Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-906 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [14C]-TAK-906 in Healthy Male Subjects

NCT Number: NCT04454918

SAP Approve Date: 10 August 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.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-906-1007
CELERION STUDY NUMBER: CA24217

A Phase 1 Study to Assess Absolute Bioavailability of TAK-906 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]-TAK-906 in Healthy Male Subjects

Version: Final

Date**:** 10 August 2020

Prepared by:

PPD

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Based on:

Protocol Dated: 30 March 2020

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Study Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-906 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]-TAK-906 in Healthy Male Subjects

PPD

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

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
$AUC_{extrap\%}$	area under the concentration-time curve from the last quantifiable concentration to infinity calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC∞.
AUC_{∞}	area under the concentration-time curve from time 0 extrapolated to infinity calculated using the observed value of the last quantifiable concentration
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 t 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/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
CL	total clearance after intravenous administration, calculated using the observed value of the last quantifiable concentration.
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
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
V_{ss}	volume of distribution at steady state after intravenous administration, calculated using the observed value of the last quantifiable concentration.
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.
WHO	World Health Organization

Note: The PK parameters presented in the clinical study report (CSR) and in the in-text tables will be subscripted, whereas the PK parameters presented in the end-of-text tables will not be subscripted. In addition, AUC_{∞} and λ_z will be presented as AUC_{inf} and Lambdaz in the end-of-text tables, respectively.

4.0 OBJECTIVES

4.1 Primary Objectives

Period 1 (Absolute Bioavailability [ABA])

- To determine the oral ABA (F) of TAK-906 following single oral (capsule) administration of 50 mg of TAK-906 and single intravenous (IV) microtracer dose administration of 100 µg (~1 µCi) of [^{14}C]-TAK-906.

Period 2 (Absorption, Distribution, Metabolism, and Elimination [ADME])

- To determine the mass balance of TAK-906 in urine and feces following a single oral (solution) administration of 50 mg (~100 µCi) of [^{14}C]-TAK-906.

4.2 Secondary Objective

Period 1 (ABA)

- To determine the plasma pharmacokinetic (PK) parameters of TAK-906 and metabolite, M23, following single oral (capsule) administration of 50 mg of TAK-906.
- To determine plasma PK parameters of total radioactivity following a single IV administration of 100 µg (~1 µCi) of [^{14}C]-TAK-906.
- To determine plasma PK parameters of [^{14}C]-TAK 906 following a single IV administration of 100 µg (~1 µCi) of [^{14}C]-TAK-906.

Period 2 (ADME)

- To determine the plasma PK parameters of TAK-906 and metabolite M23 following a single oral (solution) administration of 50 mg (~100 µCi) of [^{14}C]-TAK-906.
- To determine plasma and whole blood PK parameters for total radioactivity following a single oral (solution) administration of 50 mg (~100 µCi) of [^{14}C]-TAK-906.

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4.4 Safety Objectives

Period 1 (ABA)

- To evaluate the safety and tolerability of TAK-906, administered as a single oral dose (capsule) of TAK-906 followed by single IV microtracer dose administration of [^{14}C]-TAK-906.

Period 2 (ADME)

- To evaluate the safety and tolerability of TAK-906, administered as a single oral dose (solution) of [^{14}C]-TAK-906.

4.5 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), after at least a 10-hour fast, 6 subjects will receive a single unlabeled oral 50 mg dose of TAK-906 as capsules. At approximately 45 minutes (0.75 hour) post oral dosing (ie, 15 minutes prior to the median t_{max} for the oral unlabeled dose [~ 1.1 hours]), subjects will receive a 15-minute IV infusion of a microtracer dose of 100 µg (~1 µCi) [^{14}C]-TAK-906. Serial blood sampling will be performed up to Day 5 (ie, Hour 96) to determine the PK of TAK-906 and M23 in plasma for the oral dose and total radioactivity and PK of [^{14}C]-TAK-906 in plasma for the IV dose. Urine and fecal output will also be collected up to the morning of Day 5 (ie, Hour 96) to determine total radioactivity levels and [^{14}C]-TAK-906 PK and until a discharge criterion 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 per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) but no less than Day 5 for 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 a discharge criterion is met or up to Day 7. Subjects will return to the clinic on Day -1 of Period 2 for Check-in procedures. There will be a washout period of at least 7 days between the dose in Period 1 and the dose in Period 2. As per site preference, subjects may be confined throughout the washout period.

