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

SAP Approve Date: 16 April 2020

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-831-1008
CELERION STUDY NUMBER: CA28631

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

Version: Final

Date: 16 April 2020

Prepared by:

PPD

Based on:

Protocol Dated: 29 October 2019
Protocol Clarification Letter Dated: 17 February 2020

1.1 Approval Signatures

Study 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

PPD

Date

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

ABA	absolute bioavailability; F (often expressed as a percent, ie, %F)
ADME	absorption, distribution, metabolism, and elimination
Ae	amount of drug eliminated
AE	adverse event
AUC	area under the curve
AUC_{∞}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_t	area under the concentration-time curve from time 0 to time at which the both the analyte of interest and total radioactivity are quantifiable, ie, time-matched AUC.
BLQ	below the limit of quantitation
BMI	body mass index
C_{eoi}	concentration at the end of infusion
CL_R	renal clearance
C_{max}	maximum observed concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CRU	clinical research unit
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
DMP	Data Management Plan
ECG	electrocardiogram
eCRF	electronic case report form
Geom CV	geometric coefficient of variation
Geom Mean	geometric mean
ICF	informed consent form
ICH	International Conference on Harmonisation
IV	intravenous
ln	natural log
LSM	least-square means

Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings
t_{max}	time of maximum observed concentration
WHO	World Health Organisation

4.0 OBJECTIVES

4.1 Hypothesis

Not applicable.

4.2 Primary Objectives

Period 1 (Absolute Bioavailability [ABA])

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

Period 2 (Absorption, Distribution, Metabolism, and Elimination [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 pharmacokinetics (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.

4.3 Secondary Objective

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.

4.4 Exploratory Objectives

CCI

[redacted]

4.5 Study Design

This is an open-label, 2-period, single dose study in 6 healthy male 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 of ~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 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 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 samples [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 adverse events (AEs) have occurred since the last study visit.

The study schematic is presented in Table 4.a.

Table 4.a 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), [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, and [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.

The planned dose levels of TAK-831 that were evaluated are outlined in Table4.b.

Table 4.b Planned TAK-831 and [^{14}C]TAK-831 Doses

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

[a]Administered over 15 minutes from 1.25 to 1.5 hours after the oral dose of TAK-831.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

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 and feces relative to the administered radioactive dose.
- Total radioactive recovery in urine and feces and the percent of the radioactive dose excreted in the urine and feces.
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_{last}, and AUC_t for TAK-831 in plasma.
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_{last}, and AUC_t for total radioactivity concentration equivalents in plasma and whole blood.
- Renal clearance (CL_R) of TAK-831 in urine.

5.2 Secondary Endpoints

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}, AUC_t, 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.

5.3 Exploratory Endpoints

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The sample size of 6 healthy male 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All PK analyses will be conducted using Phoenix® WinNonlin® Version 7.0, or higher. All statistical analyses will be conducted using SAS® Version 9.4, or higher. All data recorded on the CRF will be listed by subject. All tables, figures and listings (TFLs) shells and numbering list specified in the Clinical Pharmacology Analysis Plan (CPAP) will be included.

Arithmetic mean (mean), median, and geometric mean (Geom Mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (Geom CV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the recorded data. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) around the ratio will be reported using 2 decimal places.

Concentration values below the limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are obvious outliers (eg, BLQ value between measurable values), in which case they will be treated as missing.

For the calculation of PK parameters, if actual times are missing, nominal times will be used instead.

A subject's PK parameter data will be included in the listings but excluded from the descriptive statistics if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's maximum concentration value in that period
- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)

The details on PK parameter calculations will be outlined in the CPAP including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other terminal disposition phase rate constant (λ_z)-dependent parameters
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter WinNonlin® output file used to generate the TFLs
- Data presented in in-text and end-of-text figures
- Figures for individual subjects presented in Appendix 16.2.6

For demographic data where appropriate, variables will be summarized descriptively over all subjects. For the categorical variables, the count and proportions of each possible value will be tabulated over all subjects, where applicable. The denominator for the proportion will be based on the number of subjects who provided non missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, SD, minimum, median, and maximum values will be tabulated.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Day 1 for each period is defined as the date on which a subject is administered their first dose of the study drug(s) in each period. Other study days are defined relative to Day 1 with Day -1 being the day prior to Day 1 of each period. Study day prior to the first dose of each treatment will be calculated as: date of assessment/event - date of treatment (Day 1); study day on or after the date of first dose will be calculated as: date of assessment/event - date of treatment (Day 1) + 1.

7.2 Study Treatments

On Day 1 of Period 1 (ABA Study Period), subjects received 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 received a 15-minute IV infusion of a microdose of 50 µg (~1 µCi) [^{14}C]TAK-831.

There was 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 received a single dose of 500 mg (~100 µCi) [^{14}C]TAK-831 as an oral suspension.

7.3 Analysis Sets

Safety Set:

All subjects who received at least one dose of the study drug(s) will be included in the safety set. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

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. In terms of criteria for evaluable subjects, please see CPAP.

