Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-831 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [14C]TAK-831 in Male Healthy Subjects

NCT Number: NCT04234672

Protocol Approve Date: 29 October 2019

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

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

PROTOCOL

A Phase 1 Study to Assess Absolute Bioavailability of TAK-831 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]TAK-831 in Male Healthy Subjects

Study Identifier:	TAK-831-1008
Compound:	TAK-831
Date:	29 October 2019
Version/Amendment Number:	Final

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, Massachusetts USA 02139 Telephone: +1 (617) 679-7000	TAK-831
Study Identifier: TAK-831-1008	**Phase:** 1
Protocol Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-831 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]TAK-831 in Male Healthy Subjects	

Study Design:

This is an open-label, 2-period, single-dose study in 6 male healthy subjects.

On Day 1 of Period 1 (absolute bioavailability [ABA] Study Period), subjects will receive a single unlabeled oral 500 mg dose of TAK-831 as tablets. At 1.25 hours (75 minutes) post oral dosing (ie, 15 minutes prior to the median t_{max} for the oral unlabeled dose [approximately (~) 1.5 hours]), subjects will receive a 15-minute intravenous (IV) infusion of a microdose of 50 µg (approximately equivalent to 1 microcurie [~1 µCi]) [^{14}C]TAK-831. Serial blood sampling will be performed up to Day 5 to determine the pharmacokinetics (PK) of TAK-831 in the plasma for the oral dose and [^{14}C]-total radioactivity and PK of [^{14}C]TAK-831 in the plasma for the IV dose. Urine and fecal output will also be collected up to the morning of Day 5 postdose to determine [^{14}C]TAK-831 concentrations. Subjects will remain in the CRU and continue with urine and feces collection until one of the discharge criteria is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 8 but no less than Day 5 for [^{14}C]-total radioactivity excretion in urine and feces.

In Period 1, subjects will be confined in the clinical research unit (CRU) for at least 5 days (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until one of the discharge criteria is met or up to Day 8. Subjects will return to the CRU on Day -1 of Period 2 for Period 2 procedures.

There will be a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

On Day 1 of Period 2 (absorption, distribution, metabolism, and elimination [ADME] Study Period), subjects will receive a single dose of 500 mg (~100 µCi) [^{14}C]TAK-831 as an oral suspension. Serial blood sampling will be performed and urine and feces will be collected to determine the PK of TAK-831 in plasma and urine, and total radioactivity in plasma, whole blood, urine, and feces, CCI [redacted]. Complete urinary and fecal output will be collected during the confinement period until discharge criteria are met (anticipated to be 10 days postdose or less).

In Period 2, subjects will be confined in the CRU for at least 5 days postdose (ie, Day 6) and until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples. If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples within 10 days postdose (ie, Day 11), the subject will continue to stay at the CRU until 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected, whichever occurs first, or until Day 14. If neither one of the 2 discharge criteria is met by Day 14, at the discretion of the Sponsor, the subject may be required to return to the CRU for urine and fecal sample collection in two 24-hour periods at approximately 7 and 14 days after discharge from the CRU (eg, Days 21 and 22 and Days 28 and 29). Subjects will be confined in the CRU for these 24-hour sample collection periods.

Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

In both Periods 1 and 2, any subject who experiences emesis within 3 hours post oral dosing will be excluded in the

final data analysis and may be replaced with a new subject. For a subject who drops out in Period 2, the replacement subject will be required to complete Period 2 only. If a subject experiences emesis after dosing in Period 2, vomitus will be collected throughout the study and assayed for total radioactivity.

The clinic will contact all subjects (including subjects who terminate the study early) 30 ± 2 days after the last study drug administration to determine if any adverse events (AEs) have occurred since the last study visit.

Study Primary Objectives:

Period 1 (ABA)

- To determine ABA of TAK-831 following a single microdose IV administration of 50 µg (~1 µCi) [^{14}C]TAK-831 and a single oral administration of 500 mg TAK-831 tablets.

Period 2 (ADME)

- To assess the mass balance (ie, cumulative excretion of total radioactivity in urine and feces) following a single oral administration of 500 mg (~100 µCi) [^{14}C]TAK-831 suspension.
- To characterize the PK of TAK-831 in plasma and urine, and total radioactivity concentration equivalents in plasma and whole blood following a single oral suspension dose of 500 mg (~100 µCi) [^{14}C]TAK-831.

Study Secondary Objectives:

Period 1 (ABA)

- To determine the PK of [^{14}C]TAK-831 following a single IV administration of 50 µg [^{14}C]TAK-831 and the PK of TAK-831 following a single oral administration of 500 mg TAK-831 tablets.

Periods 1 (ABA) and 2 (ADME)

- To assess the safety of TAK-831 during the ABA and ADME study periods.

Study Exploratory Objectives:

CCI [redacted]

Study Subject Population: Healthy adult male subjects

Planned Number of Subjects:	**Planned Number of Sites:**
6	1
Dose Levels: Period 1: 500 mg of TAK-831 50 µg (~1 µCi) [^{14}C]TAK-831 Period 2: 500 mg (~100 µCi) [^{14}C]TAK-831	**Route of Administration:** Period 1: Oral (tablets) IV infusion Period 2: Oral (suspension)
Duration of Treatment: Period 1: On Day 1, subject will receive a single oral dose of TAK-831 (tablets) followed by a 15-minute IV dose of [^{14}C]TAK-831 at 1.25 hours (75 minutes) post oral dose.	**Planned Study Duration:** Approximately 65 days including the Screening Period

Period 2: On Day 1, subject will receive a single oral dose of [^{14}C]TAK-831 (suspension).	

Main Criteria for Inclusion:

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

1. Healthy, adult, male, 19-55 years of age, inclusive, at screening.
2. Weighs at least 45 kg and body mass index (BMI) ≥18.0 and <32.0 kg/m^2 at screening.
3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
4. Subjects who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception as indicated in Appendix D or true sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined for male subjects as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 95 days after the last dosing.
5. Must agree not to donate sperm from the first dosing until 95 days after the last dosing.
6. Is able to swallow multiple tablets.
7. Understands the study procedures and agrees to participate by providing written informed consent, and be willing and able to comply with all study procedures and restrictions.

Main Criteria for Exclusion:

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

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of gastritis, gastrointestinal tract, gastric bypass surgery, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.
4. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
5. History or presence of alcohol or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds.
7. Smokes more than 20 cigarettes or equivalent per day within 3 months prior to the first dose and is unwilling to discontinue use of any tobacco- or nicotine-containing products during the confinement period(s) of the study.
8. Has a risk of suicide according to the Investigator's clinical judgment (eg, per C-SSRS), or has made a suicide attempt in the previous year prior to screening.
9. Positive urine drug or alcohol results at screening or first check-in.
10. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
11. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
12. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
13. Orthostatic vital sign results with a decrease in systolic >20 mmHg or decrease in diastolic >10 mmHg, and increase in pulse of >20 bpm at screening.
14. QTcF interval is >460 msec or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.

15. Estimated creatinine clearance <80 mL/min at screening.
16. Has tattoo(s) or scarring at or near the site of IV infusion or any other condition which may interfere with infusion site examination, in the opinion of the Investigator.
17. Has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
18. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks prior to first dosing.
19. Has received radiolabeled substances or has been exposed to radiation sources within 12 months of first dosing or is likely to receive radiation exposure or radioisotopes within 12 months of first dosing such that participation in this study would increase their total exposure beyond the recommended levels considered safe (ie, weighted annual limit recommended by the ICRP of 3000 mrem).
20. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study, including the follow-up period. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered approximately on Day 4 (Period 1) or Day 8 (Period 2) to ensure defecation, with agreement between the study Investigator and Sponsor Physician. Additional administration of milk of Magnesia may be needed on other days at discretion of the Investigator and Sponsor Physician.
    - Any drugs known to be significant inducers of uridine diphosphate glucuronosyltransferase or sulfotransferase, including St. John's Wort, within 28 days prior to the first dosing and throughout the study, including the follow-up period. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with study drug(s).
    - Alcohol, as defined in Table 7.a.
21. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
22. Donation of blood or significant blood loss within 56 days prior to the first dosing.
23. Plasma donation within 7 days prior to the first dosing.
24. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study are:

Period 1 (ABA):

- Absolute bioavailability (F) as percent F (%F) for TAK-831.