On Day 1 of Period 2 (ADME Study Period), after at least a 10-hour fast, the subjects will receive a single dose of 50 mg (~100 µCi) [^{14}C]-TAK-906 as an oral solution. Serial blood sampling and urine and feces output will be collected. The PK of TAK-906 and M23 will be determined in plasma and urine; plasma, whole blood, urine, and feces will be collected for total radioactivity determination; and plasma, urine, and feces will be collected to characterize the metabolite profiles of TAK-906. Complete urinary and fecal output will be collected until at least the morning of Day 6 (ie, Hour 120). Subjects will be confined in the clinic until at least this time and until a discharge criterion is met (ie, 90% 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 per 24 hour

interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 14 days postdose (ie, Day 15). After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the CRU to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis. In each of the 2 consecutive intervals, both urine and fecal samples have to be collected and counted for total radioactivity, ie, if only urine or feces is collected in a day, this day is not considered to be one of the 2 consecutive intervals. 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 dose will be excluded in the final data analysis and will be replaced with a new subject. If a subject experiences emesis after dosing in Period 2, vomitus will need to be collected as much as possible and assayed for total radioactivity. For a subject who drops out in Period 2, the replacement subject will be required to complete Period 2 only.

The clinic will contact all subjects (including subjects who terminate the study early) via phone call, 30 ± 2 days after the last study drug administration to determine if any adverse event (AEs) have occurred since the last study visit. The subjects may be requested to return the site for further safety assessment, due to reported AEs, at the Investigator's discretion.

The study schematic is presented in Table 4.a.

Table 4.a Study Schematic

Screening	Treatment Period 1 [a]			
Within 28 days of first dosing on Period 1	Day -1	Day 1		Days 2 - 7
	Check-in	Oral Dosing at Hour 0	IV Dosing at Hour 0.75	
		Plasma, urine, and fecal sampling for ABA and safety monitoring for at least 96 hours post oral dose [b]		
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[a] Dosing in each period will be separated by at least 7 days.
[b] Subjects will be confined in the clinic until at least the morning of Day 5 (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until a discharge criterion 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 per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 7.

Treatment Period 2 [c]			Follow-up
Day -1	Day 1	Days 2 – 15	30 ± 2 days after last dosing
Check-in	Oral Dosing at Hour 0		
	Plasma, whole blood, urine, and fecal sampling for PK, total radioactivity, and metabolite profiling, and safety monitoring for at least 120 hours postdose, or up to approximately 336 hours postdose if discharge criteria are not met. Additional urine and feces samples may be taken in two blocks of Days 20, 21, 22 and Days 27, 28, and 29.		
< - - - - - - - - - - - - confinement [d] - - - - - - - - - - - - >			

[c] Day -1 of Period 2 may be the same day as Day 7 of Period 1.
[d] Subjects will be confined in the clinic until at least the morning of Day 6 and until discharge criterion is met (ie, 90% 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 per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 14 days postdose (ie, Day 15). After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the CRU to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 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.

The treatment descriptions and planned dose levels of TAK-906 and [^{14}C]-TAK-906 are outlined in Table 4.b.

Table 4.b Planned TAK-906 and [^{14}C]-TAK-906 Doses

	Dose	Route of Administration
Period 1 (Treatment A)		
TAK-906	50 mg	Oral (capsule)
[^{14}C]-TAK-906	100 µg (~1 µCi)	IV[a]
Period 2 (Treatment B)		
[^{14}C]-TAK-906	50 mg (~100 µCi)	Oral (solution)

[a]Administered over 15 minutes from 0.75 to 1 hour after the oral dose of TAK-906.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

Period 1 (ABA):

- Ratio of dose normalized AUC_∞ of TAK-906 and [^{14}C]-TAK 906 in plasma (or AUC_{last} in the case AUC_∞ is incalculable).

Period 2 (ADME):

- Cumulative recovery of radioactivity in urine (Cum%Dose[UR]) and feces (Cum%Dose[FE]) separately and both routes combined, expressed as a percent of total oral radioactive dose administered.

