



Title: A Randomized, Open-Label, Single-Dose, 2-Period, Crossover Design, Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 T2 Tablet Formulation in Healthy Subjects

NCT Number: NCT03101293

Protocol Approve Date: 11 April 2016

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

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PROTOCOL

A Randomized, Open-Label, Single-Dose, 2-Period, Crossover Design, Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 T2 Tablet Formulation in Healthy Subjects

Phase 1, Food Effect Study of TAK-831

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015

Study Number: TAK-831-1004

IND Number: 132,633 **EudraCT Number:** Not applicable.

Compound: TAK-831

Date: 11 April 2016 **Version/Amendment Number:** Amendment 01

Amendment History:

Date	Amendment Number	Amendment Type	Region
15 February 2017	Initial Version		
11 April 2017	01	Not applicable	United States

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Takeda Pharmacovigilance Takeda Development Center Americas, Inc. PPD
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

Electronic signatures may be found on the last page of this document.

PPD



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1.3 Protocol Amendment 01 Summary of Changes

Rationale for Amendment No. 01

This document describes the changes in reference to the Protocol Incorporating Amendment No. 01.

The primary purpose of this amendment is to update the protocol regarding additional ECG time points at the expected C_{max} of the TAK-831 tablet, to add the investigator's clinical judgment as a criterion for withdrawing a subject due to liver function test abnormalities, and to correct inconsistencies in the description of contraception requirements. Other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only. For specific descriptions of text changes and where the changes are located, see [Appendix E](#).

Changes in Amendment No. 1

1. Addition of investigator's clinical judgment as criterion for withdrawing subject due to liver function test abnormalities.
2. Correction of inconsistencies in the description of contraception requirements.
3. Addition of extra ECG timepoints.

INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator

Date

Investigator Name (print)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.		Compound: TAK-831																																						
Title of Protocol: A Randomized, Open-Label, Single-Dose, 2-Period, Crossover Design, Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 T2 Tablet Formulation in Healthy Subjects		IND No.: 132,633		EudraCT No.: Not applicable.																																				
Study Number: TAK-831-1004		Phase: 1																																						
Study Design: TAK-831-1004 is a phase 1, randomized, open-label, single-dose, 2-period crossover study designed to characterize the pharmacokinetics (PK) of TAK-831 400 mg and assess the effect of food on the bioavailability of TAK-831 400 mg, when administered as four 100 mg oral tablets of the T2 formulation in healthy male and female adult subjects. At Check-in (Day -1) of Period 1, 16 healthy male and female subjects, aged 18 to 55 years, inclusive, who meet the study entry criteria will be enrolled in the study. On Day 1 of Period 1, eligible subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences, which will define the order in which they will receive the TAK-831 regimens in Periods 1 and 2 (Table 1). Dosing between periods will be separated by a washout interval of ≥ 7 days. Table 1. Study Treatment Sequences <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">Treatment Sequence</th> <th rowspan="2">Number of Subjects</th> <th colspan="2">Regimen</th> </tr> <tr> <th>Period 1</th> <th>Period 2</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>8</td> <td>A</td> <td>B</td> </tr> <tr> <td>2</td> <td>8</td> <td>B</td> <td>A</td> </tr> </tbody> </table> Regimen A=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1 with water; Regimen B=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1, 15 minutes after starting ingestion of Ensure Plus. For both regimens, subjects will fast for ≥ 10 hours overnight before dosing. The study will include a Screening Period (Days -28 to -2), 2 treatment periods, and a Follow-up Phone Call (14 \pm 2 days after last dose of study drug). In each period, subjects will be admitted to the clinic on Day -1 (Check-in) and will remain confined to the clinic until completion of study procedures on the morning of Day 3. Subjects will return to the clinic for study assessments on Days 4, 6, and 8 in each period. Subjects will receive a single dose of TAK-831 on Day 1 of each period. Blood samples will be collected over 72 hours postdose to measure plasma concentrations of TAK-831 for PK assessments in each period. CCI Safety will be evaluated throughout the study. The schematic of the study design is presented in Table 2. Table 2. Schematic of Study Design <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">Screening</th> <th colspan="3">Treatment Periods 1 and 2</th> <th rowspan="2">Study Exit</th> <th rowspan="2">Follow-up (a)</th> </tr> <tr> <th>Check-in and Predose Assessments</th> <th>Dosing and Study Assessments</th> <th>PK, PD, and Safety Assessments</th> </tr> </thead> <tbody> <tr> <td>Days -28 to -2</td> <td>Day -1</td> <td>Day 1</td> <td>Days 1 to 3 Days 4 to 8</td> <td>Period 2 Day 8 (Study Day 16)</td> <td>Study Day 23 (± 2)</td> </tr> <tr> <td colspan="6" style="text-align: center;">←----- Confinement -----→</td> </tr> </tbody> </table> (a) The Follow-up Visit will occur (14 days after the last dose of study drug) by telephone unless abnormal, clinically significant findings were observed at Study Exit. In these cases, subjects will be brought back into the clinic for re-evaluation at the investigator's discretion.						Treatment Sequence	Number of Subjects	Regimen		Period 1	Period 2	1	8	A	B	2	8	B	A	Screening	Treatment Periods 1 and 2			Study Exit	Follow-up (a)	Check-in and Predose Assessments	Dosing and Study Assessments	PK, PD, and Safety Assessments	Days -28 to -2	Day -1	Day 1	Days 1 to 3 Days 4 to 8	Period 2 Day 8 (Study Day 16)	Study Day 23 (± 2)	←----- Confinement -----→					
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←----- Confinement -----→																																								

<p>Primary Objectives</p> <ul style="list-style-type: none"> To determine the PK of a single oral dose of TAK-831 400 mg in the fasted state and to estimate the effect of food on the PK of a single oral dose of TAK-831 400 mg when administered as the new T2 tablet formulation in healthy subjects. <p>Secondary Objective</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of a single oral dose of TAK-831 400 mg in healthy subjects in the fed and fasted states. 	
<p>Subject Population: Healthy male and female subjects aged 18 to 55 years, inclusive. Women of childbearing potential will be excluded.</p>	
<p>Number of Subjects: Per treatment sequence: 8 healthy subjects Estimated total: 16 healthy subjects</p>	<p>Number of Sites: 1 in the United States</p>
<p>Dose Level: TAK-831 400 mg (as four 100 mg T2 tablets)</p>	<p>Route of Administration: Oral</p>
<p>Duration of Treatment: Single dose in each of 2 treatment periods.</p>	<p>Period of Evaluation: 8 days per period, with a washout interval ≥ 7 days between the dose in Period 1 and Period 2.</p>
<p>Main Criteria for Inclusion:</p> <ul style="list-style-type: none"> The subject is a healthy adult male or healthy adult female of nonchildbearing potential. The subject is aged 18 to 55 years, inclusive, at the time of informed consent and first study drug dose. The subject weighs ≥ 45 kg and has a body mass index between 18.0 and 30.0 kg/m², inclusive, at Screening. 	
<p>Main Criteria for Exclusion:</p> <ul style="list-style-type: none"> If female, the subject is of childbearing potential (eg, premenopausal, not sterilized). The subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention). The subject has a lifetime history of suicidal ideation as evidenced by a score ≥ 3 in the Columbia-Suicide Severity Rating Scale at Screening or Baseline, or a history of suicidal behavior. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or Ensure Plus. The subject has any dietary restrictions or preferences that may interfere with the conduct of the study. 	
<p>Main Criteria for Evaluation and Analyses:</p> <p>Primary Endpoints: The following PK parameters of TAK-831 derived for each period:</p> <ul style="list-style-type: none"> Maximum observed plasma concentration (C_{max}). Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}). Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}). <p>Secondary Endpoints</p> <ul style="list-style-type: none"> Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE). 	

