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

Protocol Approve Date: 27 February 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.
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TAKEDA PHARMACEUTICALS

PROTOCOL

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

Study Identifier: TAK-788-1002

Compound: TAK-788

Date: 27 February 2019

Version/Amendment Number: Amendment 1

Amendment History:

Date	Amendment Number	Amendment Type	Region
18 December 2018	Initial Version		United States
27 February 2019	01	Not Applicable	United States

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, Massachusetts USA 02139 Telephone: +1 (617) 679-7000	TAK-788
Study Identifier: TAK-788-1002 (CA25518)	**Phase:** 1
Protocol Title: 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	
Trial Design: An open-label, 2-period, single-dose study in 6 male healthy subjects. On Day 1 of Period 1 (absolute bioavailability [ABA] Study Period), after at least a 10-hour fast, 6 subjects will receive 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 [approximately (~) 4 hours]), subjects will receive a 15-minute intravenous (IV) infusion of a microdose of 50 µg (approximately equivalent to 2 microcurie ~[2 µCi]) [^{14}C]-TAK-788. Serial blood sampling will be performed to determine the pharmacokinetics (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. Urine and fecal output will also be collected up to the morning of Day 5 postdose to determine [^{14}C]-TAK-788 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 day for at least 2 consecutive intervals where both a urine and fecal sample are collected) but no less than Day 5 for [^{14}C]-total radioactivity excretion in urine and feces. In Period 1, subjects will be confined in the clinical research unit (CRU) for at least 5 days (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until a discharge criterion is met or up to Day 8. Subjects will return to the clinic on Day 9 (Period 2, Day -1) for Period 2. There will be a washout period of approximately 9 days between doses in Period 1 and the dose in Period 2. On Day 1 of Period 2 (absorption, distribution, metabolism, and elimination [ADME] Study Period), after at least a 10-hour fast, subjects will receive a single dose of 160 mg (~100 µCi) [^{14}C]-TAK-788 as an oral solution. Serial blood sampling will be performed and urine and feces will be collected to determine the PK of TAK-788 and its metabolites (AP32960 and AP32914) in plasma, whole blood, and urine, and total radioactivity in plasma, whole blood, urine, and feces, and to characterize the metabolite profiles of TAK-788 in plasma, urine, and feces. Complete urinary and fecal output will be collected during confinement period until discharge criteria are met (anticipated to be 10 days or less). In Period 2 subjects will be confined in the clinic 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 day for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 10 days postdose. Release of subjects who do not meet a discharge criterion by Day 11 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. In both Periods 1 and 2, any subject who experiences emesis within 8 hours post the 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. 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 have occurred since the last study visit.	

Trial Primary Objectives:

Period 1 (ABA)

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

Period 2 (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 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.

Secondary Objectives:

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.

Exploratory Objective:

CCI [redacted]

Trial Subject Population: Healthy adult male subjects

Planned Number of Subjects:	**Planned Number of Sites:**
6	1
Dose Levels: Period 1: 160 mg of TAK-788 50 µg (~2 µCi) [^{14}C]-TAK-788 Period 2: 160 mg (~100 µCi) [^{14}C]-TAK-788	**Route of Administration:** Period 1: Oral (capsules) IV infusion Period 2: Oral (solution)
Duration of Treatment: Period 1: On Day 1, subject will receive a single oral dose followed by a 15 minute IV dose at 3.75 hours post oral dose. Period 2: On Day 1, subject will receive a single oral dose.	**Planned Trial Duration:** Approximately 65 days including Screening Period

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Criteria for Inclusion:

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

1. Healthy, adult, male, 19 - 55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 20 years prior to the first dosing and throughout the study, based on subject self-reporting.
3. Body mass index (BMI) ≥18 and <30.0 kg/m^2 at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or electrocardiograms (ECGs), as deemed by the investigator or designee.
5. Normal baseline pulmonary function tests (PFTs) (≥80% of predicted normal for spirometry and lung volumes) within 7 days prior to the first dosing.
6. Subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in Appendix D or abstain from sexual intercourse during the study until 94 days after the last dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with your preferred and usual lifestyle.
7. Must agree not to donate sperm from the first dosing until 94 days after the last dosing.
8. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

