Title: A Phase 1, Open-Label, Randomized, Single Dose, 5-Period, 5-Treatment, Study to Evaluate the Relative Bioavailability and Effect of Food on TAK-831 Tablet Formulations in Healthy Subjects

NCT Number: NCT03706469

Protocol Approve Date: 28 September 2018

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

- Named persons or organizations associated with the study.
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TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Open-Label, Randomized, Single Dose, 5-Period, 5-Treatment, Study to Evaluate the Relative Bioavailability and Effect of Food on TAK-831 Tablet Formulations in Healthy Subjects

Study Identifier:	TAK-831-1006
Compound:	TAK-831
Date:	28 September 2018
Version/Amendment Number:	Final Protocol

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LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, Massachusetts USA 02139 Telephone: +1 (617) 679-7000	TAK-831
Study Identifier: TAK-831-1006 (CA24822)	**Phase:** 1
Protocol Title: A Phase 1, Open-Label, Randomized, Single Dose, 5-Period, 5-Treatment Study to Evaluate the Relative Bioavailability and Effect of Food on TAK-831 Tablet Formulations in Healthy Subjects	
Trial Design: An open-label, 5-period, 5-treatment, relative bioavailability (BA) and food-effect study in 16 healthy adult subjects. On Day 1 of each treatment period subjects will receive a single oral dose of TAK-831. In Treatment Periods 1-4, each subject will receive two dose levels of the T2 formulation and two dose levels of the T3 formulation under fasted conditions, per the randomization schedule, to assess the relative BA of the two formulations. In Treatment Period 5, all subjects will receive a single oral dose of T3 formulation under fed conditions, in order to assess the food effect. In each treatment period, serial blood samples will be collected for 72 hours postdose to determine the pharmacokinetics (PK) of TAK-831 in plasma following administration of different formulations and/or different feeding conditions. There will be a washout period of at least 7 days between each dose of study drug (s). The clinic will contact all subjects (including subjects who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.	
Trial Primary Objectives: • To assess the oral BA of TAK-831 T3 tablet formulation relative to TAK-831 T2 tablet formulation under fasting conditions. • To assess the effect of food on the PK of TAK-831 T3 tablet formulation. **Secondary Objectives:** • To determine the safety and tolerability of single doses of TAK-831 T2 and T3 tablet formulations.	

<table>
<tr><td colspan="2">Trial Subject Population: Healthy adult male and female subjects</td></tr>
<tr><td>Planned Number of Subjects:
16</td><td>Planned Number of Sites:
1</td></tr>
<tr><td>Dose Levels:
Treatment A (Reference, Fasted):
50 mg TAK-831 T2 (2 x 25 mg T2 tablets) under fasted conditions
Treatment B (Test, Fasted):
50 mg TAK-831 T3 (2 x 25 mg T3 tablets) under fasted conditions
Treatment C (Reference, Fasted):
600 mg TAK-831 T2 (6 x 100 mg T2 tablets) under fasted conditions
Treatment D (Test, Fasted):
600 mg TAK-831 T3 (2 x 300 mg T3 tablets) under fasted conditions
Treatment E (Test, Fed):
600 mg TAK-831 T3 (2 x 300 mg T3 tablets) under fed conditions</td><td>Route of Administration:
Oral</td></tr>
<tr><td>Duration of Treatment:
On Day 1 of each treatment period, subject will receive a single oral dose of assigned TAK-831 formulation.</td><td>Planned Trial Duration:
Approximately 70 days including screening period</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:
Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:
1. Healthy, adult, male or female, 19-55 years of age, inclusive, at screening.
2. Body mass index (BMI) ≥ 18.0 and < 30.0 kg/m^2 at screening</td></tr>
</table>

3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or electrocardiographs (ECGs), as deemed by the Investigator or designee.
4. For a female of childbearing potential, use one of the following acceptable birth control methods:
   - Surgical sterilization of the partner (vasectomy for 4 months minimum prior to the first dosing).
   - Physical barrier method (eg, condom, diaphragm) with spermicide for at least 14 days prior to the first dosing and throughout the study.

   In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 35 days following the last dose/dosing.
5. For a female of non-childbearing potential, females must have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:
   - hysteroscopic sterilization (with confirmation from the subject that follow-up hysterosalpingogram was conducted);
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status.
6. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 95 days after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male).
7. If male, must agree not to donate sperm from the first dosing until 95 days after the last dosing.
8. Able to swallow multiple tablets.
9. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

Main Criteria for Exclusion:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.
4. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
5. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds.
7. Smokes more than 20 cigarettes or equivalent per day within 3 months prior to the first dose and is unwilling to discontinue use of any tobacco- or nicotine-containing products during the confinement period(s) of the study.
8. Has a risk of suicide according to the Investigator's clinical judgment (eg, per Columbia–Suicide Severity Rating Scale [C-SSRS]), or has made a suicide attempt in the previous year prior to screening.
9. Female subjects with a positive pregnancy test or who are lactating.
10. Positive urine drug or alcohol results at screening or first check-in.
11. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
12. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
13. Seated heart rate is lower than 40 beats per minute (bpm) or higher than 99 bpm at screening.
14. Orthostatic vital sign results with a decrease in systolic > 20 mmHg or decrease in diastolic > 10 mmHg, and increase in pulse of > 20 bpm.