Statistical Considerations:

PK:

For each regimen, TAK-831 plasma concentrations and PK parameter estimates will be summarized using descriptive statistics (N, mean, median, SD, percent coefficient of variation [%CV], minimum, maximum). In addition, geometric means will be calculated for C_{max} and area under the plasma concentration-time curves (AUCs). Individual subject plasma concentration and PK parameter data also will be listed.

Analysis of variance models will be performed on TAK-831 $\ln C_{max}$ and $\ln AUCs$. The model will include sequence, period, and regimen as fixed factors and subject-within-sequence as a random factor. Pairwise comparisons between the test regimen (Regimen B: fed state) and the reference regimen (Regimen A: fasted state) will be made and the 2-sided 90% CIs for the ratio of the central values for C_{max} and AUCs between regimens (Test: Reference) will be constructed to estimate the effect of food on TAK-831 PK.

Safety:

TEAEs will be presented in the data listings and summarized for each regimen by system organ class and preferred term (using the Medical Dictionary for Regulatory Activities) with descriptive statistics (N and percentage of subjects).

Sample Size Justification: With a sample size of 16 subjects (8 subjects per treatment sequence), allowing for a maximum of 2 dropouts, a 2-sided 90% CI for the difference in the paired means of the $\ln C_{max}$ will extend 0.23 from the observed mean. Assuming a point estimate of the food effect of 2 (observed ratio of fed vs fasting $C_{max}=2$), which means food increases C_{max} by 100%, this should lead to a lower bound of the 90% CI of 1.589 (58.9% increase) and an upper bound of the 90% CI of 2.517 (151.7% increase) for the ratios of the C_{max} central values (fed/fast). In addition, when a central value ratio of 1 is observed, the 90% CI should be approximately (-0.79, 1.26). This calculation also assumes the intrasubject %CV for C_{max} is 37.5%, which is estimated from Study TAK-831-1001 (Part 4).

3.0 STUDY REFERENCE INFORMATION

3.1 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.

3.2 Principal Investigator

PPD



3.3 List of Abbreviations

Term	Definition
%CV	percent coefficient of variation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC _∞	area under the plasma concentration-time curve from time 0 to infinity
AUC _{last}	area under the plasma concentration-time curve from time 0 to last quantifiable concentration
AUEC _{last}	area under the effect-time curve from time 0 to the last scheduled postdose time point
BMI	body mass index
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent clearance after extravascular administration
C _{max}	maximum observed plasma concentration
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
DAO	D-amino acid oxidase
ECG	electrocardiogram
eCRF	electronic case report form
E _{max}	maximum observed effect
FDA	Food and Drug Administration
FRDA	Friedreich ataxia
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NMDA	<i>N</i> -methyl-D-aspartate
OTC	over-the-counter
PD	pharmacodynamics(s)
PET	positron emission tomography

Term	Definition
PGx	pharmacogenomics(s)
PK	pharmacokinetic(s)
PT	preferred term
PTE	pretreatment event
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SRD	single rising dose(s)
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
time to E_{max}	time to reach maximum observed effect
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration

3.4 Corporate Identification

Takeda Takeda Development Center Americas and Europe

4.0 INTRODUCTION

4.1 Background

Ataxia manifests as impaired coordination of muscle movements. It is a nonspecific clinical manifestation indicative of dysfunction in the parts of the central nervous system (CNS) that coordinate movement, such as the cerebellum. The cerebellum is one of the key CNS structures responsible for collating neural information and using it in the coordination of smoothly ongoing movements, as well as participating in motor planning [1]. Patients with ataxia have trouble regulating the force, range, direction, velocity, and rhythm of muscle contractions, resulting in a characteristic type of irregular, uncoordinated movement that can manifest itself in many possible ways, such as asthenia, asynergy, delayed reaction time, and dyschronometria [1]. Patients also display instability of gait, difficulty with eye movements, dysarthria, dysphagia, hypotonia, dysmetria, and dysdiadochokinesia (impaired ability to perform rapid, alternating movements). These difficulties can affect employability, lead to disability, increase caregiver burden, and significantly reduce a person's health-related quality of life [2].

There are numerous types of ataxias, many genetically mediated and others idiopathic. Friedreich ataxia (FRDA) is the most common form of hereditary ataxia in the Western world, with an overall Caucasian prevalence of 1 in 50,000 people [3-5]. The number of individuals affected with FRDA at any given time in the United States is approximately 9000 [6]. In FRDA, a guanine-adenine-adenine (GAA) trinucleotide repeat expansion mutation in intron 1 of the frataxin gene (FXN) results in drastically reduced levels of the frataxin protein [5,7], which, in turn, leads to mitochondrial dysfunction, neurodegeneration, cardiomyopathy, diabetes mellitus, and skeletal deformities [8,9]. This disorder has a sensory ataxia component secondary to involvement of the dorsal root ganglia and spinocerebellar tracts, with loss of proprioceptive function and sensory neuropathy, as well as gradual decreases in sensory function that lead to visual and hearing impairments [10]. There is progressive destruction of the cerebellar dentate nucleus and the corticospinal tract [10].

Various compounds are under investigation [11,12]. However, there is currently no cure or approved effective treatment for any of the hereditary ataxias [13]. Thus, there is a great need to identify and develop effective therapies for patient populations with ataxia.

TAK-831 is a novel, highly selective and potent, small molecule inhibitor of D-amino acid oxidase (DAO), a peroxisomal enzyme active toward neutral D-amino acids, under development by Takeda for the treatment of various CNS disorders, including FRDA. In animal models, TAK-831

CCI

Additional information regarding the nonclinical pharmacology, pharmacokinetics (PK), and toxicology of TAK-831 is provided in the current Investigator's Brochure.

Two phase 1 studies have been conducted with TAK-831 in healthy subjects. The first study (TAK-831-1001) characterized the PK and pharmacodynamics (PD) of single-rising doses (SRD) (10 to 750 mg) and multiple-rising doses (30 to 400 mg) of a TAK-831 oral suspension, the relative bioavailability of an oral tablet (T1 formulation; 100 mg), and the effect of food (high-fat meal) on the tablet (100 mg). TAK-831 was absorbed rapidly following single and multiple doses of the oral suspension, with median time of first occurrence of C_{\max} (t_{\max}) values of 0.25 to 1 hour (range 0.17 to 2 hours). Exposure was generally dose dependent, with low intersubject variability (percent coefficient of variation [%CV] <40%). Corresponding mean terminal disposition phase half-life ($t_{1/2z}$) values ranged from 6 to 23 hours. Oral administration of a TAK-831 100 mg tablet with food increased TAK-831 exposure approximately 2-fold relative to administration without food. In the fasted state, exposure from the tablet was approximately 2-fold lower than that from the oral suspension. After single and multiple doses of TAK-831, changes from Baseline in D-serine area under the effect curve from time 0 to 24 hours (AUEC₂₄) were dose dependent.

The second study (TAK-831-1003) used positron emission tomography (PET) to investigate brain DAO enzyme occupancy by TAK-831 after a single oral dose (100 to 500 mg) in healthy male subjects. The results demonstrated that the tracer crossed the blood brain barrier in humans with highest uptake in the cerebellum and brainstem and low uptake in the frontal cortex, a distribution consistent with DAO distribution in rodents [15]. Administration of TAK-831 blocked uptake of the tracer indicating that the TAK-831 binding to brain DAO is specific. Using a multilinear analysis-1 model [16], the in vivo TAK-831 plasma concentration at 50% occupancy (EC₅₀) for brain DAO was estimated to be 12.7 ng/mL (95% CI=2.3, 23.1). In conclusion, this study demonstrates that TAK-831 accesses the DAO enzyme in the brain and displays high target occupancy at tested doses that have been shown to be safe in Study TAK-831-1001.