Criteria for Exclusion:

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

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the investigator or designee.
3. History of any illness that, in the opinion of the investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of any lung disease and current lung infection.
7. Positive urine drug or alcohol results at screening or first check-in.
8. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
9. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
10. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
11. QTcF interval is >460 msec or ECG findings are deemed abnormal with clinical significance by the investigator or designee at screening.
12. Estimated creatinine clearance <80 mL/min at screening.
13. Has tattoo(s) or scarring at or near the site of IV infusion or any other condition which may interfere with infusion site examination, in the opinion of the investigator.
14. Subject has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
15. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks of first dosing.
16. Has received radiolabeled substances or has been exposed to radiation sources within 12 months of first dosing or is likely to receive radiation exposure or radioisotopes within 12 months of first dosing such that participation in

this study would increase their total exposure beyond the recommended levels considered safe (ie, weighted annual limit recommended by the International Commission on Radiological Protection [ICRP] of 3000 millirem [mrem]).

17. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study, only after first dosing, if necessary to treat adverse events (AEs). Milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered approximately on Day 4 (Period 1) or Day 8 (Period 2) to ensure defecation, with agreement between the study investigator and Takeda physician. Additional administration of milk of Magnesia may be needed on other days at discretion of the study investigator and Takeda Physician.
    - Any drugs known to be significant inducers of cytochrome P450 (CYP) 3A enzymes and/or P-glycoprotein (P-gp), including St. John's Wort, within 28 days prior to the first dosing and throughout the study. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drug.
18. Has been on a diet incompatible with the on-study diet, in the opinion of the investigator or designee, within the 30 days prior to the first dosing and throughout the study.
19. Donation of blood or significant blood loss within 56 days prior to the first dosing.
20. Plasma donation within 7 days prior to the first dosing.
21. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

Period 1 (ABA):

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

Period 2 (ADME):

- Percent of total radioactivity recovered in urine (Cum%Dose[UR]) and feces (Cum%Dose[UR]) relative to the administered radioactive dose (Combined Cum%Dose).
- Total radioactive recovery in urine (Ae[UR]) and feces (Ae[FE]) and the percent of the radioactive dose excreted in the urine (%Dose[UR]) and feces (%Dose[FE]).
- TAK-788 metabolic profiling in plasma, urine, and feces containing sufficient amounts of radioactivity.
- PK parameters C_{max}, t_{max}, $t_{½}$, 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}, $t_{½}$, 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 (Aet_1-t_2) and renal clearance (CLR) for TAK-788 and its metabolites (AP32960 and AP32914) in urine.
- The change over time in percentage of [^{14}C]-radioactivity in whole blood relative to plasma (ie, whole blood:plasma partitioning ratio).

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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 $t_{½}$ for TAK-788, and [^{14}C]-TAK-788 and the metabolites (AP32960 and AP32914) in plasma;

Periods 1 (ABA) and 2 (ADME):

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

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

CCI [redacted]

Statistical Considerations:

Descriptive statistics will be provided for the total radioactivity (whole blood, plasma, CCI [redacted], and if applicable, emesis), plasma TAK-788 and metabolites concentrations and PK parameters, [^{14}C]-TAK-788 plasma and CCI [redacted] radioactivity concentration equivalent, using appropriate summary statistics to be fully specified in the statistical analysis plan (SAP).

Absolute bioavailability of TAK-788 will be estimated using a ninety percent (90%) confidence interval (CI) constructed for the difference in least-squares (LS) mean on the log scale for dose normalized AUC_{∞} between a single oral dose and the IV microdose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose normalized AUC_{∞} geometric mean ratio (GMR; TAK-788 administered as oral dose / [^{14}C]-TAK-788 administered as IV microdose). The AUC_{last}, AUC_t, and C_{max}, will be analyzed in a similar fashion.