15. Corrected QT interval using Fridericia's formula (QTcF) interval is >460 msec (males) or >470 msec (females) or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
16. Estimated creatinine clearance <80 mL/min at screening.
17. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study, including the follow-up period. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee.
    - Any drugs known to be significant inducers of uridine diphosphate glucuronosyltransferase (UGT) or sulfotransferase (SULT), including St. John's Wort, within 28 days prior to the first dosing and throughout the study, including the follow-up period. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drug.
18. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
19. Is lactose intolerant or unable/unwilling to eat the high-fat breakfast.
20. Donation of blood or significant blood loss within 56 days prior to the first dosing.
21. Plasma donation within 7 days prior to the first dosing.
22. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Treatment Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

The following PK parameters of TAK-831 derived after a single dose of TAK-831 on Day 1 of each treatment period:

- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUClast)
- Area under the plasma concentration-time curve from time 0 to infinity (AUC0-inf)
- Maximum observed plasma concentration (Cmax)

The secondary endpoint of the study is:

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

The exploratory endpoints of the study are:

CCI

[redacted]

Statistical Considerations:

Individual TAK-831 plasma concentration data and PK parameters will be listed by subject and treatment, and summarized by treatment (TAK-831 plasma concentrations and PK parameters) and nominal time (TAK-831 plasma concentrations).

An analysis of variance (ANOVA) will be performed on the natural-log (ln)-transformed AUClast, AUC0-inf and Cmax as follows:

- Relative bioavailability (Treatments A-D):

  The ANOVA model will include sequence, treatment, and treatment period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA will include calculation of least square means (LSM) as well as the difference between treatment LSM.

- Food Effect (Treatments D and E):

  The ANOVA model will have treatment as a fixed-effect and subject as a random-effect to account for the correlation between the repeated measures on each subject.

Ratios of LSM will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUClast, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the reference treatments.

Consistent with the two one-sided test, 90% confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed

AUClast, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the reference treatments.

Bioequivalence (Treatment B versus Treatment A and Treatment D versus Treatment C) will be claimed if the 90% CIs of the ratios of LSMs of the ln-transformed PK parameters AUClast, AUC0-inf, and Cmax of TAK-831 fall entirely within 80.00-125.00%.

Sample Size Justification:

A total 16 subjects will be randomized into 4 sequence groups in a ratio of 1:1:1:1. Assuming there are no more than 1 dropout in each sequence group, this will provide at least 12 observations for each of Treatments A, B, C and D. Based on the intra-subject variability (CV = 24.49%) of AUC from Study TAK-831-1004, this provides a two-sided 90% CI of the central value ratios (Treatment B versus Treatment A or Treatment D versus Treatment C) of (0.8484, 1.1787) if the observed central value ratio is 1. If the observed central value ratio is 1.2, the 90% CI will be (1.0180, 1.4144).

The study design will also provide at least 12 observations for each of Treatments D and E, which will provide a two-sided 90% CI of the central value ratios (Treatment E versus Treatment D) of (0.8799, 1.1365) if the observed central value ratio is 1. If the observed central value ratio is 1.6, the two-sided 90% CI will be (1.4078, 1.8184).

2.0 STUDY SCHEMATIC

Pretreatment	**Treatment Periods 1-5**				**Study Exit (a)**	**Follow up (b)**
Screening	**Predose Assessments**	**Dosing and Study Assessments**	**Safety and PK Assessments**			
Within 28 days prior to first dosing	Day -1	Day 1	Day 1-2	Days 3-4	Day 4 of Treatment Period 5	14 (±2) days after last dose
Outpatient Visit	←- - - - - - - Confinement (a) (c) - - - - - - →			Outpatient Visits		

(a) At all times, a subject may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

(b) The clinic will contact all subjects (including subjects who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.

(c) Subjects will start the confinement on Day -1 and be released from confinement after Day 2 study assessments are complete and will return to the study site on Day 3 and Day 4 for subsequent safety and PK assessments; There will be a washout period of at least 7 days between each dose.

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedures [a]		**Study Days in Each Treatment Period** [c]																				
Days →	**S** [b]	**-1**	**1**															2	3	4	**ET** [d]	**FU** [e]
Hours →		**C-I** [f]	P	0	0.25	0.5	1	1.5	2	3	4	5	6	8	10	12	24	48	72		
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X [g]																				
Medical History	X																					
Safety Evaluations																						
Full Physical Examination [h]	X																					
Height	X																					
Weight	X	X [i]																				
12-Lead Safety ECG	X		X [j]				X				X								X	X		
Vital Signs (heart rate and blood pressure)	X		X [j]				X										X		X	X		
Orthostatic Vital Signs (heart rate and blood pressure)	X																					
Vital Signs (respiratory rate and temperature)	X																					
Hematology, Serum Chemistry [k], and Urinalysis	X	X																	X	X		
Serum Pregnancy Test (females only)	X	X																	X [l]	X		
Serum FSH (postmenopausal females only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
C-SSRS Questionnaire [m]	X	X																	X	X		
AE Monitoring												X										
Concomitant Medication Monitoring	X											X										
Study Drug Administration / Pharmacokinetics																						
TAK-831 Administration				X																		
Blood for TAK-831 PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Other Procedures																						
Confinement in the CRU [n]									X													
Visit and Return Visits	X																	X	X			

a For details on Procedures, refer to Section 9.2.

b Within 28 days prior to the first study drug administration.

c There will be a washout period of at least 7 days between doses.

d To be performed prior to early termination from the study.

e The clinic will contact all subjects (including subjects who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.

f Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU. If the CRU decides to confine the subjects throughout the study, some safety events at check-in (eg, clinical laboratory tests, urine drug and alcohol screen, serum pregnancy test, vital signs, and ECGs) may not be performed at the Investigator's discretion.

g To be performed in Treatment Period 1 only.

h Symptom-driven physical examination may be performed at other times, at the Investigator's or designee's discretion.

i If screening assessment was conducted within 4-7 days prior to dosing (Day 1), weight assessment will be conducted at check-in only if in the opinion of the Investigator there is no reason to believe they have substantially changed.

j To be performed within 24 hours prior to dosing.

k Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken. Coagulation tests (PT/INR) will be performed if subjects has on-study aspartate aminotransferase or alanine aminotransferase elevated ≥3x the upper limit of normal.

l To be performed at the end of Treatment Period 5 only.

m At screening the C-SSRS Baseline/Screening version will be administered; at all other time points, the Since Last Visit version will be administered.

n As per site preference, subjects may be confined throughout the washout period.