In both phase 1 studies (TAK-831-1001, TAK-831-1003), TAK-831 was generally safe and well tolerated at the doses administered in healthy subjects. No deaths, serious adverse events (SAEs), or treatment-emergent adverse events (TEAEs) leading to discontinuation were reported in either study. The most frequently reported TEAEs in Study TAK-831-1001 were postural dizziness and headache. The rate of postural dizziness in subjects receiving TAK-831 did not markedly differ from the rate observed in subjects receiving placebo. In Study TAK-831-1003 (PET occupancy, single dose), the most common TEAEs overall were related to the catheter site (pain, bruise, or hematoma); the remaining TEAEs were consistent with those reported in Study TAK-831-1001. No concerning trends in clinical laboratory, electrocardiogram (ECG), or vital sign data were observed in either study.

4.2 Rationale for the Proposed Study

A new T2 oral tablet formulation of TAK-831 has been developed and is planned for use in future clinical studies. The purpose of the current study is to characterize the PK of a single 400 mg dose of the TAK-831 T2 tablet formulation (given the stability limitations of the current T1 tablet

formulation), and to evaluate the effect of food on the PK of a single 400 mg dose of the T2 tablet formulation (given the positive food effect observed with the current T1 tablet formulation).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

- To determine the PK of a single oral dose of TAK-831 400 mg in the fasted state and to estimate the effect of food on the PK of a single oral dose of TAK-831 400 mg when administered as the T2 tablet formulation in healthy subjects.

5.1.2 Secondary Objective

- To evaluate the safety and tolerability of a single oral dose of TAK-831 400 mg in healthy subjects in the fed and fasted states.

5.1.3 Exploratory Objectives

CCI



5.2 Endpoints

5.2.1 Primary Endpoints:

The following PK parameters of TAK-831 derived for each regimen:

- Maximum observed plasma concentration (C_{max}).
- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).

5.2.2 Secondary Endpoint

- Percentage of subjects who experience at least 1 TEAE.

5.2.3 Exploratory Endpoints

CCI



The following PK parameters for TAK-831 for each regimen:

- t_{\max} .
- $t_{1/2z}$.
- CL/F.
- V_z/F .

CCI



6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

TAK-831-1004 is a phase 1, randomized, open-label, single-dose, 2-period crossover study designed to characterize the PK of TAK-831 400 mg and assess the effect of food on the bioavailability of TAK-831 400 mg, when administered as four 100 mg oral tablets of the T2 formulation in healthy male and female adult subjects.

At Check-in (Day -1) of Period 1, 16 healthy male and female subjects, aged 18 to 55 years, inclusive, who meet the study entry criteria will be enrolled in the study. On Day 1 of Period 1, eligible subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences, which will define the order in which they will receive the TAK-831 regimens in Periods 1 and 2 (Table 6.a). Dosing between periods will be separated by a washout interval of ≥ 7 days.

Table 6.a Study Treatment Sequences

Treatment Sequence	Number of Subjects	Regimen	
		Period 1	Period 2
1	8	A	B
2	8	B	A

Regimen A=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1 with water; Regimen B=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1, 15 minutes after starting ingestion of Ensure Plus. For both regimens, subjects will fast for ≥ 10 hours overnight before dosing.

The study will include a Screening Period (Days -28 to -2), 2 treatment periods, and a Follow-up Phone Call (14 ± 2 days after last dose of study drug). In each period, subjects will be admitted to the clinic on Day -1 (Check-in) and will remain confined to the clinic until completion of study procedures on the morning of Day 3. Subjects will return to the clinic for study assessments on Days 4, 6, and 8 in each period. Subjects will receive a single dose of TAK-831 on Day 1 of each period. Blood samples will be collected over 72 hours postdose to measure plasma concentrations of TAK-831 for PK assessments in each period. CCI

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Safety will be evaluated throughout the study.

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

Figure 6.a Schematic of Study Design

Screening	Treatment Periods 1 and 2				Study Exit	Follow-up (a)
	Check-in and Predose Assessments	Dosing and Study Assessments	PK, PD, and Safety Assessments			
Days -28 to -2	Day -1	Day 1 (b)	Days 1 to 3	Days 4 to 8	Period 2 Day 8 (Study Day 16)	Study Day 23 (±2)
Confinement (c)						

(a) The Follow-up Visit will occur (14 days after the last dose of study drug) by telephone unless abnormal, clinically significant findings were observed at Study Exit. In these cases, subjects will be brought back into the clinic for re-evaluation at the investigator's discretion.

(b) Subjects will be randomly assigned to 1 of 2 treatment sequences before dosing on Day 1 of Period 1. A washout interval of ≥7 days will separate the dose in Period 1 from the dose in Period 2.

(c) Subjects will be discharged from the clinic after the Day 3 study assessments have been completed and will return to the clinic on Days 4, 6, and 8 for study assessments.

The end of the study is defined as the date the last subject completes the Follow-up Phone Call.

6.2 Justification for Study Design, Dose, and Endpoints

This phase 1 food-effect study is designed in accordance with the Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations Guidance for Industry from the Food and Drug Administration (FDA), the Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance for Industry from the FDA [17], the Guideline on the Investigation of Bioequivalence from the Committee for Medicinal Products for Human Use (CHMP) [18], and the Guideline on the Investigation of Drug Interactions from the CHMP (which includes food-effect studies) [19].

The single 400 mg dose of TAK-831 (4 × 100 mg tablets) selected for the current study is expected to be the highest dose level that will be assessed in upcoming studies in patients, based on PK, PET, and safety data from prior studies. Modeling of PET and PK data from Study TAK-831-1003 was used to determine the relationship between brain enzyme occupancy and TAK-831 plasma concentration after a single dose of TAK-831 suspension. Modeling results indicated that the exposure to TAK-831 after a total daily dose of 400 mg (4 × 100 mg tablets) corresponded to mean peak target occupancy >90% and mean trough occupancy >50%. Furthermore, this dose is considered to be safe and tolerable as exposures are expected to fall within the range of exposures previously observed in the TAK-831-1001 single ascending dose study where single doses of TAK-831 up to 750 mg were administered.

The crossover design is appropriate for the objectives of this study because each subject receives both regimens (tablet-fasted and tablet-fed) and serves as his or her own control, which reduces the variability in the PK of TAK-831. Subjects will be randomly assigned to 1 of 2 treatment sequences to avoid bias. The study design is open-label, since the primary objective is to assess objective variables, that is, PK parameters. The current study will be performed in healthy subjects rather than the target patient population to collect PK, safety, and tolerability data that will not be confounded by any comorbidities.

An increase in exposure of TAK-831 from the T1 tablet formulation after a high-fat meal was observed in Study TAK-831-1001. Because of low solubility, food is also expected to increase the

bioavailability of TAK-831 from the T2 tablet formulation. The objective of the current study is to estimate the magnitude of the food effect when TAK-831 (T2 tablet formulation) is co-administered with Ensure Plus (to be used in patients). Subjects will receive TAK-831 T2 tablets either in the fasted state or after ingesting Ensure Plus to evaluate the effect of this nutritional drink on the PK of TAK-831.

In the SRD study, the mean $t_{1/2z}$ values of TAK-831 ranged from approximately 6 to 23 hours over the 10 to 750 mg dose range, with the shorter mean $t_{1/2z}$ values generally occurring at the lower doses. Therefore, a washout interval of ≥ 7 days between the doses is sufficient to ensure that there is no drug carryover effect, and collection of PK blood samples up to 72 hours postdose is appropriate to characterize the PK of TAK-831.