Mass balance will be calculated as a sum of the percent of the CCI [redacted] relative to the administered radioactivity dose minus any radioactivity lost due to emesis (if any occurred).

Sample Size Justification:

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

2.0 STUDY SCHEMATIC

<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></td><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></td><td colspan="4">< - - - - - - - - - - - - confinement [b] - - - - - - - - - - - - ></td></tr>
<tr><td colspan="5">[a] Dosing in each period will be separated by approximately 9 days.
[b] Subjects will be confined in the clinic for at least 5 days CCI [redacted] or up to Day 8.</td></tr>
</table>

<table>
<tr><td colspan="3">Treatment Period 2</td><td>Follow-up</td></tr>
<tr><td>Day -1</td><td>Day 1</td><td>Days 2 - 11</td><td rowspan="3">30 ± 2 days after last dosing</td></tr>
<tr><td>Check-in</td><td>Oral Dosing at Hour 0</td><td></td></tr>
<tr><td></td><td colspan="2">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="3">< - - - - - - - - - - - - confinement [d] - - - - - - - - - - - - ></td><td></td></tr>
<tr><td colspan="4">[c] Predose plasma samples from in Period 2 will also be used as Day 10 samples for Period 1, as appropriate.
[d] Subjects will be confined in the clinic until a discharge criterion is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in CCI [redacted] samples CCI [redacted] Release of subjects who do not meet a discharge criterion by Day 11 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.</td></tr>
</table>

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedures [a] **Days →**	**S** [b]	**Study Days in Period 1** [c]						
		-1 (C-I [d]**)**	**1**	**2**	**3**	**4**	**5**	**6-8** [e]
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Safety Evaluations								
Full Physical Examination [f]	X	X [g]						
Height	X							
Weight	X	X [g]						
12-Lead Safety ECGs	X	X [h]	X [i]	X				
Vital Signs (heart rate and blood pressure)	X	X [h]	X [J]	X				
Vital Signs (respiratory rate and temperature)	X							
Pulmonary Function Test	X [k]							
Hematology, Serum Chemistry[l], and UA	X	X			X			
Urine Drug and Alcohol Screen	X	X						
HIV/Hepatitis Screen	X							
AE Monitoring	X							
Concomitant Medication Monitoring	X	X						
Study Drug Administration / Pharmacokinetics								
TK-788 Administration (oral)			X [m]					
[^{14}C]- TAK-788 Administration (IV)			X [n]					
Blood for TAK-788 Plasma PK [o]			X	X	X	X	X	X
Blood for [^{14}C]-TAK-788 Plasma PK [o]			X	X	X	X	X	X
CCI								
CCI								
Other Procedures								
Confinement in the CRU [e, q]	X							
Visit	X							

Study Procedures [a]	Study Days in Period 2 [c]												FU [r]
	-1 (C-I [d])	1	2	3	4	5	6	7	8	9	10	11	
Safety Evaluations													
Full Physical Examination [f]	X											X [s]	
12-Lead Safety ECG	X [h]	X [t]	X									X [s]	
Vital Signs (heart rate and blood pressure)	X [h]	X [u]	X									X [s]	
Hematology, Serum Chemistry [l], and UA	X			X								X [s]	
Urine Drug and Alcohol Screen	X												
AE Monitoring	X												
Concomitant Medication Monitoring	X												
Study Drug Administration / Pharmacokinetics													
[^{14}C]- TAK-788 Administration (oral) [m]		X											
Blood for Total Radioactivity [v]		X	X	X	X	X	X	X	X	X	X	X	
Blood for TAK-788 Whole Blood PK [v]		X	X	X	X	X	X	X	X	X	X	X	
Blood for TAK-788 Plasma PK [v]		X	X	X	X	X	X	X	X	X	X	X	
Blood for TAK-788 Metabolic Profiling [v]		X	X	X	X	X	X		X				
CCI [redacted]													
CCI [redacted]													
Other Procedures													
Confinement in the CRU [x]	X												
Phone call													X