Period 2 (ADME):

- Percent of total radioactivity recovered in urine (Cum%Dose[UR]) and feces (Cum%Dose[FE]) relative to the administered radioactive dose (Combined Cum%Dose).
- Total radioactive recovery in urine (Ae[UR]) and feces (Ae[FE]) and the percent of the radioactive dose excreted in the urine (%Dose[UR]) and feces (%Dose[FE]).
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, and AUC_{last} for TAK-831 in plasma.
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, and AUC_{last} for total radioactivity concentration equivalents in plasma and whole blood.
- PK parameters for renal clearance (CL_R) for TAK-831 in urine.

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

Period 1 (ABA):

- PK parameters C_{eoi} (IV infusion), C_{max} (oral), t_{max} (oral), AUC_{∞}, AUC_{last}, and $t_{1/2z}$ for TAK-831, and [^{14}C]TAK-831 in plasma.

Periods 1 (ABA) and 2 (ADME):

- Tabulated treatment-emergent AEs (TEAEs) and summary statistics for clinically relevant 12-lead ECGs, vital signs, and clinical laboratory tests results

CCI

[redacted]

Statistical Considerations:

Descriptive statistics will be provided for the total radioactivity (whole blood, plasma, urine, feces, and if applicable, emesis), plasma TAK-831 concentrations and PK parameters, and [^{14}C]TAK-831 plasma and urine radioactivity concentration equivalent, using appropriate summary statistics to be fully specified in the statistical analysis plan (SAP).

ABA of TAK-831 will be estimated using a ninety percent (90%) confidence interval (CI) constructed for the difference in least-squares (LS) mean on the log scale for dose normalized AUC_{∞} between a single oral dose and the IV microdose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose normalized AUC_{∞} geometric mean ratio (TAK-831 administered as oral dose / [^{14}C]TAK-831 administered as IV microdose). AUC_{last} and C_{max} will be analyzed in a similar fashion.

Mass balance will be calculated as a sum of the percent of the total radioactivity recovered in urine and feces plus any radioactivity dose due to emesis (if any occurred) relative to the administered radioactivity dose.

Sample Size Justification:

The sample size of 6 male healthy subjects was selected without statistical considerations and is deemed adequate to meet the study objectives. In addition, this sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity.

2.0 STUDY SCHEMATIC

Screening	Period 1 [a]			
Within 28 days of first dosing in Period 1	Day -1	Day 1		Days 2 - 8
	Check-in	Oral Dosing at Hour 0	IV Dosing at Hour 1.25 (75 minutes post oral dosing)	
		Plasma, urine, and fecal sampling for ABA and safety monitoring for at least 96 hours post oral dose [b]		
	<- - - - - - - - - - - - confinement [b] - - - - - - - - - - - - >			

[a] There will be a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

[b] Subjects will be confined in the CRU for at least 5 days (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until one of the discharge criteria is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample is collected) or up to Day 8.

Period 2 [a]						Follow-up
Day -1 [b]	Day 1	Days 2 - 6	Days 7 - 14	Days 21 - 22	Days 28 - 29	30 ± 2 days after last dosing
Check-in	Oral Dosing at Hour 0					
	Whole blood, plasma, urine, and fecal sampling for TAK-831 (plasma and urine), total radioactivity (plasma, whole blood, urine, and feces), CCI [redacted] and safety monitoring (as applicable) up to approximately 240 hours postdose			24-hour urine and fecal sampling for TAK-831 (urine only), total radioactivity, CCI [redacted]		
<- - - - - - confinement [c] - - - - - - >			<confinement [c] >	<confinement [c] >	<confinement [c] >	

[a] There will be a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

[b] Day -1 of Period 2 will be the same day as Day 8 of Period 1 if the washout is exactly 7 days between doses in Periods 1 and 2.

[c] Subjects will be confined in the CRU for at least 5 days postdose (ie, Day 6) and until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples. If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples within 10 days postdose (ie, Day 11), the subject will continue to stay at the CRU until 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected, whichever occurs first, or until Day 14. If neither one of the 2 discharge criteria is met by Day 14, at the discretion of the Sponsor, the subject may be required to return to the CRU for urine and fecal samples collection in two 24-hour periods at approximately 7 and 14 days after discharge from the CRU (eg, Days 21 and 22 and Days 28 and 29). Subjects will be confined in the CRU for these 24-hour sample collection periods. Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedures [a] **Days →**	**S** [b]	**Study Days in Period 1** [c]						
		-1 (C-I [d]**)**	**1**	**2**	**3**	**4**	**5**	**6-8** [e]
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Safety Evaluations								
Full Physical Examination [f]	X	X [g]						
Height	X							
Weight	X	X [g]						
12-Lead Safety ECGs	X	X [h]	X [i]					
Vital Signs (heart rate and blood pressure)		X [h]	X [j]					
Orthostatic Vital Signs (heart rate and blood pressure)	X							
Vital Signs (respiratory rate and temperature)	X							
Hematology, Serum Chemistry [k], and UA	X	X			X			
Urine Drug and Alcohol Screen	X	X						
HIV/Hepatitis Screen	X							
C-SSRS [l]	X	X					X	
AE Monitoring	X							
Concomitant Medication Monitoring	X	X						
Study Drug Administration / PK								
TK-831 Administration (oral)			X [m]					
[^{14}C]TAK-831 Administration (IV)			X [n]					
Blood for TAK-831 Plasma PK [o]			X	X	X	X	X	
Blood for [^{14}C]TAK-831 Plasma PK [o]			X	X	X	X	X	
Urine for [^{14}C]TAK-831 PK and Total radioactivity [p]		X						X
Feces for [^{14}C]TAK-831 PK and Total radioactivity [p]		X						X
Other Procedures								
Confinement in the CRU [e,q]		X						X
Visit	X							

Study Procedures [a]	**Study Days in Period 2** [c]													**FU** [r]
Days →	**-1 (C-I** [d]**)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9-11**	**12-14**	**21-22** [y]	**28-29** [y]	
Safety Evaluations														
Full Physical Examination [f]	X										X [s]			
12-Lead Safety ECG	X [h]	X [t]									X [s]			
Vital Signs (heart rate and blood pressure)	X [h]	X [u]									X [s]			
Hematology, Serum Chemistry [k], and UA	X			X							X [s]			
Urine Drug and Alcohol Screen	X													
C-SSRS [l]	X										X [s]			
AE Monitoring	X													
Concomitant Medication Monitoring	X													
Study Drug Administration / PK														
[^{14}C]TAK-831 Administration (oral)		X [m]												
Blood for Total Radioactivity [v]		X	X	X	X	X	X	X	X	X				
Blood for TAK-831 Whole Blood PK [v]		X	X	X	X	X	X	X	X	X				
Blood for TAK-831 Plasma PK [v]		X	X	X	X	X	X	X	X	X				
CCI														
Urine for Total Radioactivity, CCI, and TAK-831 PK [w]	X											X	X	
Feces for Total Radioactivity CCI	X											X	X	
Other Procedures														
Confinement in the CRU [x]	X									X		X	X	
Phone call														X

a For details on Procedures, refer to Section 9.2.

