Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-788 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [14C]-TAK-788 in Male Healthy Subjects

NCT Number: NCT03811834

SAP Approve Date: 08 August 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.
- 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-788-1002
CELERION STUDY NUMBER: CA25518

A Phase 1 Study to Assess Absolute Bioavailability of TAK-788 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [^{14}C]-TAK-788 in Male Healthy Subjects

Version: Final

Date: 08 August 2019

Prepared by:

PPD

[redacted]

Protocol Dated: 18 December 2018
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1.1 Approval Signatures

Study Title: A Phase 1 Study to Assess Absolute Bioavailability of TAK-788 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion[14]

PPD

Date

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_{∞}	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 mea

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 absolute bioavailability of TAK-788 following single microdose intravenous (IV) administration of 50 µg (~2 µCi) [^{14}C]-TAK-788 and single oral administration of 160 mg TAK-788.

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

- To assess the mass balance (ie, cumulative excretion of total radioactivity in urine and feces) and metabolic profile of TAK-788 in plasma, urine, and feces following a single oral administration of 160 mg (~100 µCi) [^{14}C]-TAK-788 solution.
- To characterize the pharmacokinetics (PK) of TAK-788 and its metabolites (AP32960 and AP32914) in plasma, whole blood, and urine, and total radioactivity concentration equivalents in plasma and whole blood following a single oral solution dose of 160 mg (~100 µCi) [^{14}C]-TAK-788.

4.3 Secondary Objective

Period 1 (ABA)

- To determine the PK of [^{14}C]-TAK-788 and its metabolites (AP32960 and AP32914) following a single IV administration of 50 µg [^{14}C]-TAK-788 and the PK of TAK-788 and its metabolites (AP32960 and AP32914) following a single oral administration of 160 mg TAK-788.

Periods 1 (ABA) and 2 (ADME)

- To assess the safety of TAK-788 during the ABA and ADME study periods.

4.4 Exploratory Objectives

CCI [redacted]

4.5 Study Design

This was 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 received a single unlabeled

oral 160 mg dose of TAK-788 as capsules. At 3.75 hours post oral dosing (ie, 15 minutes prior to the median t_{max} for the oral unlabeled dose (~4 hours), subjects received a 15-minute IV infusion of a microdose of 50 µg (~2 µCi) [^{14}C]-TAK-788. Serial blood sampling was performed to determine the PK of TAK-788 and its metabolites (AP32960 and AP32914) in the plasma for the oral dose and [^{14}C]-total radioactivity and PK of [^{14}C]-TAK-788 and its metabolites (AP32960 and AP32914) in the plasma for the IV dose. CCI [redacted]

In Period 1, subjects were 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 a discharge criterion was met or up to Day 8. Subjects returned to the clinic on Day 9 (Period 2, Day -1) for Period 2. There was a washout period of approximately 9 days between doses in Period 1 and the dose in Period 2.

On Day 1 of Period 2 (ADME Study Period), after at least a 10-hour fast, subjects received a single dose of 160 mg (~100 µCi) [^{14}C]-TAK-788 as an oral solution. Serial blood sampling was performed and urine and feces were collected to determine the PK of TAK-788 and its metabolites (AP32960 and AP32914) in plasma, whole blood, CCI [redacted] or up to 10 days postdose.

In both Periods 1 and 2, any subject who experienced emesis within 8 hours postdose will be excluded in the final data analysis and will be replaced with a new subject. If a subject experienced emesis after dosing in Period 2, vomitus was to be collected as much as possible and assayed for total radioactivity.

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

The study schematic is presented in Table 4.a.