[a] For details on Procedures, refer to Section 9.2.
[b] Within 28 days prior to the first study drug administration.
[c] There will be a washout period of approximately 9 days between doses in Period 1 and the dose in Period 2.
[d] Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU. If the CRU decides to confine the subjects throughout the washout period, some safety events at check-in (eg, clinical laboratory tests, urine drug and alcohol screen, serum pregnancy test, vital signs, and ECGs) may not be performed, following a decision by investigator's.
[e] Subjects who do not meet a discharge criterion (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 day for at least 2 consecutive intervals where both a urine and fecal sample are collected) by Day 5, will remain confined and undergo study procedures until a discharge criterion is met or up to Day 8.
[f] Full physical examinations will be conducted at scheduled time points. Symptom-driven physical examination may be performed at additional times, at the investigator's or designee's discretion.
[g] If the screening assessment was conducted within 4-7 days prior to dosing (Day 1), assessment will be conducted at check-in only if, in the opinion of the investigator, there is reason to believe they have substantially changed.
[h] To be performed within 24 hours prior to oral dosing.
[i] To be performed between 4.5 – 5 hours post oral drug administration.
[j] To be performed between 4.5 – 5 hours and at 12 hours post oral drug administration.
[k] To be conducted within 7 days prior to first dosing.
[l] Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.
[m] Oral drug administration will be performed at Hour 0 of Day 1.
[n] A 15 minute IV drug administration will begin at 3.75 hours post oral dose on Day 1 of Period 1.
[o] For a detailed blood sampling schedule refer to Table 3.a. Predose plasma samples from Period 2 will also be used as Day 10 samples for Period 1.
[p] CCI [redacted]

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[q] As per site preference, subjects may be confined throughout the washout period.
[r] The clinic will contact all subjects (including subjects who terminate the study early) 30 ±2 days after the last study drug administration to determine if any adverse events have occurred since the last study visit.
[s] To be performed at the end of Period 2 (prior to discharge) or prior to early termination from the study.
[t] To be performed at 4 hours post oral drug administration.
[u] To be performed at 4 and 12 hours post oral administration.
[v] For a detailed blood sampling schedule refer to Table 3.c.
[w] Fo[redacted] schedule refer to Table 3.d.
[x] Subjects will remain confined to the CRU until discharge criteria are met or up to a maximum stay of 10 days postdose (Day 11).
Abbreviations: AE = Adverse event, C-I = Check-in, CRU = Clinical research unit, ECG = Electrocardiogram, FU = Follow-up, HIV = Human immunodeficiency virus, IV = Intravenous, PK = Pharmacokinetics, S = Screening, UA = Urinalysis.

Table 3.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 [c]	X [c]
0.5 hour postdose (± 2 min)		X [c]	
1 hour postdose (± 2 min)		X [c]	
2 hours postdose (± 2 min)		X [c]	
3 hours postdose (± 2 min)		X [c]	
3 hours 45 min post dose	0 (predose)		X [c]
4 hours postdose (± 2 min)	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
	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 [d]	X [d]
144 hours postdose (± 15 min)	140 hours postdose (± 15 min)	X [d]	X [d]
Day 10 (Predose Day 1 of Period 2)		X [e]	X [e]

[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] Pre-IV dose samples should be stored separately away from the postdose samples to avoid cross contamination.
[d] For subjects who do not meet the discharge criteria by Day 5, blood samples will continue to be collected in 24-hour intervals until radioactivity in urine and feces combined is ≤1% of the total administered radioactivity per day 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 7.
[e] 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 3.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 blood and plasma samples should be stored separately away from the postdose samples to avoid cross contamination. Predose plasma samples from Period 2 will also be used as Day 10 samples for Period 1, as appropriate.