5.2 Secondary Endpoints

Period 1 (ABA):

- PK parameters for oral TAK-906 and M23 in plasma: C_{max}, t_{max}, AUC_{last}, AUC_{extrap}%, and $t_{1/2z}$; for TAK-906 only in plasma: V_z/F and CL/F.
- PK parameters for IV total radioactivity in plasma: C_{eoi}, t_{max}, AUC_{last}, AUC_∞, and $t_{1/2z}$.
- PK parameters for IV [^{14}C]-TAK-906 in plasma: C_{eoi}, CL, V_{ss}, AUC_{last}, AUC_{extrap}%, and $t_{1/2z}$.

Period 2 (ADME):

- PK parameters for plasma TAK-906 and M23: C_{max}, t_{max}, AUC_{last}, AUC_∞, AUC_{extrap}%, and $t_{1/2z}$; for TAK-906 only: V_z/F and CL/F.
- PK parameters for plasma and whole blood total radioactivity: C_{max}, t_{max}, time-matched AUC_t (where t is the last common time point at which total radioactivity and TAK-906 are quantifiable in the plasma of all subjects), AUC_{last}, AUC_∞, and $t_{1/2z}$.

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5.4 Safety Endpoints

Period 1 (ABA):

- AE reporting, laboratory tests, electrocardiograms (ECGs), and vital sign parameters after administration of a single oral dose (capsule) of TAK-906 followed by single IV microtracer dose administration of [^{14}C]-TAK-906.

Period 2 (ADME):

- AE reporting, laboratory tests, ECGs, and vital sign parameters after a single oral dose (solution) of [^{14}C]-TAK-906.

6.0 DETERMINATION OF SAMPLE SIZE

The sample size of 6 healthy male subjects was selected empirically 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 statistical analyses will be conducted using SAS® Version 9.4. All data recorded on the case report form (CRF) will be listed by subject.

The number of observations (n) is presented as an integer (no decimal places), 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. In the tables presenting summary statistics of

concentration data, the number of observations that are above the level of quantification (n_ABLQ) will also be presented.

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.

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 and TFLs for both Periods 1 and 2 will be outlined in the Clinical Pharmacology Analysis Plan (CPAP) and TFL Shell document 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 period/treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.
- Concentration data presented by period/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.
- Mixed effects modelling results presented in in-text and end-of-text table(s).
- Concentration-time and PK parameter data will be plotted.
- Concentration versus time and cumulative percentage of dose recovered versus time 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.

7.2 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 period/treatment will be calculated as: date of assessment/event - date of period/treatment (Day 1); study day on or after the date of first dose will be calculated as: date of assessment/event - date of period/treatment (Day 1) + 1.

7.3 Analysis Sets

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.

Safety Set:

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

7.4 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form, date of first dose, date of last dose, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets.

7.5 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 period/treatment, study completion status, including reason for discontinuation, will also be listed by subject in a table.

7.6 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.

7.7 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include any significant conditions or diseases 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 23.0 or later, 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.

7.8 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and 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-Mar-2020 b3 or later, 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.

7.9 Study Drug Exposure and Compliance

Not applicable.

7.10 Efficacy Analysis

Not applicable.

7.11 Pharmacokinetic/Pharmacodynamic Analysis

7.11.1 Pharmacokinetic Analysis

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

Table 7.a Plasma Sampling Schedule (Period 1 - ABA Study Period)

Time (hour) (relative to oral dosing)	Time (hour) (relative to intravenous infusion)	Sample Collection	
Matrix		**Plasma 1** [a]	**Plasma 2** [b]
0 (predose)		X	
0.5 hr postdose (± 2 min)		X	
0.75 hr postdose (- 2 min) [c]	0 (predose)		X
1 hr postdose (+ 2 min) [d]	End of infusion	X	X
	10 min after the end of infusion (± 2 min)		X
	20 min after the end of infusion (± 2 min)		X
1.5 hr postdose (± 2 min)	30 min after the end of infusion (± 2 min)	X	X
2 hr postdose (± 2 min)	1 hr after the end of infusion (± 2 min)	X	X
4 hr postdose (± 2 min)	3 hr after the end of infusion (± 2 min)	X	X
6 hr postdose (± 2 min)	5 hr after the end of infusion (± 2 min)	X	X
8 hr postdose (± 2 min)	7 hr after the end of infusion (± 2 min)	X	X
12 hr postdose (± 5 min)	11 hr after the end of infusion (± 2 min)	X	X
24 hr postdose (± 5 min)	23 hr after the end of infusion (± 5 min)	X	X
36 hr postdose (± 10 min)	35 hr after the end of infusion (± 10 min)	X	X
48 hr postdose (± 10 min)	47 hr after the end of infusion (± 10 min)	X	X
72 hr postdose (± 10 min)	71 hr after the end of infusion (± 10 min)	X	X
96 hr postdose (± 15 min)	95 hr after the end of infusion (± 15 min)	X	X

