, Madeira C, Alheira FV, Silva TC, Tannos FM, Vargas-Lopes C, et al. Plasma levels of D-serine in Brazilian individuals with schizophrenia. Schizophr Res 2012;142(1-3):83-7.

[7] Ohnuma T, Sakai Y, Maeshima H, Hatano T, Hanzawa R, Abe S, et al. Changes in plasma glycine, L-serine, and D-serine levels in patients with schizophrenia as their clinical symptoms improve: results from the Juntendo University Schizophrenia Projects (JUSP). Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):1905-12.

[8] Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, et al. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the N-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch Gen Psychiatry 2003;60(6):572-6.

[9] Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(5):767-9.

[10] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511(7510):421-7.

[11] Japan Sciety for the Study of Obesity. Diagnostic Criteria for Obesity 2011. Journal of Japan Society for the Study of Obesity, 2011 Oct; additional edition.

[12] General Considerations for Clinical Trials (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998).

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to a sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study site in advance to get them accepted.
3. Prepare a written informed consent form and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the study site that sufficient medical care for all clinically significant AEs related to the study are provided to subjects throughout and beyond the period when subjects participate in the study, upon obtaining consent from the subject.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study site and the Sponsor in writing.
11. Determine the need of emergency key code unblinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the Sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the Sponsor with electronic signature.
14. Discuss any proposal from the Sponsor including update of the protocol.
15. Notify the head of the study site of the end of the study in writing.

Appendix B Pregnancy and Contraception

Male Subjects and Their Female Partners

From the signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, any nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use adequate contraception. In addition, they must be advised not to donate sperm during this period or subjects should refrain from having sexual intercourse from 1 month prior to the first study drug administration throughout the study period and until 35 days after the last study drug administration. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the table on containing adequate contraception below.

Female Subjects and Their Male Partners

Female subjects of childbearing potential* will be excluded from this study.

* Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation), or who are postmenopausal (eg, defined as at least 2 years since last regular menses with an FSH of >40 IU/L).

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documented absence of sperm in the ejaculate, or have had a bilateral orchidectomy.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate.

Barrier methods (each time the subject has intercourse)	Intrauterine device (IUD)	Hormonal contraceptives
Male condoms with a spermicide	Copper T PLUS condom Progesterone T PLUS condom	Combined pill

Subjects will be provided with information on acceptable methods of contraception for 95 days after last dose of study drug, as part of their informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy in partners and of sperm donations for 95 days after their last dose of study drug.

Pregnancy

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

If the pregnancy in the partner of a male subject occurs during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of his right to receive treatment information. If the subject chooses to receive unblinded treatment information, that individual's blind should be broken by the investigator or sub-investigator. Any subjects randomized to placebo need not be followed.

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

All female subjects and the the female partners of male subjects who became pregnant will be followed to final outcome, using the pregnancy form, with the consent of the female subjects or the female partners of those male subjects. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after any birth of a child will also be conducted.

Appendix C Acceptable Time Window for Study Procedure

<Cohort 1>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
	Follow-up period	Day 23	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Study treatment period (Part 1)	Day 1 72 hours postdose	Day 4 from awakening to discharge
	Washout period	Day 8	Not applicable
	Study treatment period (Part 2)	Day 9 72 hours postdose	Day 12 from awakening to discharge
	Follow-up period	Day 23	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 2 and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicabled
	Treatment period (Part 1)	Day 1 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Urinary drug tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Washout period	Day 8	Not applicable
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
Samples for PGx measurements	Treatment period (Part 1)	Day 1 predose	Not applicable
Blood samples for PK	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 1 hour postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 24 hours postdose	Within ± 2 hours
	Treatment period (Part 2)	Day 9 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, and FSH

<Cohorts 2-4>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Days 5-10 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Days 12-13 predose	From awakening to immediately prior to dose
		Day 14 predose	From awakening to immediately prior to dose
		Days 15-16 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 1, 4, 12, 24, and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 48 hours postdose	Day 19 from awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 2 and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 11 predose	From awakening to immediately prior to dose
		Day 17 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
Samples for PGx measurements	Treatment period (Single dose part)	Day 1 predose	Not applicable

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PK	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	Within 15 minutes predose
		Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 0.5, 1, 1.5, and 2 hours postdose	Within ± 5 minutes
		Day 17 4, 8, 12, 16 and 24 hours postdose	Within ± 15 minutes
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 1 hour postdose	Within ± 15 minutes
		Day 17 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
Cerebrospinal fluid samples for PD (If performed after Cohort 3)	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 3 hours
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 24 hours postdose	Within ± 2 hours
	Teatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, FSH, and urinary drug tests

Total blood sampling volumes for an individual subject is shown below:

<Cohort 1>

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)
		Screening	Day -1	Days 1-4	Day 8	Days 9-12	
Clinical Laboratory Tests	20	1	1	1	1	1	100
Blood samples for PK	4	-	-	12	-	12	96
Blood samples for PD	6	-	3	9	-	9	126
Samples for PGx Measurements	6	-	-	1	-	-	6
						Total Blood Sampling Volume	**328**

-: No blood collection

<Cohorts 2-4>

Sample Type	Sample Volume (mL)	Number of Samples									Total Volume (mL)
		Screening	Day -1	Day 1	Day 2	Day 3	Day 4	Day 11	Day 14	Days 17-18	Day 19	
Clinical Laboratory Tests	20	1	1	-	-	-	-	1	-	-	1	80
Blood samples for PK	4	-	-	8	2	1	1	1	1	10	-	96
Blood samples for PD	6	-	3	5	1	-	-	1	1	6	-	102
Samples for PGx Measurements	6	-	-	1	-	-	-	-	-	-	-	6
										Total Blood Sampling Volume		**284**

-: No blood collection

TAKEDA PHARMACEUTICALS

PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK 831 in Healthy Adult Asian Subjects

Phase 1 Study of TAK-831 in Healthy Adult Asian Subjects

Study Identifier: TAK-831-1002

Compound: TAK-831

Date: 30 July 2018

Version/Amendment Number: Original Version

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Study Identifier: TAK-831-1002	**Phase:** 1
Title of Study: Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK 831 in Healthy Adult Asian Subjects	
Trial Design: This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of TAK-831 in healthy adult Asian subjects. This study will include up to 4 cohorts of healthy adult Japanese or Chinese subjects. In Cohort 1, a single dose of TAK-831 will be administered under a 3 sequential dose escalation design, and the safety, PK and PD will be assessed. Eight healthy adult Japanese subjects will be randomized in dosing orders of A (100 mg→300 mg), B (100 mg→placebo), and C (placebo→300 mg) at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Day 1 and Day 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge. Cohort 2 will include 8 healthy adult Japanese subjects. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge. Cohorts 3 and 4 will be optional, in which a single dose will be administered followed by multiple doses, and may be studied based on emerging data from the prior cohorts. Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.	
Trial Primary Objective: To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects. **Secondary Objectives:** To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.	
Target: Healthy adult Asian subjects	
Planned Number of Subjects: Cohort 1: 8 subjects Cohorts 2 to 4: 8 subjects per cohort	**Planned Number of Sites:** 1 site
Dose Levels: <Cohort 1> Single dose at 100 mg on Day 1 (Part 1) and 300 mg on Day 9 (Part 2) (fasted) <Cohort 2> Single dose at 600 mg on Day 1. Multiple doses	**Route of Administration:** Oral

(once-daily) at 600 mg on Days 4 to 17 (fasted) <Cohort 3> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted) <Cohort 4> Single dose+multiple dose (once daily). The dose will be defined based on the result of Cohort 1 or Cohort 2. (fasted)	
Duration of Treatment: <Cohort 1> Part 1: Single dose on Day 1 Part 2: Single dose on Day 9 <Cohorts 2 to 4> Single dose on Day 1 and once-daily multiple doses on Days 4 to 17, for 14 days, in each Cohort	**Planned Trial Duration:** <Cohort 1> Screening period: Day -28 to -1 Treatment period: Days 1 to 12 Follow-up period: Day 23 <Cohorts 2 to 4> Screening period: Day -28 to -1 Treatment period: Days 1 to 19 Follow-up period: Day 31

Inclusion Criteria:

Subject eligibility will be determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) $\geq$18.5 kg/m^2 and $\leq$25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the birth control requirements.

Exclusion Criteria:

The subject must be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or diseases.
2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the

trial procedure in the previous trial to the Screening Visit of the current trial.

3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).
5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms at the Screening Visit or Check-in.

Main Criteria for Evaluation and Analyses:

Primary Endpoint

Safety: Adverse event, laboratory tests, vital signs, weight, 12-lead electrocardiogram

Secondary Endpoints

Pharmacokinetics: The following parameters will be calculated.

C_{max} (Cohort 1, Day 1 of Cohorts 2 to 4)

$C_{max,ss}$ (Day 17 of Cohorts 2 to 4)

t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 4)

AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 4)

AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 4)

AUC_{τ} (Days 1 and 17 of Cohorts 2 to 4)

Statistical Considerations:

Pharmacokinetics:

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of TAK-831 in plasma will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time will be presented. Plasma PK parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Days 1

and 9 for Cohort 1 and Day 1 for Cohorts 2 to 4. Additional analyses on dose linearity will be included if appropriate.

Pharmacodynamics:

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2 and 4, as well as Cohort 3. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

Safety:

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2 and 4, and for Cohort 3.