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

c There will be a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

d Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU. If subjects are confined throughout the washout period, some safety events at check-in of Period 2 (eg, clinical laboratory tests, urine drug and alcohol screen, vital signs, and ECGs) may not be performed, following a decision by the Investigator.

e Subjects who do not meet one of the discharge criteria (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected) by Day 5, will remain confined and undergo study procedures until one of the discharge criteria is met or up to Day 8. Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

f Full physical examinations will be conducted at scheduled time points. Symptom-driven physical examination may be performed at additional times, at the Investigator's or designee's discretion. If confinement extends more than 10 days postdose in Period 2, a full physical examination will be repeated at the discharge day. If the subject returns to the CRU to collect urine and fecal samples in two blocks of 24-hour confinement period on Days 21 and 22 and Day 28 and 29 at the discretion of the Sponsor, a full physical examination will be repeated on each discharge day.

g If the screening assessment was conducted within 4-7 days prior to dosing (Day 1), assessment will be conducted at check-in only if, in the opinion of the Investigator, there is reason to believe they have substantially changed.

h To be performed within 24 hours prior to oral dosing.

i To be performed at 1 and 4 hours post oral drug administration.

j To be performed at 1 hour post oral drug administration.

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

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

m Oral drug administration will be performed at Hour 0 of Day 1.

n A 15-minute IV drug administration will begin at 1.25 hours (75 minutes) post oral dose on Day 1 of Period 1.

o For a detailed blood sampling schedule refer to Table 3.a.

p For a detailed urine and fecal sampling schedule refer to Table 3.b.

q Subjects who meet discharge criteria prior to Day 8 may be confined throughout the washout period at the discretion of the CRU.

r The clinic will contact all subjects (including subjects who terminate the study early) 30 ±2 days after the last study drug administration to determine if any AEs have occurred since the last study visit.

s To be performed at the end of Period 2 (prior to discharge) or prior to early termination from the study.

t To be performed at 4 hours post oral drug administration.

u To be performed at 4 and 12 hours post oral administration.

v For a detailed blood sampling schedule refer to Table 3.c.

w For a detailed urine and fecal sampling schedule refer to Table 3.d.

x Subjects will remain confined to the CRU for at least 5 days postdose (ie, Day 6) and until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples. If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples within 10 days postdose (ie, Day 11), the subject will continue to stay at the CRU until 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected, whichever occurs first, or until Day 14. If neither one of the 2 discharge criteria is met by Day 14, at the discretion of the Sponsor, the subject may be required to return to the CRU for urine and fecal samples collection in two 24-hour periods at approximately 7 and 14 days after discharge from the CRU (eg, Days 21 and 22 and Days 28 and 29). Subjects will be confined in the CRU for these 24-hour sample collection periods. Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

y Only for subjects who do not meet neither one of the 2 discharge criteria by Day 14 and at the discretion of the Sponsor.

Abbreviations: AE = Adverse event, C-I = Check-in, C-SSRS = Columbia-suicide severity rating scale, CRU = Clinical research unit, ECG = Electrocardiogram, FU = Follow-up, HIV = Human immunodeficiency virus, INR = International normalized ratio, IV = Intravenous, PK = Pharmacokinetics, PT = Prothrombin time, S = Screening, UA = Urinalysis.

Table 3.a Blood Collection Schedule after the Oral and Intravenous Doses of TAK-831 (Period 1 - ABA Study Period)

Study Day	Time (relative to oral dosing)	Time (relative to IV infusion)	Blood Sample Collection (oral dose)	Blood Sample Collection (IV dose)
	Matrix		Plasma Sample 1 [a]	Plasma Sample 2 [b]
Day 1	0 (predose)		X [c]	X [c]
	0.5 hour postdose (± 2 min)		X [c]	
	1 hour postdose (± 2 min)		X [c]	
	1.25 hours postdose (- 2 min)	0 (predose)		X [c]
	1.5 hours postdose (± 2 min)	End of infusion	X	X
		5 min after the end of infusion (± 2 min)		X
		15 min after the end of infusion (± 2 min)		X
	2 hours postdose (± 2 min)	30 min after the end of infusion (± 2 min)	X	X
		1 hour after the end of infusion (± 2 min)		X
	4.5 hours postdose (± 2 min)	3 hours after the end of infusion (± 5 min)	X	X
	6.5 hours postdose (± 2 min)	5 hours after the end of infusion (± 5 min)	X	X
	8.5 hours postdose (± 2 min)	7 hours after the end of infusion (± 5 min)	X	X
	12.5 hours postdose (± 5 min)	11 hours after the end of infusion (± 5 min)	X	X
Day 2	24.5 hours postdose (± 5 min)	23 hours after the end of infusion (± 5 min)	X	X
	36.5 hours postdose (± 10 min)	35 hours after the end of infusion (± 10 min)	X	X
Day 3	48.5 hours postdose (± 10 min)	47 hours after the end of infusion (± 10 min)	X	X
Day 4	72.5 hours postdose (± 10 min)	71 hours after the end of infusion (± 10 min)	X	X
Day 5	96.5 hours postdose (± 15 min)	95 hours after the end of infusion (± 15 min)	X	X

[a] For determination of TAK-831 in plasma following oral tablet dose.
[b] For determination of [^{14}C]-total radioactivity, and [^{14}C]TAK-831 in plasma following IV infusion.
[c] Pre-IV dose samples should be stored separately away from the postdose samples to avoid cross contamination.

Table 3.b Urine and Fecal Sampling Schedule (Period 1 – ABA Study Period)

Study Day	Time Interval (hours) (Relative to Oral Dosing) Matrix	Urine Sample Collection Urine [a]	Feces Sample Collection Feces [b]
Days -2 to 1	-48 to 0 hours (predose)	X [c, d]	X [d, e]
Day 1	0-1.25 hours (prior to IV dosing)	X [d]	X [d]
Day 1	1.25-12 hours	X	X (1.25-24 hours)
Days 1 to 2	12-24 hours	X	
Days 2 to 3	24-48 hours	X	X
Days 3 to 4	48-72 hours	X	X
Days 4 to 5	72-96 hours	X [f]	X [f]
Days 5 to 6 (if required)	96-120 hours	X [g]	X [g]
Days 6 to 7 (if required)	120-144 hours	X [g]	X [g]
Days 7 to 8 (if required)	144-168 hours	X [g]	X [g]

[a] Urine sample for [^{14}C]TAK-831 and [^{14}C]-total radioactivity following IV infusion.

[b] Feces sample for [^{14}C]TAK-831 and [^{14}C]-total radioactivity following IV infusion.

[c] Predose urine sample is to be obtained within 24 hours prior to IV infusion and prior to oral dosing.

[d] Pre-IV dose samples should be stored separately away from the postdose samples to avoid cross contamination.

[e] Predose fecal sample is to be obtained within 48 hours prior to oral dosing. Subjects will be asked to bring a fecal sample at check-in (if produced within 48 hours prior to oral dosing). Feces produced between check-in and dosing will also be collected as a predose sample with the sample produced nearest to oral dosing to be retained as the only predose sample.

[f] Including the urine and fecal sample collected on the morning of Day 5 (when passed) prior to furlough. Subjects will be asked to provide a urine and a fecal sample prior to release from the clinic on Day 5.

[g] For subjects who do not meet a discharge criterion by Day 5, samples will continue to be collected in 24-hour intervals until radioactivity in urine and feces combined is ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected, the excretion of radioactivity is ≥80% of the administered radioactive dose, or up to Day 8.