Abbreviations: AE = Adverse events, C-I = Check-in, C-SSRS = Columbia Suicidality Symptoms Rating Scale, CRU = Clinical research unit, ECG = Electrocardiogram, ET = Early termination, FU = Follow-up, HIV = Human immunodeficiency virus, P = Predose, PK = Pharmacokinetics, PT/INR = Prothrombin time/International normalized ratio, S = Screening.

4.0 INTRODUCTION

4.1 Background

Ataxia constitutes a neurological sign consisting of a lack of voluntary coordination of muscle movements. It is a nonspecific clinical manifestation implying dysfunction of the parts of the central nervous system that coordinate movement, such as the cerebellum [1]. The most common hereditary ataxia (approximately 50% of cases) is Friedreich ataxia (FRDA), a debilitating, life-shortening, and degenerative multiple system disorder [2,3]. Patients with FRDA has a guanine-adenine-adenine trinucleotide repeat expansion mutation in intron 1 of the frataxin gene and suffer from drastically reduced levels of the frataxin protein [4, 5], which in turn leads to neurodegeneration, cardiomyopathy, diabetes mellitus and skeletal deformities [3]. The sensory ataxia component of FRDA involves progressive loss of coordination and muscle strength leads to motor incapacitation However, there is currently no cure or approved effective treatment for any of the hereditary ataxias [1]. Thus, there is a great need to identify and develop effective therapies for patient populations with ataxia.

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves, including hallucinations, delusions, psychosis (positive symptoms), lack of motivation and reduced social interaction (negative symptoms), and poor information processing, impaired ability to focus on objectives, and abnormalities of working memory and learning (cognitive symptoms) [7]. Hypofunction of *N*-methyl-D-aspartate (NMDA) receptors is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain [8]. 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 [9-12]. D-serine has been demonstrated to be a co-agonist of NMDA glutamate receptors that, along with glutamate, mediates NMDA receptor transmission, synaptic plasticity and other physiologic functions. D-serine is also a known endogenous ligand for the δ2 glutamate receptor which has been implicated in synaptic plasticity and long-term depression [1]. Adding to the above evidence of a potential role of D-amino acid oxidase (DAO) in the pathophysiology of schizophrenia, a weak inhibitor of DAO, sodium benzoate, demonstrated efficacy in positive, negative, and cognitive symptoms in a proof-of-concept study in subjects with schizophrenia [713].

TAK-831 is a highly selective and potent inhibitor of D-amino acid oxidase, a peroxisomal enzyme active toward neutral D-amino acids and associated with the metabolism of D-serine. TAK-831 was shown to increase D-serine levels in the cerebellum of normal mice and to be efficacious in a mouse model of FRDA. It also demonstrated a positive effect on cognition and social interaction in rodent cognition and behavioral models. TAK-831 is under development for the treatment of FRDA, cognitive impairment associated with schizophrenia, and negative symptoms of schizophrenia [14].

Pharmacokinetics

Four phase 1 clinical studies have been conducted in healthy subjects. TAK-831 was rapidly absorbed following both single-dose (10 to 750 mg) and multiple-dose (30 to 1200 mg) oral administration of suspension or tablet formulation under fasting conditions. TAK-831 plasma concentration generally reached maximal levels within median 0.25 to 2 hours after dosing. Exposure was generally dose dependent with mean t½ values ranging from 6 to 23 hours across the dose range studied. Accumulation was negligible, and steady-state was attained by the fourth day of daily dosing.

The effect of food on the PK profile of two TAK-831 tablet formulations (T1 and T2) was investigated. Under fasting conditions, TAK-831 mean Cmax and AUC values following oral administration of a single 100 mg dose of the T1 tablet formulation were lower approximately 64% and 50%, respectively, when compared to those of the oral suspension. Coadministration of TAK-831 T1 tablet with a standard Food and Drug Administration (FDA) high-calorie high-fat breakfast increase mean Cmax and AUC0-inf values by approximately 2-fold. The exposure of TAK-831 is similar between T2 and T1 tablet under fasting conditions. The relative bioavailability estimates of TAK-831 T2 tablet 400 mg under fed (nutrition drink) versus fasted conditions showed that nutrition drink had minimal effect on TAK-831 exposure.

Safety

To date, TAK-831 has been administered to a total of 117 healthy subjects in 3 completed phase 1 studies (TAK-831-1001, TAK-831-1003, and TAK-831-1004); 88 subjects received single doses ranging from 10 to 750 mg and 29 subjects received multiple doses ranging from 30 to 400 mg for

up to 13 days. TAK-831 or placebo have been administered to an additional 33 healthy subjects across 4 cohorts in the ongoing blinded TAK-831-1005 study at doses ranging from 100 to 1200 mg once daily (QD) for 14 days.