A treatment-emergent adverse event (TEAE) refers to an adverse event that occurs after the start of study treatment. The frequency of all TEAEs, drug-related TEAEs , all TEAEs by intensity, drug-related TEAEs by intensity, TEAEs leading to study drug discontinuation, and serious TEAEs will be summarized. TEAEs will be coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

For continuous values of laboratory findings, vital signs and other safety parameters, summary statistics will be provieded for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

Sample Size Justification:

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, PK and PD of each cohort. This is not based on any statistical rationale.

2.0 STUDY SCHEMATIC

Figure 2.a shows the schematic of the trial design.

Figure 2.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - - Hospitalization - - - - -►		◄- - - - Hospitalization - - - -►			

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion

Sequence of administration	Part 1	Washout interval	Part 2
	Day 1 to 4	Day 5 to 8	Day 9 to 12
A	TAK-831 100 mg	Washout	TAK-831 300 mg
B	TAK-831 100 mg		Placebo
C	Placebo		TAK-831 300 mg

<Cohorts 2 to 4>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening	Hospitalization	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- - - - - - - - - - - - - - - - - - - Hospitalization - - - - - - - - - - - - - - - - - - -►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion

3.0 SCHEDULE OF STUDY PROCEDURES

<Cohort 1>

	Screening period		Treatment period										Early Termination	Follow-up visit
	Screening	Hospitalization	Part 1				Washout interval		Part 2					
Day	-28 to -2	-1	1	2	3	4	5 to 7	8	9	10	11	12		23 (±2)
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Demographics, medical history	X													
Prior medications	X													
Physical examination	X	X	X			X		X				X	X	X (l)
Vital signs (a)	X	X	X	X	X	X		X	X	X	X	X	X	X (l)
Weight, height, BMI (b)	X	X				X		X				X	X	X (l)
12-lead electrocardiogram (ECG) (c)	X	X	X			X		X	X			X	X	X (l)
Laboratory tests (d)	X	X				X		X				X	X	X (l)
Immunological test, alcohol tests	X													
FSH (e)	X													
Urinary drug tests	X	X						X						
C-SSRS (f)	X	X				X		X				X	X	
Sample collection for pharmacogenomic (PGx) Measurements (g)			X											
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X			X	X	X	X	X(k)	
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X	X	X			X	X	X	X		
Urine sample (for future tests) (j)		X		X						X			X	
Study drug administration			X						X					
Adverse events	X	X	X----------continuous monitoring----------X											
Concomitant medications	X	X	X----------continuous monitoring----------X											
Hospitalization		X	X----------X					X	X----------X					

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 1, on Day 8, predose on Day 9, and 1, 4, 12, 24, 36, 48 and 72 hours postdose on Day 9.

(b) Height will be measured at Screening only. Weight will be measured at Screening visit, Day -1, 72 hours postdose on Day 1, Day 8, 72 hours postdose on Day 9.

(c) 12-lead ECG will be measured at Screening, Day -1, predose, 2 and 72 hours postdose on Day 1, Day 8, predose on Day 9, 2 and 72 hours postdose on Day 9.

(d) Laboratory tests will be performed at Screening, on Day -1, 72 hours postdose on Day 1, on Day 8, and at 72 hours postdose on Day 9.

(e) FSH will be measured in postmenopause women only.

(f) C-SSRS will be investigate at Screening, Day -1, Day 4, Day 8, and Day 12.
(g) Samples for PGx measurements will be collected predose on Day 1.
(h) Samples for PK assessment will be collected predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 9, and 0.5, 1. 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(i) Samples for PD assessment will be collected on Day -1 (at 20, 16, 12 hours predose on Day 1), predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose, 1, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 9.
(j) Urine samples will be collected on Day -1, 24 hours postdose on Day 1, and 24 hours postdose on Day 9.
(k) Samples for PK assessment at discontinuation will be collected if it is possible.
(l) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

<Cohorts 2 to 4>

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening	Hospitalization	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Demographics, medical history	X																					
Prior medications	X																					
Physical examination	X	X	X																		X	X (m)
Vital signs (a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (m)
Weight, height, BMI (b)	X	X																			X	X (m)
12-lead electrocardiogram (ECG) (c)	X	X	X			X							X						X		X	X (m)
Laboratory tests (d)	X	X											X								X	X (m)
Immunological test, alcohol tests	X																					
FSH (e)	X																					
Urinary drug tests	X	X																				
C-SSRS (f)	X	X																			X	X
Sample collection for pharmacogenomic (PGx) Measurements (g)			X																			
Blood sample collection for pharmacokinetic (PK) assessment (h)			X	X	X	X							X			X			X	X		X (l)
Blood sample collection for pharmacodynamic (PD) assessment (i)		X	X	X									X			X			X	X		
Cerebrospinal fluid sample collection for pharmacodynamic (PD) assessment (j)		X																		X		
Urine sample (for future tests) (k)		X		X																X		X	

	Screening period		Treatment period																		Early Termination	Follow-up visit
	Screening	Hospitalization	Single dose part			Multiple dose part																
Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	31 (±2)
Study drug administration			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events	X	X	X----------continuous monitoring----------X																			X	X
Concomitant medications	X	X	X----------continuous monitoring----------X																			X	X
Hospitalization		X	X----------X																				

BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; FSH, follicle-stimulating hormone

(a) Vital signs will be measured at Screening, Day -1, predose, 1, 4, 12, 24, 36 and 48 hours postdose on Day 1, predose on Days 4 to 16, predose on Day 17, and 1, 4, 12, 24, and 48 hours postdose on Day 17.
(b) Height will be measured at Screening only. Weight will be measured at Screening, on Day -1, and 48 hours postdose on Day 17.
(c) 12-lead ECG will be measured at Screening, Day -1,presdose and 2 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose, 2 and 48 hours postdose on Day 17.
(d) Laboratory tests will be performed at Screening, Day -1, predose on Day 11, and at 48 hours postdose on Day 17.
(e) FSH will be measured in postmenopause women only.
(f) C-SSRS will be investigate at Screening Visit, Day -1, and Day 19.
(g) Samples for PGx measurements will be collected predose on Day 1.
(h) Samples for PK assessment will be collected predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose on Day 1, predose on Day 4, predose on Day 11, predose on Day 14, predose, 0.5, 1. 1.5, 2, 4, 8, 12, 16, and 24 hours postdose on Day 17.
(i) Samples for PD assessment will be collected at 20, 16, and 12 hours predose on Day 1, predose, 1, 4, 8, 12, and 24 hours postdose on Day 1, predose on Day 11, predose on Day 14, predose, 1, 4, 8, 12, and 24 hours postdose on Day 17.
(j) Samples for PD assessment will be collected on Day -1 and 24 hours postdose on Day 17 (if it is performed in Cohort 3 and thereafter).
(k) Urine samples will be collected on Day -1, at 24 hours postdose on Day 1, and 24 hours postdose on Day 17.
(l) Samples for PK assessment at discontinuation will be collected if it is possible.
(m) The Follow-up Visit will occur by telephone or at the study site if the subject visits the site.

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. Schizophrenia usually develops at late adolescence or early adulthood and manifests in maximum 1% of the population. For those who have relatives of first degree with schizophrenia, the incidence rate is higher by 10% (the concordance rate for schizophrenia in identical twins is 40% to 65%) [1][2][3]. Symptoms of schizophrenia can be subdivided into 3 broad classes: positive, negative, and cognitive symptoms [4]. Positive symptoms include hallucinations, delusions, and disordered thought and speech, and can be summarized as psychosis. Negative symptoms include reduced emotion, reduced ability to experience pleasure (anhedonia), lack of motivation, and reduced social interaction. Finally, cognitive symptoms include poor information processing, impaired ability to focus on objectives, and abnormalities of working memory and learning [4]. Currently available antipsychotics are broadly effective for the treatment of positive symptoms. However, the negative symptoms and cognitive impairment of schizophrenia are the known particular aspects that cause dysfunction, for which no therapy has been approved. There still are significant unmet medical needs.

Hypofunction of N-methyl-D-aspartic acid (NMDA) receptor is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain [5]. D-amino acid oxidase (DAAO) contributes to the metabolism of D-serine in the brain and is highly expressed in the cerebellum. Changes in the D-serine levels or D-serine to total serine ratios have been reported in the plasma of patients with schizophrenia both naive and under drug treatment [6]-[9]. 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 DAAO resides [10]. Therefore, inhibition of DAAO is considered to be a promising target in treatment of schizophrenia.

TAK-831 is a highly selective and potent inhibitor of DAAO. TAK-831 increased D-serine levels in the cerebellum of normal mice and showed efficacy in a mouse model of Friedreich ataxia (FRDA) mouse models. It also demonstrated a positive effect on cognition and social interaction in rodent cognition and behavioral models.

As stated above, TAK-831 is expected to provide a therapeutic effect on FRDA and cognitive impairment as well as negative symptoms associated with schizophrenia.

4.2 Rationale for the Proposed Study

TAK-831 is currently under development for the treatment of FRDA and cognitive impairment as well as negative symptoms of schizophrenia. Three overseas phase 1 studies in healthy adults (single and multiple dose study [TAK-831-1001], positron emission tomography [PET] study to determine DAAO brain enzyme occupancy [TAK-831-1003], and a study to evaluate the food effect [TAK-831-1004]) have been conducted so far, in which TAK-831 was well-tolerated.