Table 3.c Blood Collection Schedule (Period 2 - ADME Study Period)

Study Day	Matrix	Sample collected for analysis in Whole Blood	Sample collected for analysis in Plasma		
	Time (Relative to Oral Suspension Dosing)	Blood Sample [a]	Plasma Sample 1 [b]	Plasma Sample 2 [c]	Plasma Sample 3 [d]
Day 1	0 (predose)	X [e]	X [e]	X [e]	X [e]
	0.25 hour postdose (± 2 min)	X	X	X	
	0.5 hour postdose (± 2 min)	X	X	X	X
	1 hour postdose (± 2 min)	X	X	X	X
	2 hours postdose (± 2 min)	X	X	X	
	4 hours postdose (± 2 min)	X	X	X	X
	6 hours postdose (± 2 min)	X	X	X	
	8 hours postdose (± 2 min)	X	X	X	X
	12 hours postdose (± 5 min)	X	X	X	X
Day 2	24 hours postdose (± 5 min)	X	X	X	X
	36 hours postdose (± 10 min)	X	X	X	
Day 3	48 hours postdose (± 10 min)	X	X	X	X
Day 4	72 hours postdose (± 10 min)	X	X	X	X
Day 5	96 hours postdose (± 15 min)	X	X	X	
Day 6 (if required)	120 hours postdose (± 30 min)	X	X	X	X
Day 7 (if required)	144 hours postdose (± 30 min)	X	X	X	
Day 8 (if required)	168 hours postdose (± 30 min)	X	X	X	X
Day 9 (if required)	192 hours postdose (±1 hour)	X	X	X	
Day 10 (if required)	216 hours postdose (±1 hour)	X	X	X	
Day 11 (if required)	240 hours postdose (±1 hour)	X	X	X	

[a] Blood sample 1 – Blood sample for total [^{14}C] determination (total radioactivity) in whole blood.
[b] Plasma sample 1 – Blood sample for total [^{14}C] determination in plasma.
[c] Plasma sample 2 – Blood sample for TAK-831 PK in plasma.
[d] Plasma sample 3 – Blood sample for CCI [redacted]
[e] Predose blood and plasma samples should be stored separately away from the postdose samples to avoid cross contamination.

Table 3.d Urine and Fecal Sampling Schedule (Period 2 - ADME Study Period)

Study Day	Time Interval (hour) (Relative to Oral Suspension Dosing) Matrix	Urine Sample Collection Urine [a]	Feces Sample Collection Feces [b]
Day -1 to 1	-24 to 0 hour (predose)	X [c]	X [d]
Day 1	0-12 hour	X	X (0-24 hour)
Days 1 to 2	12-24 hour	X	
Days 2 to 3	24-48 hour	X	X
Days 3 to 4	48-72 hour	X	X
Days 4 to 5	72-96 hour	X	X
Days 5 to 6	96-120 hour	X	X
Days 6 to 7 (if required)	120-144 hour	X	X
Days 7 to 8 (if required)	144-168 hour	X	X
Days 8 to 9 (if required)	168-192 hour	X	X
Days 9 to 10 (if required)	192-216 hour [e]	X	X
Days 10 to 11 (if required)	216-240 hour [e]	X	X
Days 11 to 12 [e] (if required)	240-264 hour [e]	X	X
Days 12 to 13 [e] (if required)	264-288 hour [e]	X	X
Days 13 to 14 [e] (if required)	288-312 hour [e]	X	X
Days 21 to 22 [e] (if required)	480-504 hour [e]	X	X
Days 28 to 29 [e] (if required)	648-672 hour [e]	X	X

[a] Urine samples for total [^{14}C] determination, for CCI [redacted] and for assessment of TAK-831 PK.

[b] Feces samples for total [^{14}C] determination (total radioactivity) and for CCI [redacted]

[c] Predose urine sample is to be obtained within 24 hours prior to dosing. Predose urine samples should be stored separately away from the postdose samples to avoid cross contamination.

[d] Predose fecal sample is to be obtained within 48 hours prior to dosing. Subjects will be asked to bring a fecal sample at check-in (if produced within 48 hours prior to dosing). Feces produced between check-in and dosing will also be collected as a predose sample with the sample produced nearest to dosing to be retained as the only predose sample. Predose fecal samples should be stored separately away from the postdose samples to avoid cross contamination.

[e] Samples will continue to be collected in 24-hour intervals until radioactivity in urine and feces combined is ≥90% of the administered radioactive dose or up to 10 days postdose (Day 11). If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples within 10 days postdose (ie, Day 11), the subject will continue to stay at the CRU until 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected, whichever occurs first, or until Day 14. If neither one of the 2 discharge criteria is met by Day 14, at the discretion of the Sponsor, the subject may be required to return to the CRU for urine and fecal samples collection in two 24-hour periods at approximately 7 and 14 days after discharge from the CRU (eg, Days 21 and 22 and Days 28 and 29). Subjects will be confined in the CRU for these 24-hour sample collection periods.

4.0 INTRODUCTION

4.1 Background

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves, including hallucinations, delusions, psychosis (positive symptoms), lack of motivation and reduced social interaction (negative symptoms), and poor information processing, impaired ability to focus on objectives, and abnormalities of working memory and learning (cognitive symptoms; van Os 2009). Hypofunction of *N*-methyl-D-aspartate (NMDA) receptors is considered a potential mechanism in the pathophysiology of schizophrenia, which could be mitigated with increased D-serine levels in the brain (Krystal 2003). Changes in the D-serine levels or D-serine to total serine ratios have been reported in the plasma of patients with schizophrenia both naive and under drug treatment (Calcia 2012, Ohnuma 2008, Hashimoto 2003, Hashimoto 2005). D-serine has been demonstrated to be a co-agonist of NMDA glutamate receptors that, along with glutamate, mediates NMDA receptor transmission, synaptic plasticity and other physiologic functions. D-serine is also a known endogenous ligand for the δ2 glutamate receptor which has been implicated in synaptic plasticity and long-term depression (Kakegawa 2011). Adding to the above evidence of a potential role of D-amino acid oxidase (DAO) in the pathophysiology of schizophrenia, a weak inhibitor of DAO, sodium benzoate, demonstrated efficacy in positive, negative, and cognitive symptoms in a proof-of-concept study in subjects with schizophrenia (van Os 2009, Lane 2013).

TAK-831 is a highly selective and potent inhibitor of D-amino acid oxidase, a peroxisomal enzyme active toward neutral D-amino acids and associated with the metabolism of D-serine. TAK-831 was shown to increase D-serine levels in the cerebellum of normal mice. It also demonstrated a positive effect on cognition and social interaction in rodent cognition and behavioral models. TAK-831 is under development for cognitive impairment associated with schizophrenia and negative symptoms of schizophrenia (IB 2019).

Pharmacokinetics

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[redacted]

CCI [redacted]

Safety

To date, TAK-831 has been administered to a total of 199 healthy subjects in 5 completed phase 1 studies (TAK-831-1001, TAK-831-1003, TAK-831-1004 TAK-831-1005, and TAK-831-1006) and to 40 subjects with Friedreich ataxia in a completed phase 2 study. Three studies are ongoing, including a phase 1 study in healthy adult Asian subjects (TAK-831-1002), and two phase 2 studies in adult subjects with schizophrenia (TAK-831-2001 and TAK-831-2002).

CCI [redacted]

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

Refer to the Investigator's Brochure (IB) for detailed background information on TAK-831 (IB 2019).

4.2 Rationale for the Proposed Study

CCI [redacted]

The primary purposes of the present study are to characterize the ABA (Period 1) and the absorption, metabolism, excretion, and mass balance of TAK-831 after single oral administration (Period 2) in healthy adult male subjects, by collecting plasma, urine, and feces samples for drug concentration analysis, and plasma, whole blood, urine, and fecal samples for total radioactivity analysis CCI [redacted]. The study will provide data required to evaluate the mass balance

CCI of TAK-831 in humans. Based on preliminary data in healthy subjects, the geometric mean plasma terminal $t_{1/2z}$ of TAK-831 is approximately 15 hours; thus, more than 90% of the radioactivity should be eliminated within 60 hours postdose.

4.3 Benefit/Risk Profile

The dose of study drug administered in this study is not anticipated to induce any potential risk or benefit to healthy subjects participating in this study. The dose of 500 mg TAK-831 in both T2 tablets and suspension formulation is administered according to the dosing recommendations found in the IB (IB 2019), was previously found to be well tolerated, and is not anticipated to induce any potential health risk.