The primary PK endpoints in this study, C_{max} and area under the plasma concentration-time curve (AUC), are standard PK parameters used to assess the effect of food on drug exposure. The use of standard noncompartmental PK parameters to assess the bioavailability of TAK-831 is well accepted in food-effect studies. Safety variables are included as the secondary endpoint (TEAEs) and exploratory endpoints ^{CCI} [REDACTED] to determine the tolerability of a single dose of TAK-831. These variables are routinely used for assessing safety and tolerability in clinical pharmacology studies. Additional exploratory endpoints are ^{CCI} [REDACTED]

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for TAK-831, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Two or more subjects experience an SAE.*
- Two or more subjects experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 times the upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.*
- One or more subjects experience ALT and/or AST elevations $>3 \times ULN$ in the presence of a total bilirubin increase $>2 \times ULN$ or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (ie, “Hy’s Law cases”).

- Two or more subjects experience ALT and/or AST elevations $>3\times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).*

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

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is a healthy adult male or healthy adult female of nonchildbearing potential.
4. The subject is aged 18 to 55 years, inclusive, at the time of informed consent and first study drug dose.
5. The subject weighs ≥ 45 kg and has a body mass index (BMI) between 18.0 and 30.0 kg/m², inclusive at Screening.
6. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use barrier method of contraception (eg, condom with spermicidal cream or jelly)* from signing of informed consent throughout the duration of the study and for 95 days after last dose. The female partner of a male subject should also be advised to use a highly effective method of contraception.*

* Definitions and highly effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 30 days prior to randomization.
2. The subject has received TAK-831 in a previous clinical study.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has uncontrolled, clinically significant neurologic (including seizure disorders), cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, or endocrine disease, psychiatric disorder, or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would

contraindicate taking TAK-831, or a similar drug in the same class, or that might interfere with the conduct of the study.

5. The subject has evidence of current cardiovascular, CNS, hepatic, hematopoietic, renal, metabolic, or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash.
6. The subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
7. The subject has a lifetime history of suicidal ideation as evidenced by a score ≥ 3 in the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening or Baseline, or a history of suicidal behavior.
8. The subject has a history of cancer, except basal cell carcinoma or in situ cervical cancer that has been in remission for ≥ 5 years prior to first dose of study drug.
9. The subject has a known hypersensitivity to any component of the formulation of TAK-831 or Ensure Plus.
10. If female, the subject is of childbearing potential (eg, premenopausal, not sterilized).
11. If male, the subject intends to donate sperm during the course of this study or for 95 days after the last dose of study drug.
12. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in (Day -1) of Period 1 or 2.
13. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 3 or more units per day on 1 occasion per week or 7 or more units in any given week) within 1 year prior to Screening or is unwilling to agree to abstain from alcohol and drugs throughout the study. One unit is equivalent to a half-pint of beer or 1 single measure of spirits or 1 small glass of wine.
14. The subject has taken any excluded medications, supplements, or dietary products during the time periods listed in [Table 7.a](#).
15. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) antibody/antigen at Screening or a known history of HIV infection.
16. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 28 days prior to Check-in (Day -1) of Period 1. Cotinine test is positive at Screening or Check-in (Day -1) of Period 1 or 2.
17. The subject has poor peripheral venous access.

18. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 45 days prior to first dose of study drug.
19. The subject has an abnormal (clinically significant) ECG at Screening or Check-in (Day -1) of Period 1 or 2. Entry of any subject with an abnormal (not clinically significant) ECG must be approved and documented by signature by the principal investigator or designee.
20. The subject has a QT interval with Fridericia correction method (QTcF) >450 msec (males) or >470 msec (females) or PR interval outside the range of 120 to 220 msec, confirmed with 1 repeat testing, at Screening or Check-in (Day -1) of Period 1 or 2.
21. The subject has a supine blood pressure outside of the range of 90 to 140 mm Hg for systolic and 50 to 90 mm Hg for diastolic, confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in (Day -1) of Period 1 or 2.
22. The subject has a resting heart rate outside of the range of 40 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes, at Screening Visit or Check-in (Day -1) of Period 1 or 2.
23. The subject has abnormal clinical laboratory test values that suggest a clinically significant underlying disease or has ALT and/or AST >1.5×ULN at Screening or Check-in (Day -1) of Period 1 or 2.
24. The subject has any dietary restrictions or preferences that may interfere with the conduct of the study.

7.3 Excluded Medications, Supplements, Dietary Products

Use of the agents listed in [Table 7.a](#) is prohibited from the time points specified until completion of all study-related activities, including the Follow-up Phone Call.

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

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

CYP=cytochrome P-450, OTC=over-the-counter.

(a) Occasional use of acetaminophen (≤ 1 g/day) or other medication as approved by Takeda on a case-by-case basis is allowed.

(b) Inclusive of but not limited to H1N1 and other influenza vaccinations.

(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine.

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

7.4 Diet, Fluid, Activity Control

Subjects will be confined to the clinic from Check-in (Day -1) through completion of study procedures on Day 3 in each period.

During each confinement period, subjects will be served standardized meals (except for Ensure Plus) and an evening snack, each containing ~30% fat (relative to total calories), and no additional food or drink (except for Ensure Plus for Regimen B and water for both regimens) will be allowed. For each regimen, the meals served on the day of dosing (Day 1) should be identical for all subjects. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor before the start of the study. The meal start and stop times and the amount consumed will be recorded in the source document and appropriate electronic case report form (eCRF) page for the Day -1 snack and all meals (including Ensure Plus) served on Day 1.

For each regimen, TAK-831 will be administered on Day 1 after an overnight fast of ≥ 10 hours. For Regimen A (fasted state), subjects will be orally administered TAK-831 with 240 mL of water.

For Regimen B (fed state), subjects will start consuming Ensure Plus 15 minutes before oral administration of TAK-831. Ensure Plus is a nutritional drink of 237 mL (8 fl oz) and has 355 total calories. Of the total calories, 103 calories are from fat, with the total fat content (11 g) being 17% of the daily value based on a 2000 calorie diet; 52 calories are from protein, with the total protein content (13 g) being 26% of the daily value based on a 2000 calorie diet; and 201 calories are from carbohydrate, with the total carbohydrate content (51 g) being 17% of the daily value based on a 2000 calorie diet. Subjects should complete the Ensure Plus in 15 minutes or less; TAK-831 should be administered with 240 mL of water 15 minutes after the start of this meal. For each regimen, subjects will fast for an additional 4 hours after dosing. Subjects will be allowed to consume water ad libitum except for 1 hour before dosing and 1 hour after dosing.

For each regimen, subjects will not receive breakfast on Day 1 (dosing day). Lunch will be served 4 hours after dosing (after the 4-hour PK and PD blood sample collections), dinner ~9 hours after dosing, and a snack ~12 hours after dosing (after the 12-hour PK and PD blood sample collections). No meals will be served after the snack. Subjects will be fasting for ≥ 10 hours before collection of blood samples for clinical laboratory tests (except for those collected at Screening).

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

Foods and beverages that are prohibited during the study are listed in [Table 7.a](#).

Subjects will remain upright (seated, standing, or ambulatory) for 4 hours after dosing, except as necessitated by the occurrence of an adverse event (AE) or study procedures (eg, obtaining 12-lead ECG). Subjects will refrain from strenuous and/or unaccustomed exercise throughout the entire study until Study Exit.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to [Section 9.1.17](#).

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

- Liver Function Test (LFT) Abnormalities

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see [Section 9.1.8](#)), if the following circumstances occur at any time during study drug treatment:

- ALT or AST $>8 \times$ ULN, or
- ALT or AST $>5 \times$ ULN and persists for >2 weeks or based on clinical judgment of the investigator, or

- ALT or AST $>3\times$ ULN in conjunction with elevated total bilirubin $>2\times$ ULN or INR >1.5 , or
 - ALT or AST $>3\times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
 3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.
 4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

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

5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.
Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.
7. Severe gastrointestinal intolerance. The subject develops severe gastrointestinal intolerance that cannot be ameliorated by supportive treatment.
8. Other.