In addition, two phase 1 studies in healthy adults (study with single and multiple doses at high dose level [TAK-831-1005] and bioequivalence study [TAK-831-1006]) are being conducted or planned. Two phase 2 studies in patients with schizophrenia (small-scale crossover study to examine the cerebellar functions [TAK-831-2001], and a study to evaluate the efficacy and safety for negative symptoms of schizophrenia [TAK-831-2002]) are also underway. Besides, a phase 2 proof-of-concept (POC) study in patients with schizophrenia is being planned in China. Based on the result of these phase 2 studies, a phase 3 global study (long-term study) has been planned.

In parallel with these development plans, TAK-831 is also being developed in Japan for the treatment of cognitive impairment and negative symptoms associated with schizophrenia. In respect of FRDA, a genetic disease, since there has been no confirmed report as of June 2018 that clearly indicates the existence of Japanese patients, no development plan has been made for FRDA in Japan.

Enrollment of Japanese patients into the phase 3 global study and the phase 2 POC study in China has been considered. This study was planned to examine the safety and pharmacokinetic (PK) of TAK-831 in Japanese as well as to evaluate the safety and PK in Asian healthy subjects for the aforementioned studies.

4.3 Benefit/Risk Profile

Because this study will be conducted in healthy adults, there is no benefit to subjects.

The following risk mitigation measures will be implemented in this study. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, and the phase 1 studies (4 studies, including preliminary data of TAK-831-1005). Procedures may be added during the study as necessary based on evaluation of any additional clinical or nonclinical data.

The safety of TAK-831 has been studied in a prior single dose (up to 750 mg in suspension and 100 mg T1 tablet formulation) and multiple dose (up to 400 mg once daily [QD] in suspension) study in healthy Western subjects (TAK-831-1001), a single dose (up to 500 mg in suspension) PET study to investigate DAAO occupancy in the brain (TAK-831-1003) and a single dose food effect (400 mg T2 tablet formulation) study (TAK-831-1004). These studies have not resulted in a safety signal that would prevent additional studies. Additionally, TAK-831 given as single and 14 days multiple doses (up to 1200 mg in suspension and 600 mg T2 tablet formulation) is currently being studied in healthy adult subjects (TAK-831-1005). TAK-831 has been safe and well tolerated to date (provisional data as of end-April 2018).

- 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 pharmacodynamics (PD) monitoring (venipuncture may cause bruising), and the placement of ECG pads (which may cause some local redness and/or erythema/itching).

- In case of serious adverse events (SAE), 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 Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered to monitor emergent suicidality.

The Investigator's Brochure should be referred for more detailed safety of TAK-831.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed on the basis of the following hypothesis.

- TAK-831 given as single or multiple doses shows no safety issue and is well tolerated.
- The PK of TAK-831 given as single or multiple doses to Asian subjects is equivalent to that in Western subjects.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.2 Trial Secondary Objective

To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.

5.2.3 Trial Exploratory Objective

To assess the effect of TAK-831 on the concentrations of D-serine and L-serine in plasma (and concentrations of D-serine and L-serine in cerebrospinal fluid as necessary) after TAK-831 administration to healthy Asian subjects.

5.3 Endpoints

5.3.1 Primary Endpoint

Safety: Adverse events (AEs), laboratory tests, vital signs, weight, 12-lead electrocardiogram (ECG)

5.3.2 Secondary Endpoints

PK: The following parameters will be calculated.

- C_{max} (Cohort 1, Day 1 of Cohorts 2 to 4)
- $C_{max,ss}$ (Day 17 of Cohorts 2 to 4)
- t_{max} (Cohort 1, Days 1 and 17 of Cohorts 2 to 4)
- AUC_{last} (Cohort 1, Day 1 of Cohorts 2 to 4)
- AUC_{∞} (Cohort 1, Day 1 of Cohorts 2 to 4)
- AUC_{τ} (Days 1 and 17 of Cohorts 2 to 4)

5.3.3 Exploratory Endpoints

- PK: $R_{ac\ (Cmax)}$ and $R_{ac(AUC)}$ on Days 1 and 17 (Cohorts 2 to 4), $t_{1/2z}$, CL/F, V_z/F
- PD: Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma; $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (Days -1 and 18) (may be assessed in Cohort 3 or thereafter based on PD in plasma)

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, PK and PD of TAK-831 in healthy adult Asian subjects. This study will include up to 4 cohorts of healthy adult Japanese or Chinese subjects.

In Cohort 1, a single dose of TAK-831 will be administered at each dose level under a 3-sequential dose escalation design. Eight healthy adult Japanese subjects will be randomized to the sequence of administration A, B, and C at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Days 1 and 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge.

In Cohort 2, a single dose of study drug will be administered to healthy adult Japanese subjects, followed by multiple doses. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Cohorts 3 and 4 will be optional, in which a single dose of study drug will be administered followed by multiple doses, and may be studied based on emerging data from Cohorts 1 and 2.

Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Table 6.a shows the summary of cohorts, and Figure 6.a shows the schematic of the trial design.

Table 6.a Summary of Cohorts

Cohort	Subject	Dose	Remarks
1	Japanese 8 subjects	Part 1: 100 mg (4×25 mg T3 tablet formulation) Fasted, single dose	Wash out period between part 1 and 2 will be 8 days.
		Part 2: 300 mg (1×300 mg T3 tablet formulation) Fasted, single dose	
2	Japanese 8 subjects	600 mg (2×300 mg T3 tablet formulation) Fasted, single dose + multiple dose (once daily)	
3	Chinese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 3 may be run if emerging data from Cohorts 1 and 2 suggest ethnic-related differences in the tolerability and/or PK profile. Dose level will be determined based on the results from Cohorts 1 and 2.
4	Japanese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 4 may be run based on the emerging data from Cohorts 1 and 2 in Asian subjects.

TBD: To be decided

Figure 6.a Study Schematic

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄- - - - -Hospitalization- - - - -►			◄- - - - -Hospitalization- - - -►		

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(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 study site for re-evaluation per investigator's discretion.

<Cohorts 2 to 4>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening	Hospitalization	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄- - - - - - - - - - - - - - - - - - -Hospitalization- - - - - - - - - - - - - - - - - - -►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(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 study site for re-evaluation per investigator's discretion

6.2 Cohort transition/Dose Escalation

In Cohort 1, TAK-831 100 mg or placebo will be administered on Day 1 (Part 1) followed by confirmation of the safety and tolerability (AEs, physical examination, vital signs, weight, laboratory tests and 12-lead ECG) up to 72 hours postdose, and then TAK-831 300 mg or placebo will be administered on Day 9 (Part 2) followed by confirmation of the safety, tolerability and PK up to 72 hours postdose.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohort 1 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether the subsequent cohort should be run.

In Cohort 2, TAK-831 600 mg or placebo will be administered on Day 1, followed by confirmation of the safety and tolerability up to 72 hours postdose. Then, multiple doses of TAK-831 600 mg or placebo will be administered on Days 4 to 17. The data on safety and tolerability as well as PK up to 72 hours postdose will be examined.

The investigator will comprehensively examine the safety and tolerability data as well as PK and PD data emerging from Cohorts 1 and 2 in a blinded manner and discuss with the sponsor (including the medical expert if necessary) as to whether Cohorts 3 and 4 should be run.

In Cohort 2 and onwards, the dose will be escalated but the dose escalation will be discontinued according to the following discontinuation criteria. The dose in Cohort 2 will be adjusted based on the safety and tolerability as well as PK and PD in Cohort 1.

Discontinuation criteria for dose escalation:

- Exposures in any cohort exceed those observed at the highest dose tested in monkey (C_{max} of 3680 ng/mL, AUC_{24} of 35700 hr*ng/mL)
- 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 changes 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 for Study Population

The subject of this study is Japanese or Chinese with a purpose to support the future conduct of studies in Asian subjects. The study will be conducted in healthy adult subjects without any

disease including circulatory or cerebrovascular diseases to appropriately assess the safety and tolerability as well as PK and PD of TAK-831.

6.3.2 Rationale of Trial Design

With a purpose to assess the safety and tolerability as well as the PK and PD profiles of TAK-831 when administered to Asian subject for the first time, this study employed a design with both single and multiple doses.

6.3.3 Rationale for Dose

To this date, the highest dose of TAK-831 tested in healthy Western subjects is 1200 mg (suspension formulation) once daily in the study TAK-831-1005. Based on the preliminary results, there were no significant adverse effects reported at this dose level, and as shown in Table 6.b, the mean steady-state exposure was C_{max} of 3015 ng/mL and AUC_{24} of 10501 h*ng/mL. The dose regimen of 600 mg given once daily (T2 tablet formulation) was also well tolerated and safe in healthy Western subjects. As for the mean steady-state exposures, C_{max} was 1494 ng/mL and AUC_{24} was 5090 h*ng/mL. This exposure at 600 mg was similar to that of monkeys at 100 mg/kg/day, the no-observed-adverse-effect-level (NOAEL).

In the study TAK-831-1005, the PK and PD of TAK-831 given as multiple doses at 100 and 600 mg (per day) to non-Japanese subjects was examined. The dose of 300 mg will be further examined in the study.

Based on the above, the doses of 100, 300 and 600 mg were selected for this study in consideration to the safety in humans as well as the comparability of PK and PD between non-Japanese and Japanese subjects.