Table 4.a Study Schematic

<table>
<tr><td>Screening</td><td colspan="4">Treatment Period 1 [a]</td></tr>
<tr><td rowspan="3">Within 28 days first dosing on Period 1</td><td>Day -1</td><td colspan="2">Day 1</td><td>Days 2 - 8</td></tr>
<tr><td>Check-in</td><td>Oral Dosing at Hour 0</td><td>IV Dosing at Hour 3.75</td><td></td></tr>
<tr><td colspan="3">Plasma, CCI [redacted] sampling for ABA and safety monitoring for at least 96 hours post oral dose [b]</td></tr>
<tr><td colspan="4">< - - - - - - - - - - - - confinement [b] - - - - - - - - - - - - ></td></tr>
<tr><td colspan="5">[a] Dosing in each period was separated by approximately 9 days.
[b] Subjects were confined in the clinic for at least 5 days CCI [redacted]</td></tr>
<tr><td colspan="4">Treatment Period 2</td><td>Follow-up</td></tr>
<tr><td>Day -1</td><td colspan="2">Day 1</td><td>Days 2 – 11</td><td rowspan="4">30 ± 2 days after last dosing</td></tr>
<tr><td>Check-in</td><td colspan="2">Oral Dosing at Hour 0</td><td></td></tr>
<tr><td></td><td colspan="3">Plasma, CCI [redacted] sampling for PK [c], total radioactivity, and metabolic profiling, and safety monitoring up to approximately 240 hours postdose</td></tr>
<tr><td colspan="4">< - - - - - - - - - - - - confinement [d] - - - - - - - - - - - - ></td></tr>
<tr><td colspan="5">[c] Predose plasma samples from in Period 2 were also used as Day 10 samples for Period 1, as appropriate.
[d] Subjects were confined in the clinic until a discharge criterion was met (ie, 80% or greater of the total dose of radioactivity administered was recovered in CCI [redacted] samples CCI [redacted]. Release of subjects who did not meet a discharge criterion by Day 11 were reviewed on a case-by-case basis. Since up to an approximate 24-hour time lag was anticipated for radioactivity counting of samples, actual subject release from the CRU may have occurred 1 day after discharge criteria were met.</td></tr>
</table>

The planned dose levels of TAK-788 that were evaluated are outlined in Table 4.b.

Table 4.b Planned TAK-788 and [^{14}C]-TAK-788 Doses

	Dose	Route of Administration
Period 1 (Treatment A)		
TAK-788	160 mg	Oral capsule
[^{14}C]-TAK-788	50 µg (~2 µCi)	IV
Period 2 (Treatment B)		
[^{14}C]-TAK-788	160 mg (~100 µCi)	Oral solution

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoints of the study are the following PK parameters:

Period 1 (ABA):

- Absolute bioavailability (F) as percent F (%F) for TAK-788.

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.
- TAK-788 metabolic profiling in plasma, urine, and feces containing sufficient amounts of radioactivity.
- PK parameters C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_{last}, and AUC_t for TAK-788 and its metabolites (AP32960 and AP32914) in plasma and whole blood.
- 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.
- PK parameters for amount excreted in each collection interval (Aet1-t2) and renal clearance (CL_R) TAK-788 and its metabolites (AP32960 and AP32914) in urine.
- The change over time in [^{14}C]-radioactivity in whole blood relative to plasma (ie, whole blood:plasma partitioning ratio).

5.2 Secondary Endpoints

The secondary endpoints are the following PK and safety 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-788, and [^{14}C]-TAK-788 and the metabolites (AP32960 and AP32914) in plasma;

Periods 1 (ABA) and 2 (ADME):

- Treatment-emergent adverse events (TEAEs) assessments.
- 12-Lead electrocardiogram (ECG).
- Vital Signs.
- Clinical laboratory testing (serum chemistry, hematology, and urinalysis).

5.3 Exploratory Endpoints

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[redacted]

6.0 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.

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 9.3, 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 2 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 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 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.

7.3 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. Study completion status, including reason for discontinuation, will also be listed by subject.

7.4 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. Spirometry (pulmonary function test) measures will be taken within 7 days prior to first dosing and results will be listed by subject.

7.5 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 21.1, 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.

7.6 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-2018, 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.

7.7 Study Drug Exposure and Compliance

Not applicable.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

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

Table 7.a Blood Collection Schedule after the Oral and Intravenous Doses of TAK-788 (Period 1 - ABA Study Period)

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]
0 (predose)		X	X
0.5 hour postdose (± 2 min)		X	
1 hour postdose (± 2 min)		X	
2 hours postdose (± 2 min)		X	
3 hours postdose (± 2 min)		X	
3 hours 45 min post dose	0 (predose)		X
4 hours postdose (± 2 min)	End of infusion	X	X
4 hours 10 min postdose (± 2 min)	10 min after the end of infusion (± 2 min)		X
4 hours 20 min postdose (± 2 min)	20 min after the end of infusion (± 2 min)		X
4 hours 30 min postdose (± 2 min)	30 min after the end of infusion (± 2 min)		X
5 hours postdose (± 2 min)	1 hours after the end of infusion (± 2 min)	X	X
6 hours postdose (± 2 min)	2 hours after the end of infusion (± 2 min)	X	X
8 hours postdose (± 2 min)	4 hours after the end of infusion (± 2 min)	X	X
12 hours postdose (± 5 min)	8 hours after the end of infusion (± 2 min)	X	X
24 hours postdose (± 5 min)	20 hours after the end of infusion (± 5 min)	X	X
36 hours postdose (± 10 min)	32 hours after the end of infusion (± 10 min)	X	X
48 hours postdose (± 10 min)	44 hours after the end of infusion (± 10 min)	X	X
72 hours postdose (± 10 min)	68 hours after the end of infusion (± 10 min)	X	X
96 hours postdose (± 15 min)	92 hours after the end of infusion (± 15 min)	X	X
120 hours postdose (± 15 min)	116 hours postdose (± 15 min)	X [c]	X [c]
144 hours postdose (± 15 min)	140 hours postdose (± 15 min)	X [c]	X [c]
Day 10 (Predose Day 1 of Period 2)		X [d]	X [d]