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

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the discontinuation criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects may be considered for replacement on a case by case basis.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

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

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term “study drug” refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

TAK-831 T2 100 mg tablets will be provided as unmarked, yellow-red, film-coated tablets for oral administration. TAK-831 is manufactured by Takeda Pharmaceuticals, Osaka, Japan. The TAK-831 T2 100 mg tablets will be supplied in amber glass bottles with metal screw caps, with each bottle containing 32 tablets. Each bottle will be labeled with an open-label, single-panel label. The label will include pertinent study information and appropriate country-specific regulatory caution statements.

8.1.1.2 Ancillary Materials

Ensure Plus will be provided by the site. This nutritional drink has a total volume of 237 mL (8 fl oz) and 355 total calories. Of the total calories, 103 calories are from fat (total fat content is 17% of daily value), 201 calories are from carbohydrate (total carbohydrate content is 17% of daily value), and 52 calories are from protein (total protein content is 26% of daily value).

8.1.1.3 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:
TAK-831 T2 100 mg tablets.

8.1.2 Storage

Study drug (TAK-831 T2 100 mg tablets) and ancillary materials (Ensure Plus) must be kept in an appropriate, limited-access, secure place until used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The study drug supplies for each treatment period are indicated in [Table 8.a](#).

Table 8.a Study Drug Supplies per Treatment Period

Treatment Sequence	Regimen	
	Period 1	Period 2
1	A	B
2	B	A

Regimen A=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1 with water; Regimen B=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1, 15 minutes after starting ingestion of Ensure Plus. For both regimens, subjects will fast for ≥ 10 hours overnight before dosing.

8.1.4 Overdose

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

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

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the randomization schedule allocated to the site.

Subjects will be assigned to receive a 4-digit randomization number. The number will be assigned by the study site personnel in sequential order beginning with 1001 and ending with 1016. This 4-digit number will be used by the study site to facilitate the prelabeling of PK and PD samples, and will be the only subject identifier used on all PK and PD sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject results. This 4-digit number should only be used for the purposes described in this section. It does not replace the subject identification number, which is assigned at the time the informed consent is obtained and is used for all other procedures to identify the subjects throughout the study.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or its designee will generate the randomization schedule and will provide it to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-831 T2 100 mg tablets), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

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

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

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, will review the randomization schedule and subject dosing log prior to Day 1 in Periods 1 and 2.

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

The investigator or designee must record the current inventory of all sponsor-supplied drugs (TAK-831 T2 100 mg tablets) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs expiry date, date and amount dispensed, including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

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

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

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

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

9.1.1.1 Pharmacogenomics Informed Consent Procedure

Pharmacogenomics (PGx) informed consent is a component of the overall study informed consent. The requirements are described in Section [15.2](#). PGx sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographics to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, xanthine consumption, alcohol use, reproductive status, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.7](#)).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

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

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

On subsequent examinations, any abnormal change from the baseline physical examination must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. Any clinically significant change or new diagnosis as a result of a clinically significant change, as determined by the investigator, will be recorded as an AE in the source document and on the PTE/AE page of the eCRF.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below. Height is recorded in centimeters without decimal places and weight is recorded in kilograms (kg) with 1 decimal place. BMI should be derived as follows:

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

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

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

9.1.5 Vital Sign Procedure

Vital signs will include oral body temperature, respiratory rate, blood pressure, and heart rate (beats per minute). Blood pressure and heart rate will be measured in 2 positions: after 5 minutes supine and then after 1 and 3 minutes standing.

Vital signs should be measured at the same time of the day across visits, if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hours before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical

examination abnormalities noted at the screening or baseline examination. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be collected following an overnight fast of ≥ 10 hours (except for those collected at Screening) on the days stipulated in the Schedule of Study Procedures in [Appendix A](#).

The tests that will be performed for each clinical laboratory specimen are listed in [Table 9.a](#).

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBCs	ALT	pH
WBCs with differential (% and absolute)	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	AST	Glucose
Platelets	Total bilirubin	Blood
Prothrombin time/INR	Direct bilirubin	Nitrite
aPTT	Total protein	
	Creatinine	<u>Microscopic Analysis:</u> (a)
	Blood urea nitrogen	RBC/high power field
	Creatine kinase	WBC/high power field
	GGT	Epithelial cells, casts, etc
	Potassium	
	Sodium	
	Glucose	
	Chloride	
	Bicarbonate	
	Calcium	

Diagnostic Screening:

Serum

HIV (b)
 HBsAg and anti-HCV (b)
Female subjects only:
 hCG (for pregnancy) (d)
 FSH (b) (e)

Urine

Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c)

aPTT=activated partial thromboplastin time, FSH=follicle-stimulating hormone, GGT= γ -glutamyl transferase, hCG=human chorionic gonadotropin, RBC=red blood cell, WBC=white blood cell.

- (a) Microscopic examination of sediment to be performed only if the dipstick results are positive.
- (b) To be performed at Screening only.
- (c) To be performed at Screening and Check-in (Day -1) of Periods 1 and 2.
- (d) To be performed at Screening, Check-in (Day -1) of Period 1, and Study Exit/Early Termination.
- (e) For female subjects when menopause is suspected and subject is not surgically sterile.

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

If subjects experience ALT or AST $>3\times$ ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed preferably within 48 to 72 hours and no later than 7 days after the abnormality was noted (please refer to Section 7.5 for discontinuation criteria and Section 10.2.3 for reporting requirements related to abnormal LFT results).

If the ALT or AST remains elevated $>3\times$ ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 for reporting requirements related to abnormal LFT results).

The investigator or designee is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to the first dose of study drug will require clear and complete documentation in the source documents as to the investigator's assessment of not clinically significant before proceeding with enrollment or randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 95 days after the 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. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below. If the female partner has been using 1 of the hormonal contraceptives methods listed below for >3 months, condom use is advised but not mandated.

9.1.9.2 Female Subjects and Their Male Partners

Women of childbearing potential will not be included in this study.

9.1.9.3 *Definitions and Procedures for Contraception and Pregnancy Avoidance*

The following definitions apply for contraception and pregnancy avoidance procedures.

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

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

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, <1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are permitted, the only acceptable methods of contraception are as follows:

- Nonhormonal Methods:
 - Intrauterine device.
 - Bilateral tubal occlusion.
 - Vasectomized partner (provided that the vasectomized partner has received medical assessment of the surgical success).
 - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month before the first dose of study drug until 95 days after last dose.
- Hormonal Methods:
 - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated ≥ 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom, or diaphragm) if for shorter duration until the female partner has been on contraceptive for 3 months:
 - Oral.
 - Intravaginal (eg, ring).
 - Transdermal.

- Progestogen-only hormonal contraception associated with inhibition of ovulation initiated ≥ 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom, or diaphragm) if shorter until the female partner has been on contraceptive for 3 months:
 - Oral.
 - Injectable.
 - Implantable.
2. Unacceptable methods of contraception are as follows:
 - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
 - Spermicides only.
 - Withdrawal.
 - No method at all.
 - Use of female and male condoms together.
 - Cap/diaphragm/sponge without spermicide and without condom.
 3. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and sperm donation during the course of the study.
 4. During the course of the study, regular serum hCG pregnancy tests will be performed only for female subjects 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:
 - 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 the following:
 - Have you used the contraception consistently and correctly since the last visit?
 - Have you forgotten to use contraception since the last visit?
 - Is there a chance that your partner could be pregnant?
 5. In addition to a negative serum hCG pregnancy test at Screening, female subjects must also have a negative serum hCG pregnancy test on Day -1 of Period 1 before receiving the first dose of study drug.

9.1.10 Pregnancy

Women of childbearing potential will not be included in this study.

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

If the pregnancy occurs during administration of active study drug, for example, after Day 1 of Period 1 or within 95 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

If the female subject or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received.