In the 13-week repeat dose toxicity study in monkeys that are considered the more sensitive species than rats, adverse effects (vomiting, diarrhea, and loose stool) were noted at 600 mg/kg/day. The NOAEL was 100 mg/kg/day for both sexes.

TAK-831 has been administered at doses up to 1200 mg to non-Japanese, and no SAE has been reported with exposures exceeding the NOAEL. Besides, the adverse effects (vomiting, diarrhea, and loose stool) noted at a dose of 600 mg/kg/day in the 13-week repeat dose toxicity study in monkeys will be easily monitored in clinical trials.

Therefore, it is considered possible to administer doses exceeding the NOAEL exposure by carefully examining the safety and PK in each Cohort in this study. However, We have no information on toxicity at the level exceeding the exposure at 600 mg/kg/day in the 13-week repeated dose toxicity study in monkeys. Dose escalation will be stopped if exposures exceed that at 600 mg/kg/day in monkeys.

Table 6.b PK Parameters in 13-week Repeated Dose Toxicity Study in Monkeys and TAK-831 Given as Multiple Doses to Healthy Adult Subjects

Animal species-Study	Dose (mg/kg/day or mg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
Monkey 13-week (Da 91)	100 mg/kg/day (NOAEL)	1340 (male) 1270 (female)	7490 (male) 9190 (female)
	600 (300 BID) mg/kg/day	4650 (male) 2179 (female)	45500 (male) 25900 (female)
Human MRD (Day 16)	1200 mg QD (suspension formulation)	3015	10501
Human MRD (Day 16)	600 mg QD (T2 tablet formulation)	1494	5090

BID, twice daily; MRD, multiple repeated dose; NOAEL, no-observed-adverse-effect-level; QD, once daily

6.3.4 Rationale for Endpoints

6.3.4.1 Safety Endpoint

The safety endpoints in this study were defined to determine the safety and tolerability following a single dose and multiple dose of TAK-831. These are standard endpoints in the Phase 1 studies in healthy subjects.

Since TAK-831 involves effects on the central nervous system, the C-SSRS will be administered to assess the influence on suicidal ideation or suicidal behavior.

6.3.4.2 Pharmacokinetic Endpoint

Concentrations of TAK-831 in plasma will be examined to assess the PK of TAK-831 given as a single dose or multiple doses to healthy adult Asian subjects, and then the following PK parameters will be calculated.

- PK parameters: C_{max}, $C_{max,ss}$ (Cohorts 2 to 4), t_{max}, AUC_{last}, AUC_{∞}, AUC_{τ} (Cohorts 2 to 4), $R_{ac(Cmax)}$ (Cohorts 2 to 4), $R_{ac(AUC)}$ (Cohorts 2 to 4), $t_{1/2}$, CL/F, V_z/F

6.3.4.3 Pharmacodynamic Endpoint

Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max} following TAK-831 doses will be examined to assess the PD of TAK-831 in healthy adult Asian subjects. Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid may be assessed as necessary.

6.3.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

The objective of this section is to specify the sequence of procedures in the cases where the timing of each procedure overlaps.

- Safety evaluation will be conducted within the predetermined allowance window as far as possible.
- Blood samples for PK assessment will be collected at time points as close to the specified time as possible.
- Other procedures must be completed at time points as close to the specified or planned hours as possible irrespective of before or after the specified times.
- If the timing of blood sampling and ECG or vital signs measurement overlap, blood sampling should be prioritized. ECG or vital signs measurement may be performed within an acceptable time window (Appendix C).
- The priority may be changed upon agreement between the investigator and the sponsor based on discussion.
- Any test and procedure necessary to immediately assess safety concerns at the time of AEs must be prioritized over other regular predetermined procedures.
- The safety of subjects in the follow-up period may be confirmed by telephone unless abnormal, clinically significant findings are observed upon discharge.

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

The entire study will start when the first subject signs the informed consent form to participate in this study.

6.4.2 Definition of End of the Trial

The study will end when the last subject completes the last planned visit or follow-up visit (or last communication [may be via telephone] relating to the planned visit) or is withdrawn from the study or lost to follow up (the status that the subject cannot be reached by the investigator).

6.4.3 Definition of Trial Discontinuation

The study may be discontinued for reasons other than safety such as the followings:

- A finding (eg, PK, pharmacodynamics, efficacy, biologic targets) from the other nonclinical or clinical studies results with the study drug in the study discontinuation for non-safety related reasons.
- Data from drugs classified in the same class as the study drug, or methodologies used in this study become available and results in the study being stopped for a non-safety related reason.
- Study discontinuation due to non-scientific and non-safety-related reasons, such as slow enrollment.

Discontinuation of the clinical study for safety reasons:

- The study is prematurely terminated because other clinical or non-clinical trials where TAK-831 or other drugs of the same class are administered have confirmed unexpected safety concerns based on the methodology used in this study

6.4.4 Criteria for Premature Termination or Suspension of the Trial

6.4.4.1 Criteria for Premature Termination or Suspension of the Trial

The study will be completed as planned unless 1 or more of the following criteria are met that require temporary suspension or early termination of the study.

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

6.4.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the Sponsor, an institutional review board (IRB), or a regulatory authority elects to terminate or suspend the study, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

6.4.5 Criteria for Premature Termination or Suspension of a Study Site

6.4.5.1 Criteria for Premature Termination or Suspension of a Study Site

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

6.4.5.2 Procedure for Premature Termination or Suspension in a Study Site

In the event that the Sponsor, an IRB, or a regulatory authority elects to terminate or suspend of the study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria.

1. The subject must understand the study procedures and agree to participate by providing written informed consent (for Chinese subjects, an interpreter should be present as necessary).
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be male or female (of nonchildbearing potential) aged 20 to 55 years, inclusive, at the Screening.
4. The subject must have a body mass index (BMI) ≥18.5 kg/m^2 and ≤25.0 kg/m^2 at the Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months prior to the Screening.
6. Chinese subjects are defined as subjects who were born in mainland China, and their biological parents and grandparents must all have been of Chinese origin (for Cohort 3 only).
7. Chinese subjects who have lived out of China for more than 5 years must not have significantly modified their diets since leaving China (for Cohort 3 only).
8. The subject must be judged to be in good health by the investigator or sub-investigator, based on clinical evaluations including laboratory tests, medical history, full physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening. and prior to the first dose of study drug.
9. The subject must meet the following birth control requirements:
    - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug. No restrictions will be required for a vasectomized male subject provided the subject is at least 1 year post bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
    - Is a male subject who agrees to not donate sperm from the first dose of study drug until 95 days (5 half-lives plus 90 days) after the last dose of study drug.
    - Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
        a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or ≥6 months of spontaneous amenorrhea in females aged >45 years with

serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels should be required.

b) Hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

c) Had a tubal ligation with appropriate documentation of surgical procedure.

d) Congenital conditions such as uterine aplasia etc.

[Rationale for the inclusion criteria]

Inclusion criteria 1, 2, 5, 8 and 9:

These are standard criteria for clinical pharmacology studies in healthy adult subjects and defined in consideration to the safety of subjects.

Inclusion Criterion 3:

This is a standard criterion for clinical pharmacology studies in healthy adult subjects for sex. This is a standard criterion for clinical pharmacology studies in healthy adult subjects for age.

Inclusion Criterion 4:

This is the range of normal weight in the diagnosis criteria for obesity and obesity disease [11] proposed by the Japan Society for the Study of Obesity.

Inclusion Criterion 6:

This is set to appropriately assess the safety and PK in Chinese.

Inclusion Criterion 7:

This is set to eliminate the influence by dietary habits on the PK.

7.2 Exclusion Criteria

The subject will be excluded from participating in the study if the subject meet any of the followings.

1. The subject has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary, or presents with major neurological (including stroke and chronic seizures) abnormalities or diseases.
2. The subject has participated in another investigational trial within 4 weeks before the pretrial visit (Screening). The 4-week window will be derived from the date of the last trial procedure and/or adverse events related to the trial procedure in the previous trial to the Screening Visit of the current trial.
3. The subject is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the sponsor.
4. The subject has a history of cancer (malignancy).

5. The subject has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. The subject has a positive alcohol or drug or immunological screen.
7. The subject is of childbearing potential or lactating.
8. The subject had major surgery, received or lost 1 unit of blood (approximately 500 mL) within 8 weeks prior to the first dose of study drug.
9. The subject with any gastrointestinal surgery that could impact upon the absorption of study drug.
10. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or related compounds.
11. The subject is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
12. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
13. The subject who consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
14. The subject has a history of drug abuse.
15. The subject has a (QT interval with Fridericia's correction method) QTcF >450 msec (males) or >470 msec (females) or PR outside the range of 120 to 220 msec at the Screening Visit or Check-in.

[Rationale for the exclusion criteria]

Exclusion Criteria 1, 15:

This is set to eliminate the influence on safety evaluation for TAK-831.

Exclusion Criterion 2:

This is a minimum duration in which the previous clinical trial is considered to have no influence in reference to "General Considerations for Clinical Trials" [12] in order to ensure the safety of subjects.

Exclusion Criteria 3, 4, 6, 7, 12, 13, 14:

These are standard criteria for clinical pharmacology studies and defined in consideration to the safety of subjects.

Exclusion Criterion 5:

This is defined in consideration to the safety of subjects.

Exclusion Criteria 8, 9, 11:

This is defined in consideration to the safety of subjects. This is also defined for potential influence on PK and PD assessment.