TAK-831 was considered safe and well tolerated after multiple oral doses administered to healthy subjects up to and including 1200 mg QD (conclusions for doses of 600 to 1200 mg QD are based on preliminary blinded AE data reported by the Investigator and blinded safety endpoint data). Headache and nausea were the most commonly reported TEAE potentially related to treatment; AEs that were mild to moderate in intensity and generally self-limiting. Postural dizziness was also reported, however, the rate of postural dizziness in TAK-831–treated subjects did not markedly differ from the rate observed in placebo-treated patients. There were no concerning trends in laboratory, ECG, or vital sign data.

Refer to the Investigator's Brochure (IB) for detailed background information on TAK-831 [14].

4.2 Rationale for the Proposed Study

The ongoing Phase 2 proof of concept studies in patients with schizophrenia or Friedrich ataxia currently use the T2 tablet formulation of TAK-831. The newly developed T3 tablet formulation will be used in the planned Phase 3 studies of TAK-831. The purpose of this study is to compare the PK of TAK-831 following a single oral dose of the T3 and T2 tablet formulations under fasting conditions. In addition, the effect of food on TAK-831 PK will be investigated for the T3 formulation.

4.3 Benefit/Risk Profile

The dose of study drug administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as it is a single dose administered according to the dosing recommendations found in the IB [14].

The safety monitoring practices employed by this protocol (ie, 12-lead ECG, vital signs, C-SSRS, clinical laboratory tests, AE questioning, and physical examination) are adequate to protect the subjects' safety and should detect all expected TEAEs.

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

NA

5.2 Trial Objectives

5.2.1 Trial Primary Objectives

- To assess the oral BA of TAK-831 T3 tablet formulation relative to TAK-831 T2 tablet formulation under fasting conditions.
- To assess the effect of food on the PK of TAK-831 T3 tablet formulation.

5.2.2 Trial Secondary Objective

- To determine the safety and tolerability of single doses of TAK-831 T2 and T3 tablet formulations.

5.3 Endpoints

5.3.1 Primary Endpoints

The primary endpoint of the study is:

The following PK parameters of TAK-831 derived after a single dose of TAK-831 on Day 1 of each treatment period:

- AUClast
- AUC0-inf
- Cmax

5.3.2 Secondary Endpoint

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

- Percentage of subjects who experience at least 1 TEAE.

5.3.3 Exploratory Endpoints

The exploratory endpoints of the study are:

CCI

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

An open-label, 5-period, 5-treatment, relative BA and food-effect study in 16 healthy adult subjects.

Screening of subjects will occur within 28 days prior to the first dosing

On Day 1 of each treatment period, subjects will receive a single dose of study drug. In Treatment Periods 1-4, each subject will receive two dose levels of the T2 formulation and two doses of the T3 formulation under fasted, per the randomization schedule, to assess the relative BA of the two formulations. In Treatment Period 5, all subjects will receive a single oral dose of T3 formulation under fed conditions, in order to assess the food effect. In each treatment period, serial blood samples will be collected for 72 hours postdose to determine the PK of TAK-831 in plasma following administration of different formulations and/or different feeding conditions.

There will be a washout period of at least 7 days between each dose of study drug.

The clinic will contact all subjects (including subjects who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.

Please refer to Section 2.0 for study schematics.

The planned dose levels of TAK-831 to be evaluated are outlined in Table 6.a.

Table 6.a Planned TAK-831 Doses

	Formulation	Dose	Treatment/meal condition (a)
Treatment A	T2	50 (2 x 25 mg tablets)	Fasted (b)
Treatment B	T3	50 (2 x 25 mg tablets)	Fasted (b)
Treatment C	T2	600 (6 x 100 mg tablets)	Fasted (b)
Treatment D	T3	600 (2 x 300 mg tablets)	Fasted (b)
Treatment E	T3	600 (2 x 300 mg tablets)	Fed (c)

(a) All study drugs will be administered orally with approximately 240 mL of water.

(b) In Treatments A, B, C, and D, subjects will fast overnight for at least 10 hours prior to each study drug administration (see Section 7.2.1).

(c) In Treatment E, subjects will fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat breakfast which will be entirely consumed within 30 minutes (see Section 7.2.1).

6.2 Dose Escalation

NA

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

Subjects in the study will receive a single dose of TAK-831 on Day 1 of each of the 5 treatment periods. Treatment Periods 1-4 will assess the bioavailability of TAK-831. A single-dose fasting study design using the highest strength of product is recommended as per the FDA's draft Guidance for Industry on Bioavailability and Bioequivalence Studies Submitted in NDAs or IND - General Considerations [15]. CCI [redacted] The TAK-831 T3 tablet is available as 25 mg or 300 mg

tablets. CCI [redacted] Additionally, some deviation from linearity in TAK-831 exposures have been previously observed when administered as an oral suspension over the dose range of 10 to 750 mg. Consequently, the oral bioavailability of both strengths of the T3 tablet (50 mg as 2x 25 mg tablets and 600 mg as 2x 300 mg tablets) will be assessed relative to the existing 25 mg and 100 mg strengths of the T2 tablet formulation across the clinical dose range of TAK-831.

Furthermore, because co-administration with food increased TAK-831 systemic exposure in healthy subjects (TAK-831-1001), the effect of food on the PK of the new T3 tablet formulation will be assessed at the highest dose of TAK-831 expected to be used in clinical settings in accordance with FDA BA Food Effect Guidance for Industry.

In Treatment Periods 1-4, subjects will be randomized to treatment sequences to minimize assignment bias for the BA comparison of T3 versus T2 formulation. A crossover design is used to reduce the residual variability as every subject acts as their own control. In Treatment Period 5, the effect of food on the BA of the T3 formulation will be assessed in all subjects.