All reported pregnancies, including those in female partners of male subjects, will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

Standard 12-lead ECGs will be recorded. When an ECG is scheduled at the same time as the blood draws or vital signs, then the blood draws and vital signs will take priority and the ECG will be obtained within 0.5 hours before or after the scheduled blood draw or vital sign assignment. If an ECG coincides with a meal, the ECG will take precedence followed by the meal.

All 12-lead ECG machines will be supplied by the study site. Subjects should be in a supine position following an approximate 5-minute rest period for ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

The investigator (or a qualified observer at the study site) will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded. The following parameters will be calculated automatically by the ECG machine and recorded on the eCRF: heart rate, RR interval, PR interval, QT interval, QRS interval, QT interval with Bazett correction method (QTcB), and QTcF interval. QTcF interval may be calculated manually by the study site. The QTcF interval is calculated as shown below:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on

thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source. The study site uses a fully validated ECG system. The investigator assessment is recorded electronically within this system.

9.1.12 PGx Sample Collection

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters, or drug targets, and may be evaluated for the genetic contribution to how the drug is broken down or how the drug affects the body. This is called a “PGx research study.” Specific purposes of this study include the following:

- Identifying genetic reasons why certain people respond differently to TAK-831.
- Finding out more information about how TAK-831 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to TAK-831.
- Identifying variations in genes related to the biological target of TAK-831.

This information may be used, for example, to develop a better understanding of the safety and efficacy of TAK-831 and other study drugs, and to improve the efficiency, design, and study methods of future research studies.

One 6-mL whole blood sample for DNA isolation will be collected at time point indicated in the Schedule of Study Procedures ([Appendix A](#)).

A portion of the DNA samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of TAK-831. Also, since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Detailed instructions for collecting, storing, handling, and shipping the PGx blood samples are provided in the laboratory manual.

9.1.13 PK Sample Collection

9.1.13.1 Collection of Blood for PK Sampling

Serial blood samples (one 4-mL sample per scheduled time) for PK analysis of TAK-831 will be collected into chilled Vacutainers containing the anticoagulant K₂EDTA, according to the schedule shown in [Table 9.b](#).

Table 9.b Collection of Blood Samples for PK Analysis

Analyte	Analysis Matrix	Dosing Day (Periods 1 and 2)	Time
TAK-831	Plasma	1	Predose (0 hour, within 15 minutes prior to dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, and 72 hours postdose.

The actual time of sample collection will be recorded on the source document and eCRF.

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

9.1.13.2 Bioanalytical Methods

Plasma concentrations of TAK-831 will be measured by high-performance liquid chromatography with tandem mass spectrometry.

9.1.14 PK Parameters

The plasma PK parameters of TAK-831 will be determined from the plasma concentration-time profiles for all evaluable subjects using noncompartmental analysis. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The plasma PK parameters that will be calculated from TAK-831 plasma concentrations for each regimen are shown in [Table 9.c](#).

Table 9.c Plasma PK Parameters

Symbol/Term	Definition
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
C_{max}	Maximum observed plasma concentration.
CL/F	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
λ_z	Terminal disposition phase rate constant.
$t_{1/2z}$	Terminal disposition phase half-life.
t_{max}	Time of first occurrence of C_{max} .
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.

Additional PK parameters may be calculated as appropriate.

9.1.15 PD Sample Collection

Serial blood samples (one 6-mL sample per scheduled time) for PD analysis of TAK-831 will be collected into chilled Vacutainers containing the anticoagulant K₂EDTA, according to the schedule shown in [Table 9.d](#).

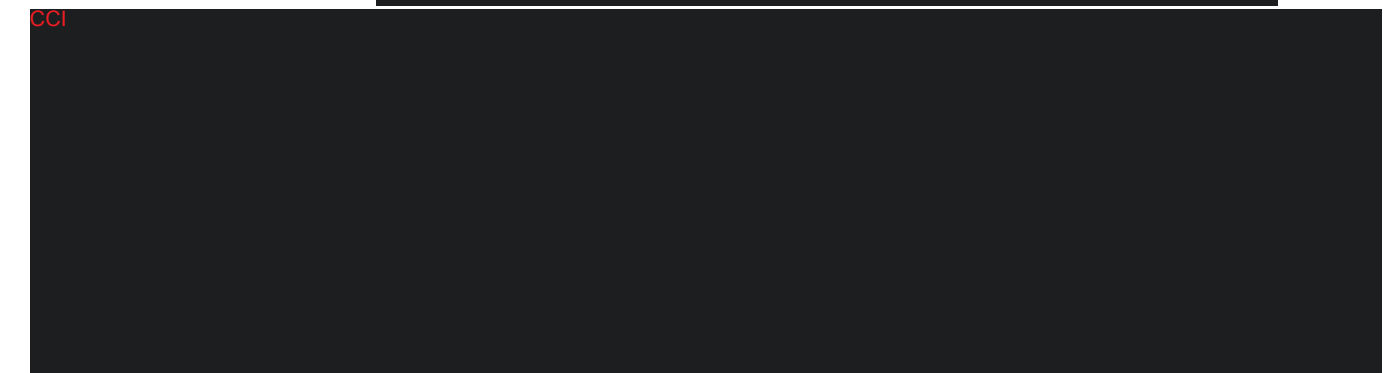
Table 9.d Collection of Blood Samples for PD Analysis



The actual time of sample collection will be recorded on the source document and eCRF. Instructions for sample processing and shipment are provided in the laboratory manual.

9.1.16 PD Parameters

PD parameters will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. CCI



9.1.17 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is withdrawn at the Screening Visit, the investigator should complete the screen failure page of the eCRF.

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

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

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

9.1.18 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

All measurements will be recorded on the source documents and in the eCRF.

9.1.19 C-SSRS

The Baseline/Screening C-SSRS will be administered in this study. The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical study of centrally-acting drugs [20,21]. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject.

9.2 Monitoring Subject Treatment Compliance

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

9.3 Schedule of Observations and Procedures

The schedule for the study-related procedures to be performed at each visit is shown in [Appendix A](#). Assessments should be completed at the designated visit/time points.

9.3.1 Screening

Subjects will be screened within 28 days prior to administration of the first dose of study drug. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.17 for procedures for documenting screen failures.

9.3.2 Study Entrance/Randomization

Eligible subjects will be admitted to the clinic on Day -1 (Check-in) of each period. Randomization will occur on Day 1 of Period 1, prior to administration of the first dose of study drug.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for study entrance, the subject should be randomly assigned to 1 of 2 treatment sequences as described in

Section 8.2. In each period, subjects will be administered the dose of study drug in the clinic under the supervision of the investigator or designee.

9.3.3 Treatment Periods 1 and 2

In each period, after administration of the single dose of study drug, subjects will remain confined to the clinic until completion of all study-related procedures on Day 3. Subjects will return to the clinic for study visits on Days 4, 6, and 8.

9.3.4 Study Exit

The Final Visit will be performed at Study Exit on Day 8 of Period 2. For all subjects receiving study drug, the investigator must complete the End-of-Study page of the eCRF.

9.3.5 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. For all subjects receiving study drug, the investigator must complete the End-of-Study page of the eCRF.

9.3.6 Follow-up Visit/Telephone Call

The Follow-up Visit will occur by telephone on Study Day 23±2 and will be for the purpose of assessing AEs and inquiring about concomitant medications taken since Study Exit. If the subject displayed abnormal, clinically significant observations at Study Exit, the subject may be brought back into the clinic at the investigator's discretion for the Follow-up Visit.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12. The genetic material will be extracted, purified, and initially stored at Covance Central Laboratory and then preserved and retained at Covance Biorepository for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

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

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

Subjects who consented and provided PGx blood samples for DNA analysis can withdraw their consent and request disposal of a stored sample at any time. The sponsor should be notified of any withdrawal of consent.