Exclusion Criterion 10:

This is set to exclude subjects who have a known hypersensitivity to any component of the formulation of TAK-831 or related compounds in consideration of the safety of subjects.

7.3 Excluded Medications Supplements, Dietary Products

Table 7.a shows excluded medications, supplements, and dietary products.

Use of the drugs listed on Table 7.a (prescribed drugs and over-the-counter [OTC] drugs), vitamins, supplements, and dietary products will be excluded from a specified time point to until discharge given the effect on the safety and PK. Use of prohibited concomitant drugs will be allowed when the investigator or sub-investigator deems it necessary to use any of the concomitant drugs for reasons including treatment of an AE.

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

Table 7.a Excluded Medications, Supplements, Dietary Products

From 28 days before admission (Day -1) to the last discharge	7 days before admission (Day -1) to the last discharge	72 hours before admission (Day -1) to the last discharge
• Prescription drugs	• OTC drugs (including aspirin or aspirin-containing drugs) (a)	• Caffeine or xanthine containing products
• Supplements (St. John's wort, ginseng, kava kava, ginkgoes, chinese herbal medicine, and melatonin)	• Vitamins	
• Vaccination/vaccine (b)	• Beverages containing grapefruit (fruit juice, flesh), star fruits (fruit juice, flesh), citrus aurantiums (high acidity), orange (seville oranges), or marmalade	
	• Apple, orange or pineapple juice	
	• Brassicaceae vegetables (kale, cress, collard greens, kohlrabi, brussels sprouts, and mustard).	
	• Meat cocked over the charcoal	
• Nicotine-containing products	• Alcohol containing products	
• CYP 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1 and 2A6 inhibitors/inducers OTC drugs (c)		

CYP: cytochrome P-450, OTC drugs: over-the-counter drugs
Note: Excludes the drug needs to be administered to treat an AE and if the investigator or sub-investigator considers necessary to use the drug
(a) Use of paracetamol (≤1 g/daily) will be allowed.
(b) Includes H1N1 and other influenza vaccines, however, not limited to these medications.
(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Diet and fluid (except water) must be ingested at least10 hours before clinical laboratory tests.

On the day before clinical laboratory tests, evening meal must be ingested by 21:00.

During hospitalization, pre-specified diets must be ingested, and other diets will be prohibited. After discharge, excessive drinking and eating must be avoided until completion of follow-up period.

7.4.2 Activity

Smoking is prohibited during the study.

Excessive exercise is prohibited during the study.

Blood donation is prohibited for at least 12 weeks (84 days) from completion of the last test.

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the visit in advance whenever possible, and should be reported the circumstances and therapy after visit. The investigator or sub-investigator should communicate that medical institution about the subject's participation in the study.

7.5 Documentation of Subject Failure

The investigator or sub-investigator must account for all subjects who sign informed consent. If a subject discontinues the study before the first study drug administration, the investigator or sub-investigator should complete the electronic case report form (eCRF).

The primary reason for subject failure is to be recorded in the eCRF using the following categories:

- Death
- AE
- Screening failure (failed inclusion criteria or did meet exclusion criteria) <specify the reasons>
- Protocol deviation
- Lost to follow up
- Withdrawal by subject <specify the reasons>
- Study terminated by the Sponsor
- Pregnancy
- Sample size sufficient
- Other <specify the reasons>

Any subject identification number, once assigned to a subject, should not be reused if the assigned subject discontinues the study prior to the first study drug administration. Nevertheless, if a reserve subject is enrolled in the other cohort, the same subject identification number may be used.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

Primary reasons for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF using the following categories. For the subject who is withdrawn from the study before the first study drug administration in Period 1, refer to Section 7.5.

1. Death
   The subject died on study.

   Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). Refer to Section 10.2.9.3 for reporting procedures.

2. 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.

The study drug will be immediately discontinued if a condition meets any following criteria during the treatment, and appropriate follow-up will be performed (clinical laboratory tests will be repeatedly performed until the clinical laboratory test profiles have normalized or returned to baseline, refer to Section 9.2.9.1):

- Liver Function Test (LFT) Abnormalities
  - ALT or AST >8×the upper limit of normal (ULN), or
  - ALT or AST >5×ULN and persists for more than 2 weeks, or
  - ALT or AST >3×ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (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%)
- Prolonged QT/QTcF intervals

  If at least one remarkable prolonged QT interval was observed on 12-lead ECG (eg, absolute value of QTcF intervals >500 msec or an increase >60 msec from baseline), and the investigator or sub-investigator considered inappropriate to continue the study.

3. Protocol deviation
   The discovery after the start of the first study drug administration 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.
4. 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 in the subject's source documentation.
5. Pregnancy
   If a subject was found to be pregnant.

   Note: Participation in the study is immediately discontinued for any pregnancy. Refer to Appendix B for the procedures.
6. Voluntary withdrawal
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
7. Study terminated by the Sponsor
   The Sponsor terminates the study.

8. Other

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

7.7 Procedures for Discontinuation or Withdrawal of a Subject

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

7.8 Subject Replacement

The Part 1 in Cohort 1 and Cohorts 2-4 can have a few reserve subjects considered eligible for participation in the study based on screening test. If a subject has not received the study drug as scheduled during the study owing to any reason occurring before the study drug administration, a reserve subject will be allowed to participate in the study.

If a subject withdraws from the study after initiation of the study drug, the subject will not be replaced with a reserve subject.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

[Drug product]

Code name: TAK-831

Dosage form and strength:

TAK-831 tablet is a yellowish-red film-coated tablet containing 25 or 300 mg of TAK-831.

TAK-831 placebo tablet contains no TAK-831 and has same appearance as TAK-831 tablet.

8.1.1 Clinical Study Drug Labeling

Study drug labeling will show name of the study drug, quantity and storage condition of the study drug, manufacture number, expiration date, protocol number, name and address of the Sponsor, and statement the drug is for clinical trial use only.

8.1.2 Clinical Study Drug Inventory and Storage

TAK-831 is stored at a room temperature (1°C to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used, or returned to the Sponsor or its designee. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Randomization Code Creation and Storage

The personnel responsible for randomization (the Sponsor's designee) will prepare the randomization table/schedule prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.4 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigator must store the emergency key until the time of an emergency blind break or the end of the trial.

Since maintenance of the blind may be compromised because of results from drug concentrations and PD assessments, such results should not be disclosed prior to blind breaking. In the event that results must be reported to the investigator prior to breaking the blind, all efforts should be made to maintain the blind (eg, by changing a medication identification number in order to avoid identification of subjects by laboratory site personnel). Detailed procedures for measuring subject drug concentration levels and PD assessments will be provided in the separately created procedure for directions on the handling of biological samples for measuring drug concentrations and PD assessments.

To unblind a subject, the study drug blind can be obtained by opening a sealed envelope.

The Sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded in the eCRF.

If the investigator or sub-investigator breaks the blinding of the study drug, study drug must be stopped immediately and that subject must be withdrawn from the study.

No change should be made to any subject assessment after unblinding (except cases where the investigator or sub-investigator is not informed of unblinding information [unblinding for open-label analysis for the Sponsor]).

8.1.5 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (a site designee) will receive the pharmacy manual created by the Sponsor, and follow the procedures for managing the Sponsor-supplied drug supplies. A copy of these procedures will be provided to the investigator as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the Sponsor-supplied drug. The manual will also describe procedures for the collection of unused medications from the subject and their return to the Sponsor, or the destruction of any unused supplies.

The on-site pharmacist (a site designee) will immediately return any unused study drugs in a sealed package to the Sponsor after the study is closed at the investigational site.

9.0 STUDY PROCEDURES

The investigator or sub-investigator should collect data according to the procedures described in the following sections. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site designee whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the initiation of any study procedures. The requirements of informed consent are described in Section 13.2.

A separate informed consent form pertaining to the collection, storage, and analysis of samples must be obtained prior to collecting any blood sample for pharmacogenomic research for this study.

9.1.1.1 Assignment of Subject Identification Number

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

9.1.1.2 Study Drug Assignment

In Cohorts 1-2 and Cohorts 3-4 (if added), the subjects will be assigned in the order of medication identification number by Cohort according to the randomization code. The medication identification number will be a 4-digit number, starting with the following number:

Cohort 1: 1001, Cohort 2: 2001, Cohort 3: 3001, Cohort 4: 4001

The assigned medication identification number will be used to identify the samples for PK by the study site and the only number to identity a subject during blood sampling for PK. The number will be always shown on the sample vials, which are sent to the laboratory to evaluate the PK. The laboratory will report the results using this number. The number will be used for only the purpose described in this section and cannot be replaced with the 7-digit subject identification number, which is assigned at the time of informed consent procedure and used in all other procedures during the clinical study period to identify a subject. In case of subject replacement, the study drug with a medication identification number for the withdrawn subject will be used by the replacing subject.

9.1.2 Inclusion and Exclusion

Each subject will be assessed according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Demographic information to be obtained will include date of birth, sex, height, weight, caffeine use, alcohol use, and smoking status of the subject.

Medical history to be obtained will include determining whether the subject has any clinically significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions. Medication history information to be obtained will include any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Subjects will be asked whether they have taken any medication other than the study drug (used from the signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC drugs, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication names, route of administrations, start and end dates, and reasons for use.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

9.2.2 Height and Weight

Each subject should have a height and weight measured. Height will be recorded in centimeters without decimal places (rounding off the first decimal place). Weight will be collected in kilograms (kg) with the first decimal place (rounding off the second decimal place).