[a] For determination of TAK-788 and metabolites in plasma following oral capsule dose.
[b] For determination of [^{14}C]-total radioactivity, and [^{14}C]-TAK-788 and metabolites in plasma following IV infusion.
[c] For subjects who did not meet the discharge criteria by Day 5, blood samples continued to be collected in 24-hour intervals until radioactivity in urine and feces combined was ≤1% of the total administered radioactivity per day for at least 2 consecutive intervals where both a urine and fecal sample were collected, the excretion of radioactivity was ≥80% of the administered radioactive dose, or up to Day 7.
[d] Predose plasma samples from in Period 2 will also be used as Day 10 samples for Period 1, as appropriate.

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Table 7.c Blood Collection Schedule (Period 2 - ADME Study Period)

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

[a] Blood Sample 1 - Blood sample for total [^{14}C] determination (total radioactivity) in whole blood.
[b] Blood Sample 2 – Blood sample for PK analysis of TAK-788 and metabolites in whole blood.
[c] Plasma sample 1 – Blood sample collected for total [^{14}C] determination in plasma.
[d] Plasma sample 2 – Blood sample collected for TAK-788 and metabolites PK in plasma.
[e] Plasma sample 3 – Blood sample collected for metabolite profiling.
[f] Predose plasma samples from Period 2 will be used as Day 10 samples for Period 1, as appropriate.

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

PK parameters calculated for this study will be 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.

Urine sample weight, fecal homogenate weight, and concentrations will be listed and summarized descriptively by PK sampling time or collection interval. 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 concentration-time data will be plotted on linear (with and without SD) and semi-log scales. Individual subject and arithmetic mean profiles of the cumulative percent of dose recovered-collection interval end 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 PK parameter AUC_{∞} will be made to evaluate the absolute bioavailability (Period 1) of TAK-788 administered as oral dose versus [^{14}C]-TAK-788 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 intravenous) as fixed effect and subject as a random effect. The inferential results (least-squares [LS] means, difference between LS means, and 90% CIs of the difference) will be exponentiated to the original scale. Geometric LS means, geometric mean ratios (GMR) and 90% CIs will be presented. The GMRs and CIs will be expressed as a percentage relative to the reference route of administration (ie, [^{14}C]-TAK-788 administered as IV microdose).

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.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and type 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.

7.11.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening, Grade 5 = Death), 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 21.1. However, only TEAEs occurring after administration of the first dose of study drug and through the follow-up (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 (ie, Single oral dose of 160 mg TAK-788 followed by a single intravenous dose of 50 µg [^{14}C]-TAK-788 [Period 1]) and those occurring at or after Period 2 Day 1 dosing will be considered treatment-emergent to Treatment B (ie, single oral dose of 160 mg [14C]-TAK-788 [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 (ie, those events reported by >5% of all subjects in each treatment, excluding SAEs) will also be summarized. 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. 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.

7.11.2 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 or early termination. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

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 points 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 (either in the PI flag or in PI comments), and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.11.3 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, 2	1	5 (Period 1) / 4 (Period 2) and 12 hours post oral dose
		2	Hour 24
	2	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.

7.11.4 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, 2	1	5 (Period 1) / 4 (Period 2) hours post oral dose
		2	Hour 24
	2	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.

7.11.5 Physical Exams

A full physical exam will be performed at screening and may be performed at Check-in in each period and prior to 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.

7.11.6 Overdose

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

7.12 Interim Analysis

No interim analysis will be performed.

7.13 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 9.3, or higher for urine and feces data.

7.14 Changes in the Statistical Analysis Plan

There are no changes in the statistical analysis plan from the protocol analysis.

8.0 REFERENCES

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	[illegible]	[illegible]