9.5 Blood Volume

Approximate blood volumes to be collected for each subject are shown in Table 9.f.

Table 9.f Approximate Blood Volume

Sample Type	Sample Volume (mL)	Screening	Number of Samples (a)									Total Volume (mL) (b)
			Periods 1 and 2									
			Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	
Clinical laboratory (c)	21	1	1	--	--	1	--	--	--	--	1 (d)	126
PK	4	--	--	10	2	1	1	--	--	--	--	112
CCI												
PGx DNA	6	--	--	1	--	--	--	--	--	--	--	6
Total Approximate Blood Sampling Volume (mL) (b)												412

-- = no samples collected.

(a) Does not include blood draws at any unscheduled visits.

(b) Total volume for study.

(c) Hematology and serum chemistry.

(d) Applies to Period 2 only.

(e) CCI

(f) The 168-hour postdose sample for Period 1 may coincide with the 24-hour predose sample on Day -1 of Period 2, in which case 2 samples will be collected at the same time.

For each subject, the maximum volume of blood collected at any single visit is approximately 70 mL (Day 1 of each period), and the approximate total volume of blood collected in the study is 412 mL.

Direct venipuncture is recommended for all blood collections, but if a catheter is used then use the saline lock (catheter) for the blood draws without the extra tubing, (eg, BD Insyte Autoguard #381434 [needle] and ICU Medical, Inc Clave Connector #PM30-2381 or similar). Any other method will need to be approved by the sponsor.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not

considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in intensity of AEs/Serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of a worsening of the pre-existing condition,

the worsening of the condition should be recorded as a PTE or 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 PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

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

10.1.4 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

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

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

10.1.5 Intensity of PTEs and AEs

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

- Mild: The event is transient and easily tolerated by the subject.
Moderate: The event causes the subject discomfort and interrupts the subject’s usual activities.
Severe: The event causes considerable interference with the subject’s usual activities.

10.1.6 Relationship of AEs to Study Drug

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

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

10.1.7 Relationship to Study Procedures

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

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

10.1.8 Start Date

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

10.1.9 Stop Date

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

10.1.10 Frequency

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

10.1.11 Action Concerning Study Drug

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

10.1.12 Outcome

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

- Unknown – the course of the AE/PTE cannot be followed up because of hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

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

Collection of AEs will commence from the time that the subject is first administered study drug (Day 1 of Period 1). Routine collection of AEs will continue until the Follow-up Phone Call (Study Day 23±2).

10.2.1.2 PTE and AE Reporting

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

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

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

8. Outcome of event.

9. Seriousness.

10.2.2 Collection and Reporting of SAEs

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

A 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 drugs.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 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 serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal LFTs

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

If a subject is noted to have ALT or AST $>3 \times \text{ULN}$ and total bilirubin $>2 \times \text{ULN}$ for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases page of the eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information 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.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

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

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

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

After lock of the clinical study database or submission of the eCRFs to the sponsor, any change of, modification of, or addition to the data on eCRFs should be made by the investigator with use of change and modification records of eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign and date the form.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), query responses/electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility.

Furthermore, International Conference on Harmonisation (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 study site agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

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

13.1.1 Analysis Sets

Safety Analysis Set

The safety analysis set will consist of all enrolled subjects who received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, other baseline characteristic, and safety summaries.

PK Analysis Set

The PK analysis set will consist of subjects from the safety set who have at least 1 measurable postdose TAK-831 plasma concentration.

PD Analysis Set

CCI

If any subjects are found to have incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis; however, all data will be presented in the subject listings.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and other baseline characteristic data will be summarized for all enrolled subjects by treatment sequence, and overall. Summary statistics (eg, number of subjects, mean, median, SD, and range) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, race, smoking status).

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

13.1.3 PK Analysis

13.1.3.1 TAK-831 Concentrations in Plasma

For each regimen, TAK-831 plasma concentrations will be summarized using descriptive statistics (mean, median, SD, %CV, minimum, and maximum) for each scheduled sampling time. Individual subject plasma concentration data will be listed.

13.1.3.2 Plasma PK Parameters

For each regimen, TAK-831 plasma PK parameter estimates will be summarized using descriptive statistics (N, mean, median, SD, %CV, minimum, and maximum). In addition, geometric means will be calculated for C_{max} and AUCs. Individual subject plasma PK parameter data will be listed.

Analysis of variance models will be performed on TAK-831 $\ln C_{max}$ and $\ln AUCs$. The model will include sequence, period, and regimen as fixed factors and subject-within-sequence as a random factor. Pairwise comparisons between the test regimen (Regimen B: fed state) and the reference regimen (Regimen A: fasted state) will be made and the 2-sided 90% CIs for the ratio of the central values for C_{max} and AUCs between regimens (Test: Reference) will be constructed to estimate the effect of food on TAK-831 PK.

Additional statistical analyses will be performed as appropriate.

13.1.4 PD Analysis

13.1.4.1 CCI [Redacted]

CCI [Redacted]

13.1.4.2 Plasma PD Parameters

CCI [Redacted]

Additional statistical or PK/PD analyses will be performed as appropriate.

13.1.5 Safety Analysis

No statistical testing will be performed or inferential statistics will be generated.

13.1.5.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. TEAEs with onset occurring within 30 days (onset date – last date of dose +1≤30) after the last dose of study drug will be included in the summary tables. TEAEs will be summarized by SOC and PT with descriptive statistics (N and percentage of subjects). The following summary tables will be generated by regimen: all TEAEs, all drug-related TEAEs, relationship of TEAEs to study drug (related vs not related), severity of TEAEs, and severity of related TEAEs. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to death, AEs leading to study drug or study visit discontinuation, and SAEs.

13.1.5.2 Clinical Laboratory Evaluations

Individual clinical laboratory test data (hematology, chemistry, and urinalysis) will be listed for all subjects. Baseline, postdose, and changes from Baseline to postdose data will be summarized by regimen for each scheduled time point using descriptive statistics. The Baseline for each regimen is defined as the last observation prior to the dose of study drug. Individual clinical laboratory test results that meet Takeda's markedly abnormal criteria (as defined in the SAP) will be listed and summarized by regimen.

13.1.5.3 Vital Signs

Individual vital sign data (oral temperature, respiration rate, blood pressure, and heart rate) will be listed for all subjects. Baseline, postdose, and changes from Baseline to postdose data will be summarized by regimen for each scheduled time point using descriptive statistics. The Baseline for each regimen is defined as the last observation prior to the dose of study drug. Individual vital sign results that meet Takeda's markedly abnormal criteria (as defined in the SAP) will be listed and summarized by regimen.

13.1.5.4 ECGs

Individual quantitative 12-lead ECG data will be listed for all subjects. Baseline, postdose, and changes from Baseline in quantitative ECG data will be summarized by regimen for each scheduled time point using descriptive statistics. The baseline is defined as the last observation prior to the dose of study drug. Individual ECG results that meet Takeda's markedly abnormal criteria (as defined in the SAP) will be listed and summarized by regimen.

13.1.5.5 Other Variables

Individual physical examination findings will be listed for all subjects.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

With a sample size of 16 subjects (8 subjects per treatment sequence), allowing for a maximum of 2 dropouts, a 2-sided 90% CI for the difference in the paired means of the $\ln C_{\max}$ will extend 0.23 from the observed mean. Assuming a point estimate of the food effect of 2 (observed ratio of fed vs fasting $C_{\max}=2$), which means food increases C_{\max} by 100%, this should lead to a lower bound of the 90% CI of 1.589 (58.9% increase) and an upper bound of the 90% CI of 2.517 (151.7% increase) for the ratios of the C_{\max} central values (fed/fast). In addition, when a central value ratio of 1 is observed, the 90% CI should be approximately (-0.79, 1.26). This calculation also assumes the intrasubject %CV for C_{\max} is 37.5%, which is estimated from Study TAK-831-1001 (Part 4).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents, where applicable. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). 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. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The investigator should document all protocol deviations.