9.2.3 BMI

BMI is calculated using the formula provided below.

Metric: BMI=weight (kg)/height $(m)^2$

The values should be calculated to the first decimal place (rounding off the second decimal place). When the BMI is used as entry criteria, then this determination must be made after rounding.

9.2.4 Vital Signs

Vital signs will include body temperature (axilla measurement), sitting blood pressure (systolic and diastolic, after resting more than 5 minutes), and pulse (beats per minute).

9.2.5 12-Lead ECG

A standard 12-lead ECG will be recorded. Subjects should be resting in a recumbent position for at least 5 minutes before each ECG measurement.

The investigator or sub-investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: normal or abnormal. If an ECG is abnormal, the investigator or sub-investigator (or a qualified observer at the investigational site) will judge clinical significance of the abnormality. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTcF.

9.2.6 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be performed at the study procedures-specified time point. The investigator or sub-investigator will evaluate suicide risks based on the information obtained from C-SSRS. For any suicidal ideation and suicidal behavior will be documented as an adverse event.

9.2.7 Study Drug Administration

In Cohort 1, a single dose of TAK-831 T3 tablet 25 mg×4 tablets or placebo will be orally administered on Day 1 (Part 1), and a single dose of TAK-831 T3 tablet 300 mg×1 tablet or placebo will be orally administered on Day 9 (Part 2).

In Cohort 2, a single dose of TAK-831 T3 tablet 300 mg×2 tablets or placebo will be orally administered on Day 1, followed by multiple doses of TAK-831 T3 tablet 300 mg×2 tablets (once daily) or placebo on Days 4-17.

The study drug will be orally administered with 150 mL of water at a fasted state (fasted at least 10 hours before administration).

In Cohorts 3 and 4, the dose of the study drug will be determined based on the data obtained from Cohorts 1 and 2.

9.2.8 AE Monitoring

AE monitoring will begin after the signing of informed consent. A complete description of AE collections and procedures is provided in Section 10.2.

9.2.9 Laboratory Procedures and Assessments

Laboratory samples will be taken following a minimum 10 hour overnight fast on the days stipulated in the Schedule of Study Procedures (Section 3.0). Refer to Appendix C for the amount of blood samples.

The investigator or sub-investigator will take responsibility for evaluation of the clinical laboratory test results and storage. The investigator will maintain a copy of the reference ranges for the laboratory used.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Red blood cell count	White blood cell count and differential leukocytes (lymphocytes, neutrophils, eosinophils, basophils, and monocytes)
Hemoglobin	Hematocrit
Platelet count	

Chemistry

Chemistry evaluations will consist of the following chemistry tests:

Albumin	Creatinine
ALP	Glucose
ALT	Sodium
AST	Calcium
γ-GTP	Creatine kinase
Total bilirubin	Potassium
Direct bilirubin	Chloride
Total protein	PT
Urea nitrogen	APTT

Urinalysis

Urinalysis will consist of the following tests:

pH	Specific gravity
Qualitative (protein, glucose, occult blood, and nitrite)	Urinary sediment (erythrocytes, leukocytes, and cylinder) (a)

(a) Will be performed for any abnormal urinalysis parameter.

Other

Immunological tests HIV antibody and antigen tests, hepatitis tests (HBs antigen and HCV antibody)
Alcohol tests (urinalysis or breath test)
Urinary drug tests
FSH (postmenopausal female subjects only)

HIV: human immunodeficiency virus, HBs: hepatitis B surface antigen, HCV: hepatitis C virus, FSH: follicle-stimulating hormone

Note: The investigator or sub-investigator will report the results of immunology, urine drug tests, and alcohol tests directly to subjects. The Sponsor will confirm the overall test results (as "Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug.

If subjects experience an ALT or AST of >3×ULN (except the tests at Screening), follow-up laboratory tests (at a minimum, serum alkaline phosphatase [ALP], ALT, AST, total bilirubin,

gamma-glutamyl transferase [γ-GTP], and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Refer to Section 7.6 and Section 10.2.9.4 for the discontinuation or withdrawal criteria of a subject and the appropriate guidance on reporting abnormal LFTs as SAEs, respectively.

9.2.9.2 Urine sample for Future Tests

Urine samples for future tests will be collected according to the Schedule of Study Procedures (Section 3.0).

If acute renal failure is suspected, urinary biomarkers such as KIM-1, NGAL, and cyctatin C may be measured using the collected sample.

9.3 Biomarker, PK, PD, and PGx Samples

Samples for PK, PD, and PGx will be collected according to the schedule of study procedures (Section 3.0). Separated procedures describe the details of sampling, handling, and transferring to central laboratory. The actual sampling time for PK and PD analyses will be documented in the subject's source documents and eCRF.

Table 9.a shows primary specimen collections.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	PK Analysis	Mandatory
Plasma sample for PD	Blood	Plasma	PD analysis	Mandatory
Cerebrospinal fluid sample for PD	Cerebrospinal fluid	Cerebrospinal fluid	PD analysis	Optional
Blood sample for DNA PGx	Blood	DNA	PGx analysis	Optional

9.3.1 PK Measurements

The following PK parameters will be calculated from plasma concentrations of TAK-831, unless otherwise specified.

Mark/Term	Definition
Plasma	
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to time of infinity
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
C_{max}	Maximum observed plasma concentration (measured value)
$C_{max, ss}$	Maximum observed steady-state plasma concentration during a dosing interval (measured value)
t_{max}	Time of first occurrence of C_{max}
$t_{1/2z}$	Terminal disposition phase half-life
λ_z	Terminal disposition phase rate constant
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration
CL/F	Apparent clearance after extravascular administration
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}
$R_{ac(AUC)}$	Accumulation ratio based on AUC

9.3.1.1 Plasma for PK Measurements

Blood samples for plasma TAK-831 concentration will be collected (Table 9.b). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.b Blood Sample Collection for PK Analysis

Dose Levels:	Date of administration	Sampling time
Single dose	1	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
	9	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	1	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, and 48 hours postdose
	4, 11, 14	Predose
	17	Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 16, and 24 hours postdose

9.3.2 PD Analysis

The following PD parameters will be calculated from plasma concentrations of D-serine and L-serine, unless otherwise specified

Mark/Term	Definition
Plasma	
$AUEC_{24}$	Area under the effect-time curve from time 0 to 24 hours postdose
E_{max}	Maximum effect
time to E_{max}	Time to reach maximum PD effect

9.3.2.1 Plasma Samples for PD Analysis

Blood samples will be collected to measure plasma D-serine and L-serine concentrations (Table 9.c). The sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples.

Table 9.c Blood Sample Collection for PD Analysis

Dose Levels:	Specimen	Date of administration	Sampling time
Single dose	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
		9	Predose, 1, 4, 8, 12, 24, 36, 48 and 72 hours postdose
Single dose+multiple dose (once daily)	Plasma	1	20, 16, and 12 hours predose, predose, 1, 4, 8, 12, and 24 hours postdose
		11, 14	Predose
		17	Predose, 1, 4, 8, 12, and 24 hours postdose

9.3.2.2 Cerebrospinal fluid samples for PD Analysis

Cerebrospinal fluid will be collected to measure D-serine and L-serine concentrations (3.0 mL per scheduled time). The cerebrospinal fluid sampling schedule may change based on emerging data but the number of samples will not exceed the number of planned samples. After Cohort 3, collection of cerebrospinal fluid in the next Cohorts will be determined based on the results of plasma D-serine and L-serine concentrations obtained from the previous Cohorts.

9.3.3 PGx Measurements

9.3.3.1 Blood Sample for DNA PGx Measurements

When sampling of whole blood for pharmacogenomic analysis occurs, the subject must sign informed consent/be consented separately for PGx sampling, storage and analysis. PGx measurement is a part of the study, but participation of a subject is optional.

One 6-mL of whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected prior to the single dosing on Day 1 from each consenting subject in the study.

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. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification by the Sponsor. “Stored samples” are defined as samples that are 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 the study drug or related drug.

The sampling of whole blood for PGx and genotyping analysis is mandatory. Every subject must sign informed consent separately for PGx sampling. DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms.

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 exploratory research with the samples for PGx measurements.

9.3.4 Confinement

Cohort 1:

Subjects will be hospitalized from Day -1 to Day 4 and Day 8 to Day 12 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Days 4 and 12.

Cohorts 2-4:

Subjects will be hospitalized from Day -1 to Day 19 and will be discharged after the investigator or sub-investigator confirm no clinically significant health problems based on the examination and tests on Day 19.

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 clinical study; it does not necessarily have to have a causal relationship with the the treatment (including the study drug) or study participation.

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered 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 or sub-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 may be considered as AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring for an abnormal value are not considered as an intervention. In addition, repeated or additional non-invasive tests for verification and evaluation of abnormality or monitoring purpose will not be considered as 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 conditions and should NOT be recorded as an AE. The observations or evaluations of first examination at baseline (eg, laboratory test, ECG, X-ray,

etc) should NOT be recorded as AEs 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). The investigator or sub-investigator 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. The investigator or sub-investigator should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a pre-existing chronic 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. The investigator or sub-investigator 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 drug or after any change in study drug, the worsening or complication should be recorded as a new AE. The investigator or sub-investigator should ensure that the event term reported captures the change in adverse event (eg, "worsening of…").