a. Plasma 1: For determination of TAK-906 and M23 in plasma. Predose samples should be stored separately away from the postdose samples to avoid cross contamination.
b. Plasma 2: For determination of total radioactivity and [^{14}C]-TAK-906 in plasma. Predose samples should be stored separately away from the postdose samples to avoid cross contamination.
c. To be withdrawn within 2 minutes prior to start of infusion.
d. To be withdrawn within 2 minutes after the end of infusion.

Table 7.b Urine and Fecal Sampling Schedule (Period 1 – ABA Study Period)

Study Day	Time Interval (hour) (Relative to Oral Dosing) Matrix	Sample Collection Urine [a]	Sample Collection Feces [b]
Day -2 to Day 1	-48 to 0 hr (predose)	X [c]	X [d]
Day 1	0-12 hr	X	X (0-24 hr)
Day 1 to Day 2	12-24 hr	X	
Day 2 to Day 3	24-48 hr	X	X
Day 3 to Day 4	48-72 hr	X	X
Day 4 to Day 5	72-96 hr	X [e]	X [e]
Day 5 to Day 6 [f]	96-120 hr	X [f]	X [f]
Day 6 to Day 7 [f]	120-144 hr	X [f]	X [f]

a. Urine sample for total radioactivity and [^{14}C]-TAK-906.
b. Feces sample for total radioactivity and [^{14}C]-TAK-906.
c. Predose urine sample is to be obtained within 24 hours prior to IV infusion and prior to oral dosing. Predose 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 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. Predose samples should be stored separately away from the postdose samples to avoid cross contamination.
e. Including the urine and fecal sample collected on the morning of Day 5 (ie, Hour 96, as/when passed) prior to release.
f. Collection only for subjects who have not met discharge criteria.

Table 7.c Blood and Plasma Sampling Schedule (Period 2 - ADME Study Period)

Matrix	Time (hour) (Relative to Oral Dosing) Sample Collection Blood 1 [a]	Plasma 1 [b], Plasma 2 [b]	Plasma 3 [b]
0 (predose) [c]	X	X	X
0.5 hr postdose (±2 min)	X	X	X
1 hr postdose (± 2 min)	X	X	X
1.5 hr postdose (± 2 min)	X	X	
2 hr postdose (± 2 min)	X	X	X
3 hr postdose (± 2 min)	X	X	
4 hr postdose (± 2 min)	X	X	X
6 hr postdose (± 2 min)	X	X	
8 hr postdose (± 2 min)	X	X	X
12 hr postdose (± 5 min)	X	X	X

Table 7.c Blood and Plasma Sampling Schedule (Period 2 - ADME Study Period)

Time (hour) (Relative to Oral Dosing)	Sample Collection		
Matrix	**Blood 1** [a]	**Plasma 1** [b], **Plasma 2** [b]	**Plasma 3** [b]
24 hr postdose (± 5 min)	X	X	X
48 hr postdose (± 10 min)	X	X	X
72 hr postdose (± 10 min)	X	X	X
96 hr postdose (± 15 min)	X	X	X
120 hr postdose (± 15 min)	X	X	X
168 hr postdose (± 1 hr) [d]	X	X	X
240 hr postdose (± 1 hr) [d]	X	X	
336 hr or before discharge (± 1 hr) [d]	X	X	

a. Blood sample for total radioactivity (Blood 1).
b. Plasma sample for TAK-906 PK and M23 metabolite (Plasma 1), Plasma sample for total radioactivity (Plasma 2), and plasma sample for metabolite profiling (Plasma 3).
c. Predose blood and plasma samples should be stored separately away from the postdose samples to avoid cross contamination.
d. Collection only for subjects confined beyond the morning of Day 6 (ie, Hour 120) and not discharged at the collection time.