TAK-831 has an apparent mean terminal half-life (t½) of approximately 6 to 23 hours in human. Therefore, a minimum 7-day washout interval between the doses is sufficient to ensure that there is no drug carryover effect.

6.3.2 Rationale for Dose

Two single dose levels (50 and 600 mg) have been selected for this study as they represent the therapeutic dose range currently tested in Phase 2 studies of TAK-831.

The highest dose of TAK-831 tested in healthy subjects was 1200 mg in oral suspension and was found to be safe and well tolerated. The exposure (both Cmax and AUC0-inf) of TAK-831 at this dose reached more than 2-fold exposure of 600 mg T2 tablet under the fasting condition and will provide adequate safety margin for the expected increase in systemic exposure for the 600 mg dose administered under fed condition.

6.3.3 Rationale for Endpoints

NA

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this study, the blood collection for plasma TAK-831 concentrations is the critical procedure and needs to be collected as close to the exact time point as possible.

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

The dose and administration of the study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 6.5.5.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

The beginning of the trial will be defined as the beginning of screening (ie, signing of the ICF) of the first subject.

6.5.2 Definition of End of the Trial

The end of study is defined as the date of the last scheduled study procedure (ie, follow-up phone call) as outlined in the Schedule of Study Procedures (Section 3.0).

6.5.3 Definition of Trial Completion

The end of the study is scheduled after completion of the evaluations in the follow-up phone call for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.5.4 Definition of Trial Discontinuation

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.5.5 Criteria for Premature Termination or Suspension of the Trial

Celerion reserves the right to terminate the study in the interest of subject welfare.

Sponsor reserves the right to suspend or terminate the study at any time.

6.5.6 Criteria for Premature Termination or Suspension of a Site

NA

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 9.1.2.2. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

Use of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 7.a.

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

Category	Between Screening and Randomization (within 28 days prior to predose [Day 1])	Post-Randomization (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to dosing	Prohibited from 48 hours prior to dosing in each treatment period and throughout the period of PK sample collection.
Xanthine and/or caffeine	Prohibited from 24 hours prior to dosing [(a)]	Prohibited from 24 hours prior to dosing in each treatment period and throughout the period of PK sample collection [(a)].
Medications	See Section 7.1	See Section 7.1
Nicotine	Prohibited from check-in	Prohibited throughout confinement
Food substance		
Poppy seeds	Prohibited from 96 days prior to dosing	Prohibited
Grapefruit/Seville orange	Prohibited from 14 days prior to dosing	Prohibited

(a) small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction.

7.2 Diet, Fluid, Activity

7.2.1 Diet and Fluid

Water (except water provided with each oral dosing) will be restricted 1 hour prior to and 1 hour after each study drug administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

In Treatments A, B, C, and D, subjects will fast overnight for at least 10 hours prior to each study drug administration and will continue to fast for at least 4 hours postdose.

In Treatment E, subjects will fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat breakfast which will be entirely consumed within 30 minutes. Subjects will fast for at least 4 hours postdose on this day. If a meal is not fully consumed, the percentage of meal not consumed will be recorded.

An example of high-fat breakfast would be 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 ounces of hash brown potatoes, and 240 mL of whole milk. The clinical site may make minor modifications to the high-fat, high-calorie meal as long as the same meal is served to all subjects and the meal meets the high-fat, high-calorie criteria (~ 800-1000 calories with at least 50% from fat) together with comparable meal volume and viscosity. The clinical site will document the amount of protein, carbohydrate, and fat and total calorie content of the test meal for the study file and provide a copy to the sponsor.

Each meal and/or snacks served at the clinical research unit (CRU) will be standardized and will be similar in caloric content and composition (except for the breakfast served as part of Treatment E) and will be taken at approximately the same time in each treatment period.

7.2.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

Subjects will be prohibited from smoking during their confinement.

7.3 Criteria for Discontinuation or Withdrawal of a Subject

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the Investigator or designee for the following reasons:

- AEs.

- Difficulties in blood collection.
- Positive drug or alcohol screen
- Positive pregnancy test.

Any subject who experiences emesis within 2 hours postdose may be discontinued, excluded from the final data analysis, and may be replaced with a new subject.

A subject may be withdrawn by the Investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

7.4 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.3. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination as described in Section 3.0.

7.5 Subject Replacement

Discontinued subjects may be replaced at the discretion of the Sponsor and the Investigator.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

8.1.1 TAK-831 T2 Tablets

A single dose of 50 mg (2 x 25 mg tablets) or 600 mg (6 x 100 mg tablets) of TAK-831 T2 tablets will be administered in Treatments A and C of the study.

TAK-831 T2 25 mg and 100 mg tablets are nonsterile, oral, tablet dosage forms, containing 25 mg and 100 mg (as freebase) of TAK-831, respectively.

8.1.2 TAK-831 T3 Tablets

A single dose of (2 x 25 mg tablets) or 600 mg (2 x 300 mg tablets) of TAK-831 T3 tablets will be administered in Treatments B, D, and E of the study.

TAK-831 T3 25 mg and 300 mg tablets are nonsterile, oral, tablet dosage form, containing 25 mg and 300 mg (as freebase) of TAK-831, respectively.

8.1.3 Clinical Study Drug Labeling

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

8.1.4 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of TAK-831 products to allow completion of this study.

The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied. All TAK-831 products will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.1.5 Clinical Study Drug Blinding

This is an open-label study.