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to the signing of informed consent are not considered AEs. However, if a preplanned procedure is performed earlier (eg, as an emergency) due to a worsening of a 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 study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the sub-investigator to decide whether a dose is to be considered as overdose, in consultation with the Sponsor.

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.9.
- 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 Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

Severity/Intensity of AEs will be classified or defined as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying disease, 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 the underlying disease, complications, concomitant medications and concurrent treatments.

10.2.3 Assigning Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

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

10.2.4 Start Date

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

10.2.5 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.

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken with Study Treatment

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

10.2.8 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/signs/symptoms have almost disappeared; the abnormal laboratory values improved, but have 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 values on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.9 Collection and Reporting of AEs, SAEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent and continue until the follow-up visit or phone call.

10.2.9.2 Reporting AEs

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

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator or sub-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 Adverse Event (Frequency)
- Severity/Intensity.
- The Investigator's or sub-investigator's opinion of the causal relationship between the event and administration of study drug(s). (Related/Not related)
- Action taken with the study drug
- Outcome of the event.
- Seriousness.
- Timing of occurrence (after administration of the study drug)

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator or sub-investigator to the Sponsor within 1 business day of the first onset or notification of the SAE, along with any relevant information. The

investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. 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 or sub-investigator's name.
- Name of the study drug(s).
- Causality assessment.

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

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator or sub-investigator should complete the follow-up SAE form or provide other written documentation immediately to the Sponsor. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory values, discharge summary, postmortem results) in the institution should be submitted to the Sponsor, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.2.9.4 Reporting of Abnormal LFTs

If a subject experiences 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 10.2.9.3. The investigator or sub-investigator will contact the monitor for discussion and investigation of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease, medical history/ongoing disease. Follow-up laboratory tests as described in Section 9.2.9 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs and Regulatory Authorities

The Sponsor will report all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs and the head of the study site. 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 the study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definitions of analysis variables, and analysis methodologies to address all study objectives.

11.1.1 Analysis Sets

In this study, 3 analysis sets are defined: the Safety Analysis Set, the PK Analysis Set, and the PD analysis Set. The definition of each analysis set will be described in the SAP.

The Sponsor will verify the validity of the definitions of the analysis sets and the rules for handling data in consultation with a medical expert, as needed, prior to unblinding the study drug assignment. The Sponsor will address all remaining uncertainties not specified at planning, and will finalize the SAP prior to unblinding of subject's treatment assignment.

11.1.1.1 Safety Analysis Set

The Safety Analysis Set will be defined as all subjects who received at least one dose of study drug.

11.1.1.2 PK Analysis Set

The PK Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PK parameter.

11.1.1.3 PD Analysis Set

The PD Analysis Set will consist of subjects who received at least one dose of study drug, and who were appropriately evaluable for at least 1 PD parameter.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the Safety Analysis Set.

11.1.3 PK Analysis

Endpoints and its analytical method

[Endpoints]

Secondary endpoints: C_{max} (Cohort 1, Day 1 in Cohorts 2 to 4), $C_{max,ss}$ (Day 17 in Cohorts 2 to 4), t_{max} (Cohort 1, Days 1 and 17 in Cohort 2 to 4), AUC_{last} (Cohort 1, Day 1 in Cohorts 2 to 4), AUC_{∞} (Cohort 1, Day 1 in Cohorts 2 to 4), AUC_{τ} (Days 1 and 17 in Cohorts 2 to 4)

Exploratory endpoints: $R_{ac(Cmax)}$ and $R_{ac(AUC)}$ (Cohort 2 to 4) on Days 1 and 17, $t_{1/2z}$, CL/F, V_z/F

[Analytical method]

In the "PK analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and treatment period for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of TAK-831 in plasma will be summarized by each scheduled sampling time using summary statistics. Individual plasma concentration data versus time will be presented. Plasma PK parameters, including dose-normalized C_{max} and AUC, will be summarized by dose and day using summary statistics. Accumulation of TAK-831 from Day 1 to Day 17 will be assessed by summarizing the ratio of C_{max} and AUC at Days 1 and 17 by dose. Dose linearity in plasma PK parameters (C_{max} and AUC) will be assessed graphically for those parameters at Day 1 and Day 9 for Cohort 1 and Day 1 for Cohorts 2 to 4. Additional analyses on dose linearity will be included if appropriate.

11.1.4 PD Analysis

Endpoints and its analytical method

[Endpoints]

- Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, $AUEC_{24}$, E_{max} and time to E_{max}
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (on Days -1 and 18) (if available)

[Analytical method]

In the "PD analysis set", the following analyses will be performed by dose for Cohort 1 and by dose and each scheduled sampling time for Cohorts 2 and 4, as well as Cohort 3.

Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in plasma and concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (if available) will be summarized by each scheduled sampling time using summary statistics. AUEC, E_{max} and time to E_{max} of D-serine, L-serine at Days -1 and 1 and 17, and the ratio of D-serine to total serine in plasma, and change and percent the change from baseline will be summarized by day using summary statistics. The potential relationship between TAK-831 exposure and biomarker response will be explored graphically. Additional statistical or PK-PD analyses will be included if appropriate.

11.1.5 Safety Analysis

Endpoints and its analytical method

[Endpoints]

AEs, laboratory findings, vital signs, weight, 12-lead ECG

[Analytical method]

In the "safety analysis set", the following analyses will be performed by dose for Cohort 1, for Cohorts 2 and 4, and for Cohort 3.

11.1.5.1 AEs

A treatment-emergent adverse event (TEAE) is defined as an AE whose date of onset occurs on or after the start of study drug.

The followings will be analyzed for TEAEs. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

- Frequency of all TEAEs
- Frequency of drug-related TEAEs
- Frequency of all TEAEs by intensity
- Frequency of drug-related TEAEs by intensity
- Frequency of TEAEs leading to study drug discontinuation
- Frequency of serious TEAEs

11.1.5.2 Clinical Laboratory Evaluation

Summary statistics will be provided for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables.

11.1.5.3 Vital Signs

Summary statistics will be provided for the observed values at each evaluation time point and changes from baseline.

11.1.5.4 Other Safety Parameters

The ECG parameters will be summarized as follows. Summary statistics will be calculated for observed values and change from baseline at each evaluation time point. Pre- and post-dose shift tables will be prepared for categorical variables. The analysis methods for other endpoints will be specified in detail in the SAP.

11.2 Determination of Sample Size

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, and PK of each cohort. This is not based on any statistical rationale.

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.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, and informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, sub-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 or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the Sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the Sponsor and the head of the study site of the deviation or changes as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the Sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

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 study 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 [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency [MHRA], and the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory authority, the Sponsor should be notified immediately. The investigator and the head of the institution guarantee 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 Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for GCP. The investigator will conduct the study according to applicable local or regional regulatory requirements in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

The IRB must be constituted according to the applicable local requirements of each participating region. The Sponsor or the designee will require documentation noting all names and titles of the members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. The Sponsor or the designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the written informed consent form, and, if applicable, subject recruitment materials and/or advertisements, if applicable, and other documents required by all applicable laws and regulations, must be submitted to the IRB for approval. The IRB's written approval of the protocol and subject written informed consent must be obtained and submitted to the Sponsor or the designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, written informed consent form) reviewed; and state the approval date. The Sponsor will notify the study site that the Sponsor has confirmed the adequacy of the study site regulatory documentation. Until the study site receives a notification, no protocol activities, including screening, may occur.

The study site must adhere to all requirements stipulated by its respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the written 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, and submission of the investigator's final status report to IRB. All IRB 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 and the 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 written informed consent form describes 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 further explains 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 approval of the written informed consent form. The written informed consent form must be approved by both the IRB and the Sponsor prior to use.

The informed consent form must be described in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines he or she will participate in the clinical study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed by the investigator or sub-investigator to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form will be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects 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 prior to analysis. Notify the 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 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, MHRA, and PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents),

including 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 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. The investigator or sub-investigator needs to obtain a prior written approval from the Sponsor to publish any information from the study externally, such as to a professional association.

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 the facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

13.5 Clinical Trial Results Disclosure

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

13.6 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study 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 or sub-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

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.2 Investigator Agreement

A separate agreement will be provided to the study site.

14.1.3 Study-Related Responsibilities

A separate contact information list (Protocol attachment 1) will be provided to the study site.

14.1.4 List of Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUEC	area under the effect-time curve
BMI	body mass index
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DAAO	D-amino acid oxidase
DNA	deoxyribonucleic acid
E_{max}	maximum effect
FDA	Food and Drug Administration
FRDA	Friedreich ataxia
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
γ-GTP	gamma-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requrements for Pharmaceuticals for Human Use
INR	international normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency

Term	Definition
NMDA	*N*-methyl-D-aspartate
NOAEL	no observed adverse effect level
PET	positron emission tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
POC	proof-of-concept
R_{ac}	accumulation ratio
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occrurrence of C_{max}
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration

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 eCRFs

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

The Sponsor or its designee will supply the study sites with access to eCRFs. The Sponsor will provide training opportunities for the 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 the Sponsor (or the designee) and will be answered by the study 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.

The 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.

The following data will not be recorded in the eCRFs.

- PGx analysis results
- Clinical laboratory test results
- Drug concentration measurement results
- PD measurement results

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 or sub-investigator with use of change and modification records of the eCRFs. The investigator must review the data change for completeness and accuracy, and must e-sign.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the Sponsor or its designee. 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 or the head of the study site agree to keep the records stipulated in Section 15.1 and those documents that include (but not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated 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.