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

Study Day	Time Interval (hour) (Relative to Oral Dosing) Matrix	Sample Collection Urine 1 [a], Urine 2 [a]	Sample Collection Feces [b]
Day -2 to Day 1	-48 to 0 hr (predose)	X [c]	X [d]
Day 1	0-12 hr	X	X (0-24 hr)
Day 1 to Day 2	12-24 hr	X	
Day 2 to Day 3	24-48 hr	X	X
Day 3 to Day 4	48-72 hr	X	X
Day 4 to Day 5	72-96 hr	X	X
Day 5 to Day 6	96-120 hr [e]	X	X
Day 6 to Day 7	120-144 hr [f]	X	X
Day 7 to Day 8	144-168 hr [f]	X	X
Day 8 to Day 9	168-192 hr [f]	X	X
Day 9 to Day 10	192-216 hr [f]	X	X
Day 10 to Day 11	216-240 hr [f]	X	X
Day 11 to Day 12	240-264 hr [f]	X	X
Day 12 to Day 13	264-288 hr [f]	X	X
Day 13 to Day 14	288-312 hr [f]	X	X
Day 14 to Day 15	312-336 hr [f]	X	X

a. Urine sample for TAK-906 and M23 PK (Urine 1); Urine sample for total radioactivity and urine sample for metabolite profiling (Urine 2).
b. Feces sample for total radioactivity and feces sample for metabolite profiling (Feces).
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. If applicable, for subject(s) who are released in Period 1 and return for Period 2, 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. Including the urine and fecal sample collected on the morning of Day 6 (ie, Hour 120, as/when passed) prior to release.
f. Collected for subjects who have not met the discharge criteria. Samples will continue to be collected in 24-hour intervals until a discharge criterion is met (ie, 90% 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 per 24 hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 14 days postdose (ie, Day 15). After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the CRU to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis.

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

Concentration (or concentration equivalent) data for the total radioactivity (whole blood [Period 2]; plasma, urine, and feces [Periods 1 and 2]; and if applicable, emesis [Period 2]), TAK-906 and M23 (plasma [Periods 1 and 2]; and urine [Period 2]), and [^{14}C]-TAK-906 (plasma, urine, and feces [Period 1])

Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive statistics.

Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive statistics.

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 period/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. Whole blood and plasma concentration-time profiles will be plotted on linear and semi-log scales. Arithmetic mean and median linear scale plots will be plotted with and without SD. For arithmetic mean and median whole blood and plasma concentration-time plots by sampling time, nominal PK sampling times will be used; for individual subject whole blood and plasma concentration-time plots by sampling time, actual PK sampling times will be used. Cumulative percentage of the dose recovered versus time will be plotted on linear scale versus nominal collection interval end time. Arithmetic mean and median linear scale plots will be plotted with and without SD.