The estimated radiation dose from a single IV administration of [^{14}C]TAK-831 (~1 µCi) and a single oral dose of [^{14}C]TAK-831 (~100 µCi) is below the radiation dose limits set forth in 21 CFR 361 for the whole body, active blood forming organs, lens of the eye, gonads, and other organs (see Section 6.3.2). Thus, the health risk resulting from exposure to radiation in the study drug is very low.

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

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

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

NA

5.2 Study Objectives

5.2.1 Study Primary Objectives

Period 1 (ABA)

- To determine ABA of TAK-831 following a single microdose IV administration of 50 µg (~1 µCi) [^{14}C]TAK-831 and a single oral administration of 500 mg TAK-831 tablets.

Period 2 (ADME)

- To assess the mass balance (ie, cumulative excretion of total radioactivity in urine and feces) following a single oral administration of 500 mg (~100 µCi) [^{14}C]TAK-831 suspension.
- To characterize the PK of TAK-831 in plasma and urine, and total radioactivity concentration equivalents in plasma and whole blood following a single oral suspension dose of 500 mg (~100 µCi) [^{14}C]TAK-831.

5.2.2 Study Secondary Objectives

Period 1 (ABA)

- To determine the PK of [^{14}C]TAK-831 following a single IV administration of 50 µg [^{14}C]TAK-831 and the PK of TAK-831 following a single oral administration of 500 mg TAK-831 tablets.

Periods 1 (ABA) and 2 (ADME)

- To assess the safety of TAK-831 during the ABA and ADME study periods.

5.2.3 Study Exploratory Objectives

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[redacted]

5.3 Endpoints

For full description of the PK parameters indicated below see Section 9.3.1.

5.3.1 Primary Endpoints

Period 1 (ABA):

- Absolute bioavailability (F) as percent F (%F) for TAK-831.

Period 2 (ADME):

- Percent of total radioactivity recovered in urine (Cum%Dose[UR]) and feces (Cum%Dose[FE]) relative to the administered radioactive dose (Combined Cum%Dose).
- Total radioactive recovery in urine (Ae[UR]) and feces (Ae[FE]) and the percent of the radioactive dose excreted in the urine (%Dose[UR]) and feces (%Dose[FE]).
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, and AUC_{last} for TAK-831 in plasma.
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, and AUC_{last} for total radioactivity concentration equivalents in plasma and whole blood.
- PK parameters for renal clearance (CL_R) for TAK-831 in urine.

5.3.2 Secondary Endpoints

Period 1 (ABA):

- PK parameters C_{eoi} (IV infusion), C_{max} (oral), t_{max} (oral), AUC_{∞}, AUC_{last}, and $t_{1/2z}$ for TAK-831, and [^{14}C]TAK-831 in plasma.

Periods 1 (ABA) and 2 (ADME):

- Tabulated TEAEs and summary statistics for clinically relevant 12-lead ECGs, vital signs, and clinical laboratory tests results.

5.3.3 Exploratory Endpoints

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[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, 2-period, single-dose study in 6 male healthy subjects.

On Day 1 of Period 1 (ABA Study Period), subjects will receive a single unlabeled oral 500 mg dose of TAK-831 as tablets. At 1.25 hours (75 minutes) post oral dosing (ie, 15 minutes prior to the median t_{max} for the oral unlabeled dose [~1.5 hours]), subjects will receive a 15-minute IV infusion of a microdose of 50 µg (~1 µCi) [^{14}C]TAK-831. Serial blood sampling will be performed up to Day 5 to determine the PK of TAK-831 in the plasma for the oral dose and [^{14}C]-total radioactivity and PK of [^{14}C]TAK-831 in the plasma for the IV dose. Urine and fecal output will also be collected up to the morning of Day 5 postdose to determine [^{14}C]TAK-831 concentrations. Subjects will remain in the CRU and continue with urine and feces collection until one of the discharge criteria is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 8 but no less than Day 5 for [^{14}C]-total radioactivity excretion in urine and feces.

In Period 1, subjects will be confined in the CRU for at least 5 days (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until one of the discharge criteria is met or up to Day 8. Subjects will return to the CRU on Day -1 of Period 2 for Period 2 procedures.

There will be a washout period of at least 7 days between the last dose in Period 1 and the dose in Period 2.

On Day 1 of Period 2 (ADME Study Period), subjects will receive a single dose of 500 mg (~100 µCi) [^{14}C]TAK-831 as an oral suspension. Serial blood sampling will be performed and urine and feces will be collected to determine the PK of TAK-831 in plasma and urine, and total radioactivity in plasma, whole blood, urine, and feces, CCI [redacted] Complete urinary and fecal output will be collected during the confinement period until discharge criteria are met (anticipated to be 10 days postdose or less).

In Period 2, subjects will be confined in the CRU for at least 5 days postdose (ie, Day 6) and until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples. If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples within 10 days postdose (ie, Day 11), the subject will continue to stay at the CRU until 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity for at least 2 consecutive intervals where both a urine and fecal sample are collected, whichever occurs first, or until Day 14. If neither one of the 2 discharge criteria is met by Day 14, at the discretion of the Sponsor, the subject may be required to return to the CRU for urine and fecal sample collection in two 24-hour periods at approximately 7 and

14 days after discharge from the CRU (eg, Days 21 and 22 and Days 28 and 29). Subjects will be confined in the CRU for these 24-hour sample collection periods.

Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

In both Periods 1 and 2, any subject who experiences emesis within 3 hours post oral dosing will be excluded in the final data analysis and may be replaced with a new subject. For a subject who drops out in Period 2, the replacement subject will be required to complete Period 2 only. If a subject experiences emesis after dosing in Period 2, vomitus will be collected throughout the study and assayed for total radioactivity.

The clinic will contact all subjects (including subjects who terminate the study early) 30 ± 2 days after the last study drug administration to determine if any AEs have occurred since the last study visit.

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

Table 6.a Planned Dose Levels of TAK-831 and [^{14}C]TAK-831

	Dose	Route of Administration
Period 1 (Treatment A)		
TAK-831	500 mg	Oral tablet
[^{14}C]TAK-831	50 µg (~1 µCi)	IV
Period 2 (Treatment B)		
[^{14}C]TAK-831	500 mg (~100 µCi)	Oral suspension

6.2 Dose Escalation

NA

6.3 Rationale for Study Design, Dose, and Endpoints

6.3.1 Rationale of Study Design

In Period 1 of the study, the ABA of TAK-831 will be estimated using a labeled IV microdose administered 1.25 hours (75 minutes) after an unlabeled oral dose in order to characterize the disposition properties of TAK-831. In order to determine ABA accurately and reliably, a healthy adult population is chosen.

Characterization of the disposition of a drug following IV administration facilitates the understanding of fundamental aspects of TAK-831's PK that cannot be determined from oral dosing alone, including bioavailability, intrinsic clearance, and volume of distribution. The results of this study will contribute to a robust understanding of the PK characteristics of TAK-831.

In Period 2 of the study, characterization of the absorption, metabolism, excretion, and mass balance of TAK-831 after oral administration of a single 500 mg (~100 µCi) [^{14}C]TAK-831 will

be achieved by collecting plasma samples for drug concentration analysis, and plasma, urine, and fecal samples for total radioactivity analysis CCI . The study will provide data required to evaluate the mass balance CCI of TAK-831 in humans.

6.3.2 Rationale for Dose

A single dose of 500 mg has been selected for this study as it is within the therapeutic dose range currently tested in Phase 2 studies of TAK-831. The highest dose of TAK-831 tested in healthy subjects was CCI in oral suspension and was found to be safe and well tolerated.

A radioactive IV dose of ~1 µCi in Period 1 (ABA) followed by an oral dose of ~100 µCi in Period 2 (ADME) were selected based on organ exposure data derived from a rat quantitative whole-body autoradiography/autoradioluminography study (see below) and the need to have sufficient specific radioactivity, for detection and analysis of parent drug and/or CCI in plasma, urine, and fecal samples.