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[redacted]

4.0 INTRODUCTION

4.1 Background

Aberrant activation of epidermal growth factor receptor (EGFR) and human epidermal growth factor 2 (HER2) plays a causal role in a subset of non–small cell lung cancer (NSCLC) and other cancers. As inhibition of wild-type (WT) EGFR is associated with dose-limiting toxicities, a tyrosine kinase inhibitor (TKI) that inhibits oncogenic EGFR and HER2 variants more potently than WT EGFR is more likely to be able to be dosed to efficacious levels. Multiple classes of activating mutations have been identified in EGFR and HER2 that vary widely in their sensitivity to available TKIs. TAK-788, formerly known as AP32788, was designed to be a potent, selective inhibitor of all activated forms of EGFR and HER2, including exon 20 insertions (not targeted by any approved TKI), more potently than it inhibits WT EGFR.

Pharmacokinetics

ccl

[redacted]

Clinical experience

TAK-788 is currently being investigated in the first-in-human phase 1/2 trial (AP32788-15-101) to determine safety and maximum tolerated dose, PK and recommended phase 2 dose, and its preliminary efficacy profile.

In mid-January 2018, 160 mg QD was identified as the maximum tolerated dose (MTD). In combination with the efficacy, safety, and pharmacokinetic (PK) results observed in the dose escalation phase of this study, 160 mg QD was also recommended as the recommended Phase 2 dose (RP2D) for phase expansion phase of the study.

As of August 2018, 95 patients have been exposed to treatment at doses of 5 to 180 mg once daily (QD) and 40 to 60 mg twice daily as part of a phase 1/2 Study of the Safety, PK, and Anti-Tumor Activity of the oral EGFR/HER2 inhibitor AP32788 in patients with NSCLC.

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The early proof-of-concept assessment on the basis of Parts 1 and 2 of the study (the dose escalation and expansion phases) confirmed that 160 mg QD was the RP2D for the Part 3 extension cohort of AP32788-15-101. The unconfirmed ORR and DCR at the 160 mg QD dose were 47.6% (10 of 21) and 85.7% (18 of 21), respectively. With respect to the safety profile, the

most common all-grade treatment-emergent adverse events (AEs) (greater than 20% incidence in all patients treated at doses ranging from 80 to 160 mg total daily dose) had the following incidences at 160 mg QD: diarrhea (71.9%), nausea (40.6%), vomiting (31.3%), and decreased appetite (28.1%). The most common Grade ≥3 treatment-emergent AE was diarrhea; the incidence was 15.6% at 160 mg QD. The dose reduction rate for patients who received 160 mg total daily dose was 27.5%.

In summary, the early proof-of-concept results suggest a clinically meaningful benefit of TAK-788 in a patient population with locally advanced or metastatic NSCLC whose tumors have EGFR exon 20 insertion mutations regardless of prior treatment history with safety profile consistent with other EGFR TKIs.

A randomized, double-blind, placebo-controlled single rising dose (SRD) study (Part 1 of Study TAK-788-1001) followed by crossover evaluation of the effects of a low-fat meal on the pharmacokinetics of TAK-788 (Part 2) in healthy subjects has been initiated in April 2018. The starting dose was 20 mg and then with each subsequent 8-subject (2 in placebo and 6 in TAK-788) cohort the dose escalated to a single dose of 40, 80, 120, up to 160 mg administered under fasting conditions (no food for at least 10 hours before and 4 hours after the TAK-788 dose). Following the completion of Part 1 where safe and tolerable doses in healthy subjects were identified, Part 2 (low-fat meal effect phase) was conducted at 120 mg and 160 mg doses where the effects of a low-fat meal on TAK-788 were evaluated in a cross-over study design with 7-day washout between 2 doses. A total of 30 subjects were administered a single dose of TAK-788 at 160 mg in Part 1 of the study and 16 subjects took 2 single doses of TAK-788 at 160 mg in Part 2 of the study. TAK-788 was generally well tolerated after 1 single dose or 2 single doses up to 160 mg TAK-788. There were no SAEs. The common AEs were Grade 1 nausea and diarrhea.