A mixed effects model will be performed on ln-transformed, dose-normalized AUC_{∞} with route (treatment) as the fixed effect and subject as the random effect. The estimate of ABA and its 90% CI will be obtained by exponentiating the difference in LS means between dosing routes and its 90% CI based on the mixed effects of AUC_{∞} on the log scale. This will provide the estimate of ABA and 90% CI for the dose-normalized AUC_{∞} GMR (TAK-906 administered as oral dose / [^{14}C]-TAK-906 administered as IV microtracer dose), respectively. AUC_{last} will be analyzed in a similar fashion if AUC_{∞} cannot be calculated. The mixed effects modelling analysis will be performed using the following SAS® code:

```
PROC MIXED;
CLASS ROUTE SUBJECT;
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. PK_PARAMETER is dose-normalized AUC_{∞}.

7.11.1.1 Analysis of Mass Balance

In Period 2, mass balance will be summarized using the following descriptive statistics: n, Mean, SD, CV%, SEM, minimum, median, maximum, Geom Mean, and Geom CV%.

7.11.1.2 Whole Blood to Plasma Partitioning Ratio

In Period 2, ratios of the total radioactivity concentration equivalents in whole blood relative to plasma (ie, whole blood:plasma partitioning ratios) will be summarized using the following descriptive statistics: n, Mean, SD, CV%, SEM, minimum, median, maximum, Geom Mean, and Geom CV%.

7.11.1.3 Metabolite Profiling

TAK-906 metabolite profiling will be performed by Takeda in plasma, urine, and feces samples from Period 2 containing sufficient amounts of radioactivity. The percentage of the dose represented by each of the metabolites, if any, will be calculated using the radioactivity concentration equivalent data combined with the metabolite profiling data. The percentage of each identified metabolite, if any, to total radioactivity in the plasma will be estimated based on plasma metabolite profiling data.

7.11.2 Pharmacodynamic Analysis

Not applicable.

7.12 Other Outcomes

Not applicable.

7.13 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.

7.13.1 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 23.0 or later where appropriate. However, only TEAEs occurring after administration of the first dose of study drug and through the follow-

up phone call (30 +/- 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 50 mg TAK-906 followed by a single intravenous dose of 100 µg (~1 µCi) [^{14}C]-TAK-906 [Period 1]) and those occurring at or after Period 2 Day 1 dosing up to safety follow up visit by phone call will be considered treatment-emergent to Treatment B (i.e., single oral dose of 50 mg (~100 µCi) [^{14}C]-TAK-906 [Period 2]).

For each period/treatment, TEAEs will be coded using MedDRA® and tabulated by SOC and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of safety set by period/treatment. The most commonly reported TEAEs (i.e, those events reported by >5% of all subjects in each period/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 period/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.

7.13.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) of Period 1 and Period 2 (Note: subjects were being confined for washout, Period 2 check-in events were not performed in the current study), 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 period/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 period/treatment baseline (above normal (H), normal (N), or below normal (L)) with those postdose time point for each period/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 clinically 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. To distinguish the PI flag from the computer CS range flags, the PI flags of "N" and "Y" will be presented as "-" and "+", respectively, in the data listing. Additionally, the PI will provide a 4th flag when the 3rd flag indicates "R" or "^". This 4th flag is intended to capture final CS (+)/NCS (-) when the 3rd flag does not document significance. 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.

7.13.3 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 (Pulse Rate and Blood Pressure)	Screen		
	1	-1	
		1	1 and 4 hours post oral dose
		End of Period 1^	
	2	-1^	
		1	1 and 4 hours post oral dose
		Discharge or ET*	
Vital Signs (Respiratory Rate and Temperature)	Screen		
	1	-1	
		1	4 hours post oral dose
		End of Period 1^	
	2	-1^	
		1	4 hours post oral dose
		Discharge or ET*	

* ET = Early termination.
^ Note: subjects were being confined for washout, Period 2 check-in (Day -1) and End of Period 1 events were not performed in the current study.

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 period/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.

7.13.4 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
		End of Period 1^	
	2	-1^	
		1	1 and 4 hours post oral dose
		Discharge or ET*	

* ET = Early termination.
^ Note: subjects were being confined for washout, Period 2 check-in (Day -1) and End of Period 1 events were not performed in the current study.

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 period/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.

7.13.5 Physical Exams

A full physical exam will be performed at screening. Abbreviated physical examinations will be performed at Day -1 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.

7.13.6 Taste Questionnaire

Subjects will complete a taste questionnaire evaluating the taste of the TAK-906 oral solution administered in Period 2. The questionnaire will be completed within 5 minutes of dosing. Taste questionnaire results will be presented in a data listing by subject.

7.13.7 Overdose

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

7.14 Interim Analysis

No interim analysis will be performed.

7.15 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 7.11.1 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 8.1 or higher for whole blood and plasma data, and using SAS® Version 9.4, or higher for urine and feces data.

7.16 Changes in the Statistical Analysis Plan

The analyses in the SAP are the same as those specified in the protocol.

8.0 REFERENCES

Clinical Pharmacology Analysis Plan (CPAP). Study Number: TAK-906-1007. A phase 1 study to assess absolute bioavailability of TAK-906 and to characterize mass balance, pharmacokinetics, metabolism, and excretion of [^{14}C]-TAK-906 in healthy male subjects.

Tables, Figures, Listings (TFL) Shells. Study Number: TAK-906-1007. Celerion Study Number: CA24217. A phase 1 study to assess absolute bioavailability of TAK-906 and to characterize mass balance, pharmacokinetics, metabolism, and excretion of [^{14}C]-TAK-906 in healthy male subjects.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	21-Aug-2020 14:42 UTC