8.1.6 Randomization Code Creation and Storage

Subjects will be randomized to 1 of 4 Treatment sequences in a 1:1:1:1 ratio (see Section 9.1.1.1) according to a randomization schedule will be generated by Celerion.

8.1.7 Clinical Trial Blind Maintenance/Unblinding Procedure

NA

8.1.8 Accountability and Destruction of Sponsor-Supplied Drugs

At the conclusion of the study, any unused TAK-831 study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product.

Subjects will be randomized to 1 of 4 Treatment sequences in a 1:1:1:1 ratio. The sequences to be used in the randomization are detailed in Table 9.a below. Subjects will receive each treatment on one occasion.

Table 9.a Sequence Groups

Sequences	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4	Treatment Period 5
1 (n=4)	A	B	D	C	E
2 (n=4)	B	C	A	D	E
3 (n=4)	C	D	B	A	E
4 (n=4)	D	A	C	B	E

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

This is a 5-period, 5-treatment crossover study. All subjects will receive each of the treatments on one occasion as detailed in Section 6.1.

9.1.2 Inclusion and Exclusion

9.1.2.1 Inclusion Criteria

Subjects must fulfill all the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 19-55 years of age, inclusive, at screening.
2. Body mass index (BMI) ≥ 18.0 and < 30.0 kg/m^2 at screening.
3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
4. For a female of childbearing potential, use one of the following acceptable birth control methods:
   - Surgical sterilization of the partner (vasectomy for 4 months minimum prior to the first dosing).
   - Physical barrier method (eg, condom, diaphragm) with spermicide for at least 14 days prior to the first dosing and throughout the study.

   In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 35 days following the last dose/dosing.
5. For a female of non-childbearing potential, females must have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:
   - hysteroscopic sterilization (with confirmation from the subject that follow-up hysterosalpingogram was conducted);

- bilateral tubal ligation or bilateral salpingectomy;
- hysterectomy;
- bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and FSH serum levels consistent with postmenopausal status.

6. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 95 days after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing of study drug. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male).
7. If male, must agree not to donate sperm from the first dosing until 95 days after the last dosing.
8. Able to swallow multiple tablets.
9. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

9.1.2.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of gastritis, gastrointestinal tract, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.

4. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
5. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds.
7. Smoke more than 20 cigarettes or equivalent per day within 3 months prior to the first dose and is unwilling to discontinue use of any tobacco- or nicotine-containing products during the confinement period(s) of the study.
8. Has a risk of suicide according to the Investigator's clinical judgment (eg, per C-SSRS), or has made a suicide attempt in the previous year prior to screening.
9. Female subjects with a positive pregnancy test or who are lactating.
10. Positive urine drug or alcohol results at screening or first check-in.
11. Positive results at screening for HIV, HBsAg, or HCV.
12. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
13. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
14. Orthostatic vital sign results with a decrease in systolic > 20 mmHg or decrease in diastolic > 10 mmHg, and increase in pulse of > 20 bpm.
15. QTcF interval is >460 msec (males) or >470 msec (females) or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
16. Estimated creatinine clearance <80 mL/min at screening.

17. Unable to refrain from or anticipates the use of:

    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study, including the follow-up period. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee.

    - Any drugs known to be significant inducers of UGT or SULT, including St. John's Wort, within 28 days prior to the first dosing and throughout the study, including the follow-up period. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drug.

18. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.

19. Is lactose intolerant or unable/unwilling to eat the high-fat breakfast.

20. Donation of blood or significant blood loss within 56 days prior to the first dosing.

21. Plasma donation within 7 days prior to the first dosing.

22. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Treatment Period 1 of the current study

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use (including number of cigarettes smoked per day) will be reported.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.1. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to subject safety.

For this study, the collection of blood for plasma TAK-831 concentrations is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

9.2.1 Full Physical Examination

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

Blood pressure and heart rate will be measured within 24 hours prior to Day 1 dosing of each treatment period for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

For orthostatic vital signs (heart rate and blood pressure), subjects should be seated and then stand upright prior to measurement of orthostatic vital signs, as per Celerion standard operating procedures.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing of each treatment period for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Columbia Suicidality Symptoms Rating Scale

The C-SSRS is a questionnaire scale to detect emergent suicide symptoms (suicidal ideation or actual suicidal behavior) during the course of this study. Assessments will be performed according

to the Schedule of Study Procedures (Section 3.0). Additional C-SSRS assessment may be performed at other times if deemed necessary. The C-SSRS is to be administered at the site by an appropriately qualified/trained individual and a copy of the questionnaire to be used will be kept in the study binder. In addition, subjects who at any time during this study spontaneously report AEs of suicidal ideation or suicidal behavior, either as an outpatient or during visit interviews, must be assessed by the Investigator or designee and referred for further mental health evaluation as clinically indicated.

9.2.7 Study Drug Administration

TAK-831 T2 and T3 tablets will be provided as described in Section 8.1.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject, as appropriate.

All doses of TAK-831 will be administered with approximately 240 mL of water.

The exact clock time of oral dosing will be recorded.

Subjects will be instructed not to crush, split or chew the TAK-831 tablets.