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The calculated radiation absorbed doses were relatively low (<2.500 mrem and <0.025 mSv) for 26 of 27 tissues for male human subjects following a single oral dose of [^{14}C]TAK-831 of 100 µCi. The highest estimated absorbed dose was in the kidneys, which represented 0.30% of the allowable 5000 mrem Food and Drug Administration (FDA) exposure limit for a single tissue.

The overall human male whole-body exposure was predicted to be 0.7633 mrem (0.0076 mSv), which represented approximately 0.025% of the allowable 3000 mrem FDA exposure limit and 0.76% of the allowable International Commission on Radiological Protection (ICRP) limit of 1 mSv and is considered to be safe.

A single oral dose of up to 100 µCi (3.70 MBq) of [^{14}C]TAK-831 is not expected to represent a major whole-body radiation exposure risk to human male subjects as defined in the FDA and ICRP guidelines.

6.3.3 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the blood, urine, and feces collections for radioactivity, plasma concentrations, and CCI for TAK-831 are the critical procedures and are required to be collected, as appropriate, as close to the scheduled times defined in this protocol as possible.

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

The dose and administration of the study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 6.5.5. Discontinued subjects may be replaced at the discretion of the Sponsor and the Investigator. In both Periods 1 and 2, any subject who experiences emesis within 3 hours post the oral dose may be discontinued, excluded from the final data analysis, and may be replaced with a new subject. For a subject who drops out in Period 2, the replacement subject will be required to complete Period 2 only.

6.5 Study Beginning and End/Completion

6.5.1 Definition of Beginning of the Study

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

6.5.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0).

6.5.3 Definition of Study Completion

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

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

6.5.4 Definition of Study Discontinuation

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

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

6.5.5 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, 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.

6.5.6 Criteria for Premature Termination or Suspension of a Site

There is no predetermined criteria for termination of suspension of a site.

Termination or suspension of a site may occur at any time at the discretion of the Sponsor.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

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

1. Healthy, adult, male, 19-55 years of age, inclusive, at screening.
2. Weighs at least 45 kg and body mass index (BMI) ≥18.0 and <32.0 kg/m^2 at screening.
3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
4. Subjects who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception as indicated in Appendix D or true sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined for male subjects as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 95 days after the last dosing.
5. Must agree not to donate sperm from the first dosing until 95 days after the last dosing.
6. Is able to swallow multiple tablets.
7. Understands the study procedures and agrees to participate by providing written informed consent, and be willing and able to comply with all study procedures and restrictions.

7.2 Exclusion Criteria

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

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of gastritis, gastrointestinal tract, gastric bypass surgery, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.
4. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
5. History or presence of alcohol or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds.
7. Smokes more than 20 cigarettes or equivalent per day within 3 months prior to the first dose and is unwilling to discontinue use of any tobacco- or nicotine-containing products during the confinement period(s) of the study.

8. Has a risk of suicide according to the Investigator's clinical judgment (eg, per C-SSRS), or has made a suicide attempt in the previous year prior to screening.
9. Positive urine drug or alcohol results at screening or first check-in.
10. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
11. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
12. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
13. Orthostatic vital sign results with a decrease in systolic >20 mmHg or decrease in diastolic >10 mmHg, and increase in pulse of >20 bpm at screening.
14. QTcF interval is >460 msec or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
15. Estimated creatinine clearance <80 mL/min at screening.
16. Has tattoo(s) or scarring at or near the site of IV infusion or any other condition which may interfere with infusion site examination, in the opinion of the Investigator.
17. Has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
18. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks prior to first dosing.
19. Has received radiolabeled substances or has been exposed to radiation sources within 12 months of first dosing or is likely to receive radiation exposure or radioisotopes within 12 months of first dosing such that participation in this study would increase their total exposure beyond the recommended levels considered safe (ie, weighted annual limit recommended by the ICRP of 3000 mrem).
20. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study, including the follow-up period. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered approximately on Day 4 (Period 1) or Day 8 (Period 2) to ensure defecation, with agreement between the study Investigator and Sponsor Physician. Additional administration of milk of Magnesia may be needed on other days at discretion of the Investigator and Sponsor Physician.
    - Any drugs known to be significant inducers of uridine diphosphate glucuronosyltransferase or sulfotransferase, including St. John's Wort, within 28 days

prior to the first dosing and throughout the study, including the follow-up period. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with study drug(s).

- Alcohol, as defined in Table 7.a.

21. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
22. Donation of blood or significant blood loss within 56 days prior to the first dosing.
23. Plasma donation within 7 days prior to the first dosing.
24. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After the first dose of study drug, ibuprofen (up to 1.2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration.

Milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered approximately on Day 4 (Period 1) or Day 8 (Period 2) to ensure defecation, with agreement between the study Investigator and Sponsor Physician. Additional administration of milk of Magnesia may be needed on other days at discretion of the Investigator and Sponsor Physician.

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

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

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

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

Category	Between Screening and Randomization (Days -28 to predose [Day 1])	Post-Randomization (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from 48 hours prior to first dosing in each period and throughout the period of PK sample collection.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing [(a)]	Prohibited from 24 hours prior to first dosing in each period and throughout the period of PK sample collection [(a)].
Medications	See Sections 7.2 and 7.3	See Sections 7.2 and 7.3
Nicotine	Prohibited from check-in	Prohibited throughout confinement
Food substance		
Poppy seeds	Prohibited from 96 days prior to first dosing	Prohibited until end of PK collection in Period 2
Grapefruit/Seville orange	Prohibited from 14 days prior to first dosing	Prohibited until end of PK collection in Period 2

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

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

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

Subjects will fast overnight for at least 10 hours prior to each oral study drug administration and will continue to fast for at least 4 hours post oral dosing.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks

7.4.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours post oral dosing, except when they are supine or semi-reclined for study procedures (eg, IV dosing on Day 1 of Period 1).

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

Subjects will be prohibited from smoking during their confinement.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

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

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

- AEs.
- Positive urine drug or alcohol results.
- Difficulties in blood collection.

Any subject who experiences emesis within 3 hours post the oral dose may be discontinued, excluded from the final data analysis, and may be replaced with a new subject. In Period 2, if a subject experiences emesis after oral dosing, vomitus will be collected throughout the study and assayed for total radioactivity.

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

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.7 Subject Replacement

Discontinued subjects may be replaced at the discretion of the Sponsor and the Investigator. For a subject who drops out in Period 2, the replacement subject will be required to complete Period 2 only.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

8.1.1 TAK-831 Tablet

A single unlabeled 500 mg dose of TAK-831 (5 x 100 mg T2 tablets) will be administered in Period 1 of the study.

Oral dose of TAK-831 drug product is a nonsterile, oral, tablet dosage form, containing 100 mg (as freebase) of TAK-831.

8.1.2 [^{14}C]TAK-831 IV Sterile Solution

An IV dose of 50 µg [^{14}C]TAK-831 (~1 µCi) will be administered as a 15-minute infusion at 1.25 hours (75 minutes) after the TAK-831 oral dose (Section 6.1) in Period 1 of the study.

The drug product is prepared in the CRU pharmacy as an IV solution. The solution will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.1.3 [^{14}C]TAK-831 Oral Suspension

A dose of 500 mg [^{14}C]TAK-831 (~100 µCi) as oral suspension will be administered in Period 2 of the study.

The drug product is prepared in the CRU pharmacy as an oral suspension. The suspension will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.1.4 Clinical Study Drug Labeling

TAK-831 tablet, [^{14}C]TAK-831 IV solution, and [^{14}C]TAK-831 oral suspension containers will be affixed with clinical labels in accordance with local regulatory requirements.

8.1.5 Clinical Study Drug Inventory and Storage

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

Celerion will provide sufficient quantities of preparation and/or dilution solutions to allow completion of the study. The same lot number will be used throughout the study.

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

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

8.1.6 Clinical Study Drug Blinding

This is an open-label study.