The investigator and the head of the study site are required to retain essential documents until the day specified as 1 or 2 below, whichever comes later. However, if the Sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the Sponsor.

1. The day on which marketing approval for the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion for the study.

In addition, the investigator and the head of the study site should retain the relevant essential documents until the receipt of a Sponsor-issued notification that states the retention is no longer required.

16.0 REFERENCES

[1] Sham PC, Gottesman, II, MacLean CJ, Kendler KS. Schizophrenia: sex and familial morbidity. Psychiatry Res 1994;52(2):125-34.

[2] Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999;56(2):162-8.

[3] Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo UH, Bassett AS, Cornblatt BA, Kestenbaum CJ, et al. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch Gen Psychiatry 1995;52(10):857-65.

[4] van Os J, Kapur S. Schizophrenia. Lancet 2009;374(9690):635-45.

[5] Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 2003;169(3-4):215-33.

[6] Calcia MA, Madeira C, Alheira FV, Silva TC, Tannos FM, Vargas-Lopes C, et al. Plasma levels of D-serine in Brazilian individuals with schizophrenia. Schizophr Res 2012;142(1-3):83-7.

[7] Ohnuma T, Sakai Y, Maeshima H, Hatano T, Hanzawa R, Abe S, et al. Changes in plasma glycine, L-serine, and D-serine levels in patients with schizophrenia as their clinical symptoms improve: results from the Juntendo University Schizophrenia Projects (JUSP). Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):1905-12.

[8] Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, et al. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the N-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch Gen Psychiatry 2003;60(6):572-6.

[9] Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(5):767-9.

[10] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511(7510):421-7.

[11] Japan Sciety for the Study of Obesity. Diagnostic Criteria for Obesity 2011. Journal of Japan Society for the Study of Obesity, 2011 Oct; additional edition.

[12] General Considerations for Clinical Trials (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998).

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to a sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study site in advance to get them accepted.
3. Prepare a written informed consent form and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the study site that sufficient medical care for all clinically significant AEs related to the study are provided to subjects throughout and beyond the period when subjects participate in the study, upon obtaining consent from the subject.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study site and the Sponsor in writing.
11. Determine the need of emergency key code unblinding of a subject in case of emergency.
12. Prepare correct and complete eCRFs, and submit them to the Sponsor with electronic signature.
13. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the Sponsor with electronic signature.
14. Discuss any proposal from the Sponsor including update of the protocol.
15. Notify the head of the study site of the end of the study in writing.

Appendix B Pregnancy and Contraception

Male Subjects and Their Female Partners

From the signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, any nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use adequate contraception. In addition, they must be advised not to donate sperm during this period or subjects should refrain from having sexual intercourse from 1 month prior to the first study drug administration throughout the study period and until 35 days after the last study drug administration. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the table on containing adequate contraception below.

Female Subjects and Their Male Partners

Female subjects of childbearing potential* will be excluded from this study.

* Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation), or who are postmenopausal (eg, defined as at least 2 years since last regular menses with an FSH of >40 IU/L).

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documented absence of sperm in the ejaculate, or have had a bilateral orchidectomy.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate.

Barrier methods (each time the subject has intercourse)	Intrauterine device (IUD)	Hormonal contraceptives
Male condoms with a spermicide	Copper T PLUS condom Progesterone T PLUS condom	Combined pill

Subjects will be provided with information on acceptable methods of contraception for 95 days after last dose of study drug, as part of their informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy in partners and of sperm donations for 95 days after their last dose of study drug.

Pregnancy

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

If the pregnancy in the partner of a male subject occurs during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of his right to receive treatment information. If the subject chooses to receive unblinded treatment information, that individual's blind should be broken by the investigator or sub-investigator. Any subjects randomized to placebo need not be followed.

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

All female subjects and the the female partners of male subjects who became pregnant will be followed to final outcome, using the pregnancy form, with the consent of the female subjects or the female partners of those male subjects. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after any birth of a child will also be conducted.

Appendix C Acceptable Time Window for Study Procedure

<Cohort 1>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
	Follow-up period	Day 23	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 1, 4, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Study treatment period (Part 1)	Day 1 72 hours postdose	Day 4 from awakening to discharge
	Washout period	Day 8	Not applicable
	Study treatment period (Part 2)	Day 9 72 hours postdose	Day 12 from awakening to discharge
	Follow-up period	Day 23	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 and 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 predose	From awakening to immediately prior to dose
		Day 9 2 and 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicabled
	Treatment period (Part 1)	Day 1 72 hours postdose	Within ± 15 minutes
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 9 72 hours postdose	Within ± 15 minutes
	Follow-up period	Day 23	Within ± 2 days
Urinary drug tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Washout period	Day 8	Not applicable
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 4	From awakening to discharge
	Washout period	Day 8	Not applicable
	Treatment period (Part 2)	Day 12	From awakening to discharge
Samples for PGx measurements	Treatment period (Part 1)	Day 1 predose	Not applicable
Blood samples for PK	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Part 1)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
	Treatment period (Part 2)	Day 9 predose	Within 15 minutes predose
		Day 9 1 hour postdose	Within ± 5 minutes
		Day 9 4, 8, 12, 24, 36, 48, and 72 hours postdose	Within ± 15 minutes
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Part 1)	Day 1 24 hours postdose	Within ± 2 hours
	Treatment period (Part 2)	Day 9 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, and FSH

<Cohorts 2-4>

Variables	Timing of procedures (standard)		Acceptable window
Testing at the time of determination of eligibility (a)	Screening	Days -28 to -2	Not applicable
Physical Exam	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
Vital Signs	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 1, 4, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Days 5-10 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Days 12-13 predose	From awakening to immediately prior to dose
		Day 14 predose	From awakening to immediately prior to dose
		Days 15-16 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 1, 4, 12, 24, and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days

Variables	Timing of procedures (standard)		Acceptable window
Weight	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 48 hours postdose	Day 19 from awakening to discharge
	Follow-up period	Day 31	Within ± 2 days
12-Lead ECG	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 predose	From awakening to immediately prior to dose
		Day 1 2 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	From awakening to immediately prior to dose
		Day 11 predose	From awakening to immediately prior to dose
		Day 17 predose	From awakening to immediately prior to dose
		Day 17 2 and 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
Clinical Laboratory Tests	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 11 predose	From awakening to immediately prior to dose
		Day 17 48 hours postdose	Within ± 15 minutes
	Follow-up period	Day 31	Within ± 2 days
C-SSRS	Screening	Days -28 to -2	Not applicable
	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 19	From awakening to discharge
Samples for PGx measurements	Treatment period (Single dose part)	Day 1 predose	Not applicable

Variables	Timing of procedures (standard)		Acceptable window
Blood samples for PK	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 0.5, 1, 1.5 and 2 hours postdose	Within ± 5 minutes
		Day 1 4, 8, 12, 24, 36 and 48 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 4 predose	Within 15 minutes predose
		Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 0.5, 1, 1.5, and 2 hours postdose	Within ± 5 minutes
		Day 17 4, 8, 12, 16 and 24 hours postdose	Within ± 15 minutes
Blood samples for PD	Hospitalization	Day 1 20, 16, and 12 hours predose	Within ± 15 minutes
	Treatment period (Single dose part)	Day 1 predose	Within 15 minutes predose
		Day 1 1 hour postdose	Within ± 5 minutes
		Day 1 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
	Treatment period (Multiple dose part)	Day 11 predose	Within 15 minutes predose
		Day 14 predose	Within 15 minutes predose
		Day 17 predose	Within 15 minutes predose
		Day 17 1 hour postdose	Within ± 15 minutes
		Day 17 4, 8, 12, and 24 hours postdose	Within ± 15 minutes
Cerebrospinal fluid samples for PD (If performed after Cohort 3)	Hospitalization	Day -1	Not applicable
	Treatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 3 hours
Urine sample (for future tests)	Hospitalization	Day -1	Not applicable
	Treatment period (Single dose part)	Day 1 24 hours postdose	Within ± 2 hours
	Teatment period (Multiple dose part)	Day 17 24 hours postdose	Within ± 2 hours

(a) Includes height, BMI, HIV antibody and antigen tests, hepatitis tests, FSH, and urinary drug tests

Total blood sampling volumes for an individual subject is shown below:

<Cohort 1>

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)
		Screening	Day -1	Days 1-4	Day 8	Days 9-12	
Clinical Laboratory Tests	20	1	1	1	1	1	100
Blood sampls for PK	4	-	-	12	-	12	96
Blood sampls for PD	6	-	3	9	-	9	126
Samples for PGx Measurements	6	-	-	1	-	-	6
						Total Blood Sampling Volume	**328**

-: No blood collection

<Cohorts 2-4>

Sample Type	Sample Volume (mL)	Number of Samples										Total Volume (mL)
		Screening	Day -1	Day 1	Day 2	Day 3	Day 4	Day 11	Day 14	Days 17-18	Day 19	
Clinical Laboratory Tests	20	1	1	-	-	-	-	1	-	-	1	80
Blood sampls for PK	4	-	-	8	2	1	1	1	1	10	-	96
Blood sampls for PD	6	-	3	5	1	-	-	1	1	6	-	102
Samples for PGx Measurements	6	-	-	1	-	-	-	-	-	-	-	6
											Total Blood Sampling Volume	**284**

-: No blood collection