Treatments are as follows:

Treatment A (Reference, Fasted)	50 mg TAK-831 T2 (2 x 25 mg T2 tablets) administered at Hour 0 on Day 1 following an overnight fast of at least 10 hours.
Treatment B (Test, Fasted)	50 mg TAK-831 T3 (2 x 25 mg T3 tablets) administered at Hour 0 on Day 1 following an overnight fast of at least 10 hours.
Treatment C (Reference, Fasted)	600 mg TAK-831 T2 (6 x 100 mg T2 tablets administered at Hour 0 on Day 1 following an overnight fast of at least 10 hours.
Treatment D (Test, Fasted)	600 mg TAK-831 T3 (2 x 300 mg T3 tablets) administered at Hour 0 on Day 1 following an overnight fast of at least 10 hours.
Treatment E (Test, Fed)	600 mg TAK-831 T3 (2 x 300 mg T3 tablets) administered at Hour 0, 30 minutes after the start of a high-fat breakfast on Day 1.

9.2.8 AE Monitoring

Subjects will be monitored throughout confinement for adverse reactions to the study formulations and/or procedures. Prior to release, subjects will be asked how they are feeling. At the beginning of subsequent treatment period subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the Investigator or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator or designee.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

9.2.9 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample is taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Blood Urea Nitrogen	Sodium
Bilirubin (total and direct)	Potassium
Alkaline phosphatase	Chloride
Aspartate aminotransferase (AST)	Glucose
Alanine aminotransferase (ALT)	Creatinine *
Albumin	

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

Coagulation

Coagulation tests will be performed if subjects has on-study ALT or AST elevated ≥3x the upper limit of normal (ULN).

Coagulation evaluations will consist of the following tests:

Prothrombin time	International normalized ratio (INR)

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen ➢ Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone) ➢ Amphetamines ➢ Barbiturates ➢ Benzodiazepines ➢ Cocaine ➢ Cannabinoids
HBsAg	
HCV *(if antibody positive, confirm RNA negative)*	
Urine alcohol screen	
FSH (for postmenopausal females only)	
Serum pregnancy test (for females only)	

9.3 PK Samples

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

For all subjects, blood samples for the determination of plasma TAK-831 will be collected in 4 mL blood collection tubes containing the appropriate anticoagulant at scheduled time points as delineated in the Schedule of Study Procedures (Section 3.0). The actual time of sample collection will be recorded on the source document in the case report form (CRF).

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

Table 9.b Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma for TAK-831 PK	Plasma		PK analysis	Mandatory

9.3.1 PK Measurements

9.3.1.1 Plasma PK Measurements

PK parameters for plasma TAK-831 concentrations will be calculated as follows, as appropriate, following oral administration:

AUClast: The area under the concentration versus time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.

AUC0-inf: The area under the concentration versus time curve, from time 0 extrapolated to infinity. AUC0-inf is calculated as AUClast plus the ratio of the last measurable plasma concentration to the elimination rate constant.

AUC%extrap: Percent of AUC0-inf extrapolated, represented as (1 – AUClast/AUC0-inf)*100.

Cmax: Maximum observed concentration.

Tmax: Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

Kel: Apparent first-order terminal elimination rate constant calculated from a semilog plot of the blood concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (eg, three or more non-zero blood concentrations).

t½: Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.

No value for Kel, AUC0-inf, AUC%extrap, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for subjects with detectable concentrations at 2 or fewer consecutive time points.

Individual and mean plasma concentration-time curves (both linear and log-linear) will be included in the final report.

9.3.2 Biomarker Measurements

NA

9.3.3 PGx Measurements

NA

9.3.4 Confinement

In each treatment period, subjects will be housed on Day -1, at the time indicated by the CRU until after the 24-hour blood draw and/or study procedures. Subjects will return for study procedures as indicated in the Schedule of Study Procedures (Section 3.0).

At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

The clinic will contact all subjects (including subjects who terminate the study early) approximately 14 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.

As per site preference, subjects may be confined throughout the washout period.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory

re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigator(s) should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, Investigator(s) should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, Investigator(s) should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (electronic [e]) case report form, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

NA

10.2 AE Procedures

10.2.1 Assigning Severity of AEs

The different categories of severity/intensity are:

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

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

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

10.2.2 Assigning Causality of AEs

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

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

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

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

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study treatment period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with

some persisting paresis).

- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

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

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call on Day 14 (± 2 days), approximately 14 days after the last dose of investigational product. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

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

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

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

10.2.8.3 Reporting SAEs

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

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

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

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

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

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

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

10.2.8.4 Reporting Special Interest AEs

NA

10.2.8.5 Reporting of Abnormal Liver Function Tests

If a subject has elevated ALT ≥3x ULN with concurrent elevated total bilirubin >2× ULN ***or*** elevated INR >1.5x ULN, contact the sponsor's medical monitor within 24 hours.

For any subject with ALT ≥3x ULN *and* total bilirubin >2x ULN *or* INR >1.5x ULN for which an alternative etiology has not been found, report the event as an SAE (Section 10.2.8.3) and contact the sponsor immediately.

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

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigator(s) and Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk

assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

All subjects who received at least one dose of the study drug(s) will be included in the safety evaluations.

11.1.1.2 PK Set

Samples from all subjects will be assayed even if the subjects do not complete the study. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

Descriptive statistics will be provided for the plasma TAK-831 concentrations using appropriate summary statistics to be fully specified in the SAP.

PK parameters for plasma TAK-831 concentrations will be calculated as described in Section 9.3.1.1.

An ANOVA will be performed on the ln-transformed AUClast, AUC0-inf and Cmax as follows:

- Relative BA (Treatments A-D):

  The ANOVA model will include sequence, treatment, and treatment period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA will include calculation of LSM as well as the difference between treatment LSM.

- Food Effect (Treatments D and E):

  The ANOVA model will have treatment as a fixed-effect and subject as a random-effect to account for the correlation between the repeated measures on each subject.