Refer to the Investigator's Brochure (IB) for detailed background information on TAK-788 (IB 2018).

4.2 Rationale for the Proposed Study

The PK of TAK-788, metabolic pathways, and routes of elimination have been evaluated *in vitro* and *in vivo* in preclinical species, being summarized in the IB (IB 2018). The pharmacokinetic profile in humans is being evaluated in an ongoing dose escalation study in patients with NSCLC, as summarized in the IB (IB 2018) and in an ongoing SRD study in healthy subjects

The primary purposes of the present study are to characterize the ABA (Period 1) and the absorption, metabolism, excretion, and mass balance of TAK-788 after single oral administration (Period 2) in healthy adult male subjects, by collecting plasma, urine, and feces samples for drug concentration analysis, and plasma, whole blood, CCI [redacted] The study will provide data required to evaluate the mass balance and the metabolic profile of TAK-788 in humans. Based on preliminary data in healthy subjects, the geometric mean plasma terminal $t_{½}$ of TAK-788 is approximately 21 hours (13-28 hours); thus, more than 90% of the radioactivity should be eliminated within 96 hours postdose.

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4.3 Benefit/Risk Profile

Based on the clinical safety data available as of 10 August 2018 from the ongoing first-in-human study in NSCLC patients (Study AP32788-15-101) and the SRD/low-fat meal effect study in healthy subjects, TAK-788 exhibits a similar safety profile to other epidermal growth factor receptor tyrosine kinase inhibitors. The MTD was determined to be 160 mg QD in NSCLC patients. A single dose of 160 mg TAK-788 selected for this study has been demonstrated to be safe and well tolerated in healthy subjects.

The estimated radiation dose from a single IV administration of [^{14}C]-TAK-788 (~2 μCi) and a single oral dose of [^{14}C]-TAK-788 (~100 μCi) is below the radiation dose limits set forth in 21 CFR 361 for the whole body, active blood forming organs, lens of the eye, gonads, and other organs (see Section 6.3.2). Thus, the health risk resulting from exposure to radiation in the study drug is very low.

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

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

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

NA

5.2 Trial Objectives

5.2.1 Trial Primary Objectives

Period 1 (ABA)

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

Period 2 (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 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.

5.2.2 Trial Secondary Objectives

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.

5.2.3 Trial Exploratory Objective

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[redacted]

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5.3 Endpoints

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

5.3.1 Primary Endpoints

The primary endpoint of the study is:

Period 1 (ABA):

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

Period 2 (ADME):

- Percent of total radioactivity recovered in urine (Cum%Dose[UR]) and feces (Cum%Dose[FE]) relative to the administered radioactive dose (Combined Cum%Dose).
- Total radioactive recovery in urine (Ae[UR]) and feces (Ae[FE]) and the percent of the radioactive dose excreted in the urine (%Dose[UR]) and feces (%Dose[FE]).
- TAK-788 metabolic profiling in plasma, urine, and feces containing sufficient amounts of radioactivity.
- PK parameters C_{max}, t_{max}, $t_{½}$, 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}, $t_{½}$, 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 (Aet_1-t_2) and renal clearance (CLR) TAK-788 and its metabolites (AP32960 and AP32914) in urine.
- The change over time in percentage of [^{14}C]-radioactivity in whole blood relative to plasma (ie, whole blood:plasma partitioning ratio).

5.3.2 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 $t_{½}$ for TAK-788, and [^{14}C]-TAK-788 and the metabolites (AP32960 and AP32914) in plasma;

Periods 1 (ABA) and 2 (ADME):

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

5.3.3 Exploratory Endpoints

CCI

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

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 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 will receive a 15-minute IV infusion of a microdose of 50 µg (~2 µCi) [^{14}C]-TAK-788. Serial blood sampling will be 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 will be confined in the clinical research unit (CRU) for at least 5 days (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until a discharge criterion is met or up to Day 8. Subjects will return to the clinic on Day 9 (Period 2, Day -1) for Period 2.