7.4 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized overall. Individual subject's dosing status by treatment, study completion status, including reason for discontinuation, will also be listed by subject in a table.

7.5 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized over all subjects. Summary statistics (number of subjects [n], mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [calculated from the date of signed Informed Consent Form [ICF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI collected at screening will be used in the baseline summaries. Demographics data will also be listed as recorded on the CRF, including the date of informed consent.

7.6 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include any significant conditions or diseases relevant to the disease under study that resolved at or before signing the ICF. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug will be classified as an adverse event. All medical and surgical history recorded during the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 22.1, and listed. The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, the MedDRA system organ class (SOC) and preferred term (PT), the start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

7.7 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between time of signing the ICF through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Dictionary, Version 01-Sep-2019 b3, and listed. The listing will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use.

7.8 Study Drug Exposure and Compliance

Not applicable.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

Blood, urine, and feces were collected as specified in Tables 7.a to 7.d.

Table 7.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 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 7.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 total radioactivity following IV infusion.

[b] Feces sample for [^{14}C]TAK-831 and 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 7.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 determination of total radioactivity in whole blood.
[b] Plasma sample 1 – Blood sample for determination of total radioactivity in plasma.
[c] Plasma sample 2 – Blood sample for TAK-831 PK in plasma.
[d] Plasma sample 3 – Blood sample for CCI
[e] Predose blood and plasma samples should be stored separately away from the postdose samples to avoid cross contamination.

Table 7.d Urine and Fecal Sampling Schedule (Period 2 - ADME Study Period)

Study Day	Time Interval (hour) (Relative to Oral Suspension Dosing)	Urine Sample Collection	Feces Sample Collection
	Matrix	Urine [a]	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 determination of total radioactivity, for CCI [redacted], and for assessment of TAK-831 PK.

[b] Feces samples for determination of 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.

The actual date and time of sample collection will be recorded on the source document and electronic case report form (eCRF).

7.10.1.1 Pharmacokinetic Analysis

Descriptive statistics will be provided for the total radioactivity (whole blood, plasma, urine, feces, and if applicable, emesis), TAK-831 (plasma and urine), and [^{14}C]TAK-831 (plasma, urine, and feces) concentrations (or concentration equivalents) and PK parameters.

All PK parameters for all analytes are listed in the CPAP for this study and will be determined using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If actual sample times are missing, nominal times may be used.

Individual urine sample weight, fecal homogenate weight, analyte concentrations, analyte amounts, and percentage of dose will be listed by time interval. Amounts and percentage of dose recovered will also be summarized descriptively for each collection interval, and the overall collection period. Summary will be done by treatment using the summary statistics listed in the CPAP. Excluded data will be presented and footnoted as such in the table listings, and those values will be excluded from the descriptive summary statistics.

Individual subject and arithmetic mean profiles of the cumulative percent of dose recovered-time data will be plotted on linear (with and without SD) scale. For summary statistics and arithmetic mean concentration-time plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

PK parameters will be summarized descriptively using the summary statistics listed in the CPAP. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive summary statistics.

A comparison of ln-transformed dose-normalized AUC_{∞} will be made to evaluate the absolute bioavailability (Period 1) of TAK-831 administered as oral dose versus [^{14}C]TAK-831 administered as IV microdose. The comparison will be done by performing an ANOVA model using PROC MIXED of SAS®. The ANOVA model will include route of administration (oral and IV) as a fixed effect and subject as a random effect. The inferential results (least-squares [LS] means, difference between LS means, and 90% confidence intervals [CIs] of the difference) will be exponentiated to the original scale. Geometric LS means, geometric LS mean ratios (GMRs) and 90% CIs will be presented. The GMRs and CIs will be expressed as a percentage relative to the reference route of administration (i.e., [^{14}C]TAK-831 administered as IV microdose). AUC_{last} and C_{max} will be analyzed in a similar fashion.

The ANOVA analysis will be performed using the following SAS® code:

```
PROC MIXED;
CLASS ROUTE;
MODEL LN(PK_PARAMETER) = ROUTE/ DDFM = KR;
RANDOM SUBJECT;
ESTIMATE "Oral vs Intravenous" ROUTE 1 -1 / cl alpha=0.1 e;
RUN;
```

Programmer Note: The coefficient estimates will be adjusted according to the route of administration decodes.

7.10.1.2 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]

7.10.2 Pharmacodynamic Analysis

Not applicable.

7.11 Other Outcomes

Not applicable.

7.12 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and relationship to study drug of TEAEs, changes from baseline in the subjects' clinical laboratory results, vital signs, and ECG's using the safety set. All clinical safety data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.12.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (Mild, Moderate, and Severe), relationship to study drug (related or not related), action relative to the study drug, outcome, and procedures. All AEs occurring during this study will be coded using MedDRA®, Version 22.1. However, only TEAEs occurring after administration of the first dose of study drug and through the follow-up phone call (31 +/- 2 days after the last study drug administration) will be summarized. A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. TEAEs occurring at or after Period 1 Day 1 oral dosing and prior to Period 2 Day 1 dosing will be considered treatment-emergent to Treatment A (i.e., single oral dose of 500 mg TAK-831 followed by a single intravenous dose of 50 µg [^{14}C]-TAK-831 [Period 1]) and those occurring at or after Period 2 Day 1 dosing will be considered treatment-emergent to Treatment B (i.e., single oral dose of 500 mg [^{14}C]-TAK-831 [Period 2]).