Each ANOVA will include calculation of LSM as well as the difference between treatment LSM.

11.1.4 Ratios and Confidence Intervals

Ratios of LSM will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUClast, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the reference treatments (ie, Treatments A and C for the relative BA assessment, and Treatment D for the food-effect assessment, as detailed below).

Consistent with the two one-sided test [16], 90% CIs for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed AUClast, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the reference treatments (ie, Treatments A and B for the relative BA assessment, and Treatment D for the food-effect assessment, as detailed below).

Bioequivalence (Treatment B versus Treatment A and Treatment D versus Treatment C) will be claimed if the 90% CIs of the ratios of LSMs of the ln-transformed PK parameters AUClast, AUC0-inf, and Cmax of TAK-831 fall entirely within 80.00-125.00%.

The comparisons of interest are as follows:

Relative Bioavailability:

- Treatment B compared with Treatment A
- Treatment D compared with Treatment C

Food Effect:

- Treatment E compared with Treatment D

11.1.5 PD Analysis

NA

11.1.6 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by subject.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.6.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number and percentage of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

11.1.6.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of time of collection and a shift table describing out of normal range shifts will be provided.

11.1.6.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

11.1.6.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by treatment and point of time of collection.

C-SSRS findings will be presented in the data listings.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 Determination of Sample Size

A total 16 subjects will be randomized into 4 sequence groups as indicated in Table 9.a in a ratio of 1:1:1:1. Assuming there are no more than 1 dropout in each sequence group, this will provide at least 12 observations for each of Treatments A, B, C and D. Based on the intra-subject variability (CV = 24.49%) of AUC from Study TAK-831-1004, this provides a two-sided 90% confidence interval of the central value ratios (Treatment B versus Treatment A or Treatment D versus Treatment C) of (0.8484, 1.1787) if the observed central value ratio is 1. If the observed central value ratio is 1.2, the 90% CI will be (1.0180, 1.4144).

The study design will also provide at least 12 observations for each of Treatments D and E, which will provide a two-sided 90% confidence interval of the central value ratios (Treatment E versus Treatment D) of (0.8799, 1.1365) if the observed central value ratio is 1. If the observed central value ratio is 1.6, the two-sided 90% CI will be (1.4078, 1.8184).

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 CRFs. 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 and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, trial drug, subject medical records, informed consent documentation, and review of CRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

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

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In

addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

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

13.1 IRB and/or IEC Approval

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

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the

trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable)

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

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

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

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

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

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

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 Investigator s or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for

any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Trial Registration

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

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

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

13.4.3 Clinical Trial Results Disclosure

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 224-554-1052

14.1.2 INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUClast	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
BA	Bioavailability
BMI	Body mass index
bpm	Beats per minute
C-SSRS	Columbia-Suicidality Symptoms Rating Scale
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CV	Intra-subject variability

DAO	D-amino acid oxidase
ECG	Electrocardiogram
FDA	Food and Drug Administration
FRDA	Friedreich ataxia
FSH	Follicle-stimulating hormone
g	Gram(s)
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
Kel	Apparent first-order terminal elimination rate constant
kg	Kilogram
LFT	Liver function test(s)
ln	Natural log
INR	International normalized ratio
LSM	Least-squares
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury

msec	Millisecond
n	Sample size
NA	Not applicable
NMDA	*N*-methyl-D-aspartate
oz	Ounce
PK	Pharmacokinetic(s)
PT	Prothrombin time
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SULT	Sulfotransferase
SUSAR	Suspected unexpected serious adverse reactions
t½	Apparent first-order terminal elimination half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum observed concentration [Cmax]
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
US	United States
USA	United States of America
WHO	World Health Organization

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 Medical Dictionary for Regulatory Activities (MedDRA®). Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

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

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

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal Investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs is made by Clinical Data Management through the Database Unlock Process after approval is granted by the Sponsor to Unlock the Database. The Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits

by study monitors. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

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

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17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the Investigator /institution retains the services of any individual or party to perform trial-related duties and functions, the Investigator /institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.

9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.

15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in c clinical research and safety reporting

purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for {5 half-lives PLUS 30 days} after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the Investigator will offer the subject the choice to receive unblinded treatment information.

26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for {5 half-lives PLUS 90 days} after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the Investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

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

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

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

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

Female Subjects and Their Male Partners

Female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a method of contraception as described below.

* A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysteroscopic sterilization (with confirmation from the subject that follow-up hysterosalpingogram was conducted), bilateral tubal ligation or bilateral salpingectomy, hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 4 month post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

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

- Non-Hormonal Methods:
  - Physical barrier method (eg, condom, diaphragm) with spermicide for at least 14 days prior to the first dosing and for at least 35 days following the last dose of study drug(s).Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success.
  - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 35 days after last dose.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Temporary sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:

a) contraceptive requirements of the study

b) reasons for use of barrier methods (ie, condom) in males with pregnant partners

c) assessment of subject compliance through questions such as

i. Have you used the contraception consistently and correctly since the last visit?

ii. Have you forgotten to use contraception since the last visit?

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

iv. Is there a chance you could be pregnant?

5. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative serum hCG pregnancy test at each check-in prior to receiving any dose of study medication.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

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

Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (TAK-831) should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 95 days after the last dose, should also be recorded following authorization from the subject's partner.

Should the pregnancy occur during or after administration of blinded drug, the Investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the Investigator.

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

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	01-Oct-2018 22:53 UTC
	Clinical Pharmacology Approval	02-Oct-2018 01:22 UTC
	Biostatistics Approval	02-Oct-2018 19:36 UTC