Every attempt will be made to collect each PK and PD blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Blood samples not collected within the window specified for the scheduled sample time should be reported to Takeda using the Protocol Deviation Form. Protocol Deviation Forms are to be completed for PK/PD samples collected outside of the windows defined in [Table 14.a](#).

Table 14.a Windows for PK and PD Blood Sample Collection

Minutes	Nominal Sampling Time
≤30 minutes predose	0 hour
±5	immediately postdose to ≤6 hours
±10	>6 hours to ≤12 hours postdose
±15	>12 hours to ≤24 hours
±30	>24 hours

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB Approval

IRBs must be constituted according to the applicable 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. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB’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 approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the study site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening, may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

Subjects who consented and provided a PGx sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify the sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a subject 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 the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, MHRA, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or 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.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

Period Day	Screening	Treatment Period 1						Treatment Period 2						ET (a)	Follow-up (b)	
	-28 to -2	-1 (Period 1 Check-in)	1	2	3	4	6	8/-1 (Period 2 Check-in)	1	2	3	4	6			8 (Study Exit)
Study Day	-28 to -2	-1	1	2	3	4	6	8	9	10	11	12	14	16		23 (±2)
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Demographics, medical history	X															
Medication history	X															
Physical examination	X	X												X	X	
Vital signs (c)	X	X	X (d)	X	X	X	X	X	X (d)	X	X	X	X	X	X	X
Weight, height, BMI (e)	X	X												X	X	
Concomitant medications (f)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X														
Clinical laboratory tests (g)	X	X			X (h)			X (i)			X (h)			X	X	
HBsAg, anti-HCV, HIV	X															
FSH (j)	X															
Pregnancy test (hCG) (k)	X	X												X	X	
Urine drug screen	X	X						X								
C-SSRS	X	X												X	X	
ECG	X	X	X (l)					X	X (l)					X	X	
DNA sample collection (m)			X													
PK blood collection (n)			X	X	X	X			X	X	X	X				
CCI																
Dispense study drug			X						X							
Confinement		X	X	X	X			X	X	X	X					
PTE assessment (p)	X	X	X													
AE assessment (q)			X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes for Appendix A are on the next page.

Footnotes for Appendix A:

ET=Early Termination.

- (a) Procedures to be performed for subjects who prematurely discontinue the study.
- (b) The Follow-up Visit will occur (14 days after the last dose of study drug) by telephone unless abnormal, clinically significant findings were observed at Study Exit. In these cases, subjects will be brought back into the clinic for re-evaluation at the investigator's discretion.
- (c) Vital signs will include oral body temperature, respiratory rate, blood pressure, and heart rate (beats per minute). Blood pressure and heart rate will be measured in 2 positions: after 5 minutes supine and then after 1 and 3 minutes standing.
- (d) Vital signs will be measured at predose (within 50 minutes before dosing) and at 1, 4, and 12 hours postdose.
- (e) Height and BMI only will be collected at Screening.
- (f) All concomitant medications taken from Screening and throughout the study will be recorded.
- (g) Hematology, serum chemistry, and urinalysis.
- (h) Blood and urine samples for clinical laboratory tests will be collected on rising.
- (i) Only 1 blood sample will be collected on this day that will serve as the Period 2 Day -1 sample.
- (j) FSH levels will be measured for female subjects when menopause is suspected and subject is not surgically sterile.
- (k) Pregnancy test will be performed for female subjects only.
- (l) 12-lead ECG will be performed at 1 hour, 2 hours, and 4 hours postdose.
- (m) One blood sample (6 mL) will be collected for DNA analysis before dosing on Day 1 of Period 1.
- (n) Blood samples (4 mL) for PK analysis will be collected at predose (within 15 minutes of dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, and 72 hours postdose in each period.
- (o) Blood samples (6 mL) for PD analysis (D-serine and L-serine) will be collected on Day -1 at 24, 20, 16, and 12 hours before the Day 1 dose and on Day 1 at predose (within 15 minutes prior to dosing) and at 4, 8, 12, 24, 36, 48, 72, 120, and 168 hours postdose in each period. The 168-hour postdose sample for Period 1 may coincide with the 24-hour predose sample on Day -1 of Period 2, in which case 2 samples will be collected at the same time.
- (p) PTEs will be collected from the time the subject signs the informed consent until the subject is first administered study drug (Day 1 of Period 1) or until screen failure.
- (q) AEs will be collected from the time the subject is first administered study drug (Day 1 of Period 1) until the Follow-up Phone Call (Study Day 23 [\pm 2]).

Appendix B Responsibilities of the Investigator

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

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

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

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

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

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

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug, 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. Male subjects must use highly effective contraception (as defined in the informed consent) from Screening, throughout the duration of the study, and for 95 days after the last dose of study drug.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other personally identifiable information. In addition, the 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.

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

The 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 the investigator's own country.

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

Appendix E Detailed Description of Amendments to Text

Change 1. Addition of investigator's clinical judgment as criterion for withdrawing subject due to liver function test abnormalities.

The primary change occurs in Section [7.5 Criteria for Discontinuation or Withdrawal of a Subject](#)

- Initial wording:
1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
 - Liver Function Test (LFT) Abnormalities

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section [9.1.8](#)), if the following circumstances occur at any time during study drug treatment:

 - ALT or AST $>8\times$ ULN, or
 - ALT or AST $>5\times$ ULN and persists for >2 weeks, or
 - ALT or AST $>3\times$ ULN in conjunction with elevated total bilirubin $>2\times$ ULN or INR >1.5 , or
 - ALT or AST $>3\times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
-

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

- Liver Function Test (LFT) Abnormalities

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study drug treatment:

- ALT or AST $>8 \times \text{ULN}$, or
- ALT or AST $>5 \times \text{ULN}$ and persists for >2 weeks **or based on clinical judgment of the investigator**, or
- ALT or AST $>3 \times \text{ULN}$ in conjunction with elevated total bilirubin $>2 \times \text{ULN}$ or INR >1.5 , or
- ALT or AST $>3 \times \text{ULN}$ with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).

Rationale for Change:

Clarifies that investigator may use clinical judgment when determining if abnormalities (even of shorter duration) make it necessary to withdraw subject from the study.

Change 2. Correction of inconsistencies in the description of contraception requirements.

The primary change occurs in Section 9.1.9.1 *Male Subjects and Their Female Partners*

Initial wording: From signing of informed consent, throughout the duration of the study, and for 95 days after the 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. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below.

Amended or new wording: From signing of informed consent, throughout the duration of the study, and for 95 days after the 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. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below. **If the female partner has been using 1 of the hormonal contraceptives methods listed below for >3 months, condom use is advised but not mandated.**

Rationale for Change:

Clarifies the intended requirements.

Change 3. Addition of extra ECG timepoints.

The primary change occurs in [Appendix A, Schedule of Study Procedures](#)

Initial wording: Footnotes for Appendix A:
...
(l) 12-lead ECG will be performed at 2 hours postdose.

Amended or new wording: Footnotes for Appendix A:
...
(l) 12-lead ECG will be performed at **1 hour**, 2 hours, **and 4 hours** postdose.

Rationale for Change:

Additional ECG measurements at 1 and 4 hours after dosing will extend these measurements to the expected time of C_{max} of the TAK-831 tablet.

Amendment 01 to An Open-Label, Single-Dose, 2-Period Sequential Design Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 Formulation T2 in Healthy Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	12-Apr-2017 14:55 UTC
	Clinical Pharmacology Approval	12-Apr-2017 15:26 UTC
	Biostatistics Approval	12-Apr-2017 16:43 UTC
	Clinical VP Approval	12-Apr-2017 19:53 UTC