For each treatment, TEAEs will be coded using MedDRA® and tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of safety set by treatment. The most commonly reported TEAEs (i.e., those events reported by >5% of all subjects in each treatment, excluding SAEs) will also be summarized separately. For the list of all AE summary tables see CPAP. In addition, TEAEs will be summarized as number of AEs and percentage of AEs for each treatment for the overview of TEAEs. Additional TEAE summary tables will be presented by severity and relationship to study drug. Similarly, a table of the events per subject will be included where if a subject has multiple AEs with different severity levels within the same term, the subject will be counted in the most severe category only. If a subject has both related and unrelated AEs with the same term, the subject will be counted as having related TEAEs only.

Should any SAEs (including all-cause mortalities) occur, they will be listed and summarized the same way as TEAE. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the study report.

7.12.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) of Period 1, Day 3 in each period, and prior to discharge in Period 2 or early termination. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI). Coagulation tests (PT/INR) will be performed if subjects has on-study aspartate aminotransferase or alanine aminotransferase elevated ≥3x the upper limit of normal.

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment and assessment time points. Change from baseline will be summarized in a similar way. Baseline is defined as the last assessment including rechecks taken prior to oral dosing on Day 1 of Period 1 (Day -1 Check-in of Period 1).

For each laboratory test, a shift table will be developed comparing the frequency of the results at treatment baseline (above normal (H), normal (N), or below normal (L)) with those postdose time point for each treatment. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a clinically significant (CS) range. If the value falls within the CS range, it will be noted as "N" for not clinical significant. If the value fails the CS range, it will be flagged with a "Y" which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. All clinically significant laboratory tests, as indicated by the PI, and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.12.3 Vital Signs

Single measurements of vital signs will be collected as outlined in Table 7.e.

Table 7.e Collection of Vital Signs

Measurement Type	Period	Day	Time Point
Vital Signs (Heart Rate and Blood Pressure)	Screen		
	1	-1	
		1	1 hour post oral dose
	2	1	4 and 12 hours post oral dose
		Discharge or ET*	
Vital Signs (Respiratory Rate and Temperature)	Screen		

* ET = Early termination

Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results by treatment and time point of collection. Change from baseline will be summarized in a similar way. Baseline is defined as the last assessment including rechecks taken prior to

Day 1 oral dosing in Period 1 (Day -1 Check-in of Period 1). Vital signs will also be displayed in a data listing by subject. Orthostatic vital signs (heart rate and blood pressure) will be collected at screening (3-minute standing minus 1-minute sitting) and will also be presented in this data listing.

7.12.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded as outlined in Table 7.f.

Table 7.f Collection of Electrocardiograms

Measurement Type	Period	Day	Time Point
12-Lead ECG	Screen		
	1	-1	
		1	1 and 4 hours post oral dose
	2	1	4 hours post oral dose
		Discharge or ET*	

* ET = Early termination

Additional unscheduled ECGs may be recorded at other times if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by treatment and time point of collection. Baseline is defined as the last assessment including rechecks taken prior to Day 1 oral dosing in Period 1 (Day -1 Check-in of Period 1). ECG data will also be displayed in a data listing by subject with QTcF > 450 ms and QTcF change from baseline > 30 ms flagged.

7.12.5 Physical Exams

A full physical exam will be performed at screening and at Check-in of each period and prior to Period 2 discharge or early termination. Symptom driven physical exams may be performed at other times at the discretion of the PI. Physical exam findings, as recorded on the CRF, will be presented in a data listing by subject.

7.12.6 Columbia Suicide Severity Rating Scale (C-SSRS)

Assessments of C-SSRS questionnaires will be performed using Baseline/Screening Version at screening and Since Last Visit Version at Check-in of each period, Day 5 of Period 1, and prior to Period 2 discharge or early termination. The C-SSRS results will be listed by subject.

7.12.7 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented as AEs.

7.13 Interim Analysis

No interim analysis will be performed.

7.14 Preliminary Analysis

If requested, QCed whole blood and plasma concentration data will be plotted using nominal times to aid in the determination of samples for repeat bioanalysis. If requested, a preliminary PK analysis will be completed as described in the CPAP and Section 7.9.1 of the SAP, with the following changes: 1) QCed data will be used (not QAed); 2) nominal times (not actual sampling times) will be used for the calculation of PK parameters in whole blood and plasma; 3) tables and figures will be created using Phoenix® WinNonlin® Version 7.0 or higher for whole blood and plasma data, and using SAS® Version 9.4, or higher for urine and feces data.

7.15 Changes in the Statistical Analysis Plan

There analyses in the statistical analysis plan are the same as those specified in the protocol.

8.0 REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	17-Apr-2020 01:03 UTC