8.1.7 Randomization Code Creation and Storage

NA

8.1.8 Clinical Study Blind Maintenance/Unblinding Procedure

NA

8.1.9 Accountability and Destruction of Sponsor-Supplied Drugs

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

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

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

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

9.1.1.2 Study Drug Assignment

This is a fixed-sequence study. All subjects will receive the same treatments as detailed in Section 6.1.

9.1.2 Inclusion and Exclusion

Subjects must satisfy all of the inclusion criteria and meet none of the exclusion criteria as outlined in Sections 7.1 and 7.2.

9.1.3 Medical History/Demography

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

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Sections 7.2 and 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

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

For this study, the collections for blood, urine, and feces for total radioactivity, plasma and urine concentrations, and CCI for TAK-831 are the critical parameters and need to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

9.2.1 Full Physical Examination

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

9.2.2 Height and Weight

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

9.2.3 BMI

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

9.2.4 Vital Signs

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

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

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

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

9.2.5 12-Lead ECG

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

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

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

9.2.6 Columbia-Suicide Severity Rating Scale

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

9.2.7 Study Drug Administration

TAK-831 oral tablet and [^{14}C]TAK-831 oral suspension and IV solution will be provided as described in Section 8.1.

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

Treatments A and B are described as follows:

Treatment A: 500 mg TAK-831 in tablets (5 x 100 mg T2 tablets) administered orally at Hour 0 on Day 1 followed by 50 µg (~1 µCi) [^{14}C]TAK-831 IV solution administered at Hour 1.25 (75 minutes post oral dosing) for 15 minutes.

Treatment B: 500 mg (~100 µCi) [^{14}C]TAK-831 oral suspension administered at Hour 0 on Day 1.

The oral doses of TAK-831 and [^{14}C]TAK-831 will be administered following an overnight fast with approximately 240 mL of water, then will be instructed to fast for an additional 4 hours. All subjects may then consume water *ad libitum* with the exception of 1 hour before and 1 hour after oral administration. The exact clock time of oral dosing will be recorded.

The IV dose will be administered over approximately 15 minutes. The start and end time of the IV infusion will be recorded.

The pharmacy at the CRU will provide the IV dose ready for the 15-minute infusion, the oral tablets dose in individual unit dose containers, and the oral suspension dose in a glass bottle for each subject.

9.2.8 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study formulations and/or procedures as described in Section 10.0.

9.2.9 Laboratory Procedures and Assessments

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

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

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

Chemistry

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

Chemistry evaluations will consist of the following standard chemistry panel:

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

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

Coagulation

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

Coagulation evaluations will consist of the following tests:

Prothrombin time
International normalized ratio (INR)

Urinalysis

Urinalysis will consist of the following tests:

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

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

Other

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

9.3 PK Samples

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

Instructions for plasma, urine, fecal samples processing and handling will be provided separately.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Period 1				
Plasma for TAK-831 PK	Plasma		PK analysis	Mandatory
Plasma for total radioactivity and [^{14}C]TAK-831 PK	Plasma		Total radioactivity and PK analysis	Mandatory
Urine for [^{14}C]TAK-831 PK	Urine		Total radioactivity recovery and PK analysis	Mandatory
Feces for [^{14}C]TAK-831 PK	Feces		Total radioactivity recovery and PK analysis	Mandatory
Period 2				
Blood for total radioactivity	Blood		Total radioactivity	Mandatory
Plasma for total radioactivity	Plasma		Total radioactivity	Mandatory
Plasma for TAK-831 PK	Plasma		PK analysis	Mandatory
CCI [redacted]				
Urine for total radioactivity	Urine		Total radioactivity	Mandatory
Urine for TAK-831 PK	Urine		PK analysis	Mandatory
CCI [redacted]				
Feces for total radioactivity	Feces		Total radioactivity	Mandatory
CCI [redacted]				

9.3.1 PK Measurements

9.3.1.1 Whole Blood and Plasma for PK Measurements

The following PK parameters for whole blood and plasma radioactivity concentration equivalents (plasma in both Periods 1 and 2, whole blood in Period 2 only) and for plasma TAK-831 concentrations (Periods 1 and 2) will be calculated, unless otherwise specified:

AUC_{last}: Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.

AUC_t: Area under the concentration-time curve from time 0 to time of the last common time point "t" at which total radioactivity and TAK-831 are quantifiable for all subjects.

AUC_∞: Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.

AUC_{extrap}%:	Area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}.
C_{max}:	Maximum observed concentration.
λ_z:	Terminal disposition phase rate constant.
t_{max}:	Time of first occurrence of C_{max}.
$t_{1/2z}$:	Terminal disposition phase half-life.

The following PK parameters for plasma concentrations of [^{14}C]TAK-831 following IV infusion (Period 1) will be calculated, unless otherwise specified:

AUC_{last}:	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_t:	Area under the concentration-time curve from time 0 to time of the last common time point "t" at which plasma total radioactivity and plasma TAK-831 are quantifiable for all subjects (plasma only).
AUC_{∞}:	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
AUC_{extrap}%:	Area under the curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}.
C_{eoi}:	Concentration at the end of infusion.
λ_z:	Terminal disposition phase rate constant.
$t_{1/2z}$:	Terminal disposition phase half-life.

No value for λ_z, AUC_{∞}, AUC_{extrap}%, or $t_{1/2z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

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

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

The ABA parameters for TAK-831 (Period 1) will be calculated as follows:

F:	Absolute bioavailability, calculated for plasma TAK-831.
%F:	Percent absolute bioavailability, calculated for plasma TAK-831 as [Dose (IV) x AUC_{∞} (oral)] / [Dose (oral) x AUC_{∞} (IV)] x 100.

9.3.1.2 Urine for PK Measurements

The following PK parameters for urine [^{14}C]TAK-831 concentrations (Period 1; IV dose), and for TAK-831 concentrations and urine total radioactivity (both Periods 1 and 2) will be calculated, unless otherwise specified:

Ae_{t1-t2}:	Amount of drug excreted in urine from time 1 to time 2.
Ae(UR):	Cumulative amount excreted in urine.
%Dose(UR):	Percent of administered radioactive dose excreted in urine within a given collection interval.
Cum%Dose(UR):	Cumulative percent of administered dose excreted in urine.
CL_R:	Renal clearance.

Total radioactivity excreted in urine will be presented in mass equivalent units.

9.3.1.3 Feces for PK Measurements

The following PK parameters for fecal [^{14}C]TAK-831 concentrations (Period 1; IV dose), and for fecal total radioactivity (both Periods 1 and 2) will be calculated, unless otherwise specified:

Ae(FE):	Cumulative amount of total radioactivity excreted in feces.
%Dose(FE):	Percent of administered radioactive dose excreted in feces within a given collection interval.
Cum%Dose(FE):	Cumulative percent of administered dose excreted in feces.

Total radioactivity excreted in feces will be presented in mass equivalent units.

9.3.1.4 Additional PK Measurements

The following PK parameters for combined urine and fecal total radioactivity (Period 1, IV dose and Period 2) will be calculated, unless otherwise specified:

Combined Cum%Dose:	Cumulative combined percent of administered dose excreted in urine and feces.

9.3.2 Biomarker Measurements

NA

9.3.3 PGx Measurements

NA

9.3.4 Confinement

In Period 1, subjects will be housed on Day -1, at the time indicated by the CRU until at least after the Day 5 blood draw and/or study procedures and until one of the discharge criteria is met or up to Day 8. Subjects will be eligible for discharge in Period 1, if they meet either one of the following discharge criteria:

- ≥80% of the total dose of radioactivity administered has been recovered in the urine and feces; or
- There is ≤1% of the total administered radioactivity in each of two consecutive 24-hour intervals where both a urine and fecal sample is provided.

Subjects who meet discharge criteria prior to Day 8 may be confined throughout the washout period at the discretion of the CRU.

In Period 2, subjects will be housed on Day -1, at the time indicated by the CRU, for at least 5 days postdose (ie, Day 6) and until ≥90% of the total dose of radioactivity administered has been recovered in the urine and feces.

If less than 90% of the total dose of radioactivity administered is recovered in urine and fecal samples within 10 days postdose (ie, Day 11), subjects will be eligible for discharge if they meet either of the following discharge criteria or until Day 14:

- ≥80% of the total dose of radioactivity administered has been recovered in the urine and feces; or
- There is ≤1% of the total administered radioactivity in each of two consecutive 24-hour intervals where both a urine and fecal sample is provided.

If neither one of the 2 discharge criteria is met by Day 14, at the discretion of the Sponsor, the subject may be required to return to the CRU for urine and fecal sample collection in two 24-hour periods at approximately 7 and 14 days after discharge from the CRU (eg, Days 21 and 22 and Days 28 and 29). Subjects will be confined in the CRU for these 24-hour sample collection periods.

All urine and fecal collections will be analyzed for radioactivity levels to determine if the discharge criteria are met.

It is expected that the majority (≥90%) of the administered radioactivity will be recovered within 60 hours post TAK-831 dose.

Release of subjects who do not meet a discharge criterion by Day 8 (Period 1) and/or Day 14 (Period 2) will be reviewed on a case-by-case basis.

Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

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

The clinic will contact all subjects (including subjects who terminate the study early) 30 ± 2 days after the last study drug administration to determine if any AEs have occurred since the last study visit.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

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

of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the

database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

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

10.1.1 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

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

10.1.2 Special Interest AEs

There are no AEs of Special Interest for TAK-831.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

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

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

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

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal

relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

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

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

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

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has

not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."

- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

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

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call on Day 31 (± 2 days), approximately 30 days after the last dose of investigational product. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

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

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

- Event term.

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

10.2.8.3 Reporting SAEs

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

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

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

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

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

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

SAE Follow-Up

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

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

10.2.8.4 Reporting Special Interest AEs

NA

10.2.8.5 Reporting of Abnormal LFTs

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

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

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

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

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

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

11.1.1 Analysis Sets

11.1.1.1 Safety Set

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

11.1.1.2 PK Set

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

11.1.2 Analysis of Demography and Other Baseline Characteristics

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

11.1.3 PK Analysis

Descriptive statistics will be provided for the total radioactivity (whole blood, plasma, urine, feces, and if applicable, emesis), TAK-831 concentrations and PK parameters (plasma and urine), and [^{14}C]TAK-831 plasma and urine radioactivity concentrations equivalent, using appropriate summary statistics to be fully specified in the SAP.

PK parameters for whole blood and plasma concentrations (as appropriate) and total radioactivity will be calculated as described in Section 9.3.1.1 and for urine and feces, as described in Sections 9.3.1.2 and 9.3.1.3, respectively.

ABA of TAK-831 (Period 1) will be estimated using a 90% CI constructed for the difference in LS mean on the log scale for dose normalized AUC_{∞} between a single oral dose and the IV microdose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose normalized AUC_{∞} geometric mean ratio (TAK-831 administered as oral dose / [^{14}C]TAK-831 administered as IV microdose). AUC_{last} and C_{max} will be analyzed in a similar fashion.

11.1.4 Analysis of Mass Balance

In Period 2, mass balance will be calculated as a sum of the percent of the total radioactivity recovered in urine and feces plus any radioactivity dose lost due to emesis (if any occurred) relative to the administered radioactivity dose.

CCI

[redacted]

11.1.7 PD Analysis

NA

11.1.8 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by subject.

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

11.1.8.1 AEs

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

11.1.8.2 Clinical Laboratory Evaluation

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

11.1.8.3 Vital Signs

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

11.1.8.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

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

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization drug and will be listed by subject.

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

11.2 Interim Analysis and Criteria for Early Termination

NA

11.3 Determination of Sample Size

The sample size of 6 male healthy subjects was selected without statistical considerations and is deemed adequate to meet the study objectives. In addition, this sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee (Clinical Research Organization) and by the IRB or IEC.

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

12.2 Protocol Deviations

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

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

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

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

13.1 IRB and/or IEC Approval

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

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

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the

revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

13.3 Subject Confidentiality

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

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

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

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

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

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

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

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

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

13.4.3 Clinical Study Results Disclosure

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	PPD

14.1.2 INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

~	Approximately
%	Percent
%Dose(FE)	Percent of administered radioactive dose excreted in feces within a given collection interval
%Dose(UR)	Percent of administered radioactive dose excreted in urine within a given collection interval
%F	Percent absolute oral bioavailability
[^{14}C]	Carbon-14; radiocarbon
ABA	Absolute bioavailability
ADME	Absorption, distribution, metabolism, and elimination
AE	Adverse event
$Ae_{t1\text{-}t2}$	Amount of drug excreted in the urine from time 1 to time 2
Ae(FE)	Amount of total radioactivity excreted in feces within a given collection interval
Ae(UR)	Amount of total radioactivity excreted in urine within a given collection interval
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{extrap}%	Area under the curve from the last quantifiable concentration to infinity calcufate dusing the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_t	Area under the concentration-time curve from time 0 to time t
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity
BMI	Body mass index
bpm	Beats per minute
C-SSRS	Columbia-suicide severity rating scale
C_{eoi}	Concentration at end of infusion
CFR	Code of Federal Regulations
CI	Confidence interval
CL_R	Renal clearance
cm	Centimeter
C_{max}	Maximum observed concentration
CRF	Case report form
CRU	Clinical research unit

CYP	Cytochrome P450
DAO	D-amino acid oxidase
ECG	Electrocardiogram
F	Bioavailability
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
λ_z	Terminal disposition phase rate constant
LS	Least-squares
µCi	Microcurie
µg	Microgram
m^2	Meters squared
MBq	Megabecquerel
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
mrem	Millirem
msec	Millisecond
mSv	Millisievert
NA	Not applicable
nCi	Nanocurie
NMDA	*N*-methyl-D-aspartate
oz	Ounce
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
QD	Once daily
SAE	Serious adverse event

SAP	Statistical analysis plan
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2z}$	Terminal disposition phase half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time of first occurrence of C_{max}
TRA	Total radioactivity
ULN	Upper limit of normal
US	United States
USA	United States of America

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan.

15.1 CRFs

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor in the format as decided upon between Celerion and the Sponsor (eg, CD, flashdrive, SFTP). This will be documented in the Data Management Plan (if applicable).

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

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

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

15.2 Record Retention

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

an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

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

16.0 REFERENCES

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17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

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

Appendix B Elements of the Subject Informed Consent

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

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

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 95 days after the last dose of study drug. If the partner of the subject is found to be pregnant during the study, the Investigator will offer the subject the choice to receive additional treatment information.
26. A statement that clinical study information from this study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

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

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

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

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, 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 throughout the duration of the study, and for 95 days after last dose of study drug. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with the subject's preferred and usual lifestyle.

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 (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). Acceptable methods of contraception are:
    - Non-Hormonal Methods:
        - Intrauterine device (IUD).
        - Bilateral tubal occlusion.
        - Vasectomised subject (has received medical assessment of the surgical success).
        - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 95 days after the last dose.
    - Hormonal Methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
            - Oral †.

- Intravaginal † (eg, ring).
- transdermal †.

– Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;

- oral †.
- Injectable.
- Implantable.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
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, all subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in subjects with pregnant partners
   c) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in subjects with pregnant partners.

- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Women will not be included in this study.

If a female partner of a subject becomes pregnant during the subject's participation in this study, the Sponsor must be contacted immediately by faxing a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee (see Section 14.1.1).

Any pregnancies in the partner of a male subject during the study or for 95 days after the last dose, should also be recorded following authorization from the subject's partner.

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

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	30-Oct-2019 19:49 UTC
	Biostatistics Approval	31-Oct-2019 13:19 UTC
	Clinical VP Approval	01-Nov-2019 10:56 UTC