There will be 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 will receive a single dose of 160 mg (~100 µCi) [^{14}C]-TAK-788 as an oral solution. Serial blood sampling will be performed and urine and feces will be collected to determine the PK of TAK-788 and its metabolites (AP32960 and AP32914) in plasma, whole blood, and urine, and total radioactivity in plasma, whole blood, CCI [redacted], and to characterize the metabolite profiles of TAK-788 in plasma, CCI [redacted] will be collected during confinement period until discharge criteria are met (anticipated to be 10 days or less).

In Period 2 subjects will be confined in the clinic until a discharge criterion is met (ie, 80% or greater of the CCI [redacted]

In both Periods 1 and 2, any subject who experiences emesis within 8 hours post the 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.

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

The planned dose levels of TAK-788 to be evaluated are outlined in Table 6.a.

Table 6.a 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

6.2 Dose Escalation

NA

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

In Period 1 of the study, the ABA of TAK-788 will be estimated using a labeled IV microdose administered 3.75 hours after an unlabeled oral dose in order to characterize the disposition properties of TAK-788. In order to determine absolute bioavailability accurately and reliably, a healthy adult population is chosen.

Characterization of the disposition of a drug following IV administration facilitates the understanding of fundamental aspects of TAK-788's PK that cannot be determined from oral dosing alone, including bioavailability, intrinsic clearance, and volume of distribution. The results of this trial will contribute to a robust understanding of the PK characteristics of TAK-788.

In Period 2 of the study, characterization of the absorption, metabolism, excretion, and mass balance of TAK-788 after oral administration of a single 160 mg (~100 µCi) [^{14}C]-TAK-788 will be achieved by collecting plasma samples for drug concentration analysis, and plasma, CCI [redacted] and metabolic profiling. The study will provide data required to evaluate the mass balance and the metabolic profile of TAK-788 in humans.

6.3.2 Rationale for Dose

The likely therapeutic dose of TAK-788 is expected to be 160 mg for oral administration. The 160 mg dose is likely to provide exposures commensurate with a clinically efficacious dose, and

was selected in order to have sufficient mass of drug, and sufficient specific radioactivity, for detection and analysis of parent drug and/or metabolites in plasma, urine, and fecal samples.

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

The estimated radiation absorbed doses to human tissues of the concomitant dosing in both periods of the study was estimated based on data from pigmented and non-pigmented Long-Evans rats following a single oral 10 mg/kg (~100 µCi/kg) dose of [^{14}C]-TAK-788. The overall whole body effective dose, defined as the equivalent total detriment to the health of the affected individual from non-uniform doses to tissues, based on assigned tissue weighting factors, was calculated. Based on the rat ADME study, the bioavailability of the oral drug in rat is 25%. For safety purposes, a conservative approach was taken for the purpose of exposure calculations (accounting for potential differences between the animal model and human estimate) and the bioavailability was assumed to be 10%. The overall whole-body radiation dose in male subjects following administration of a single IV dose of 2 µCi of [^{14}C]-TAK-788 (using a conversion ratio of x10 to account for a 10% bioavailability) followed by a single oral dose of 100 µCi (3.7 megabecquerels [MBq]) of [^{14}C]-TAK-788 was calculated to be 6.3996 mrem (0.06399 milliSieverts [mSv]), approximately 0.21% of the allowable 3000 mrem-exposure limit established by the Food and Drug Administration (FDA) and approximately 6.40% of the allowable 1 mSv ICRP limit. The highest estimated absorbed dose was in the adrenal gland modulla, which had a value of 555.04 mrem (5.550 mSv), and represented 11.10% of the allowable 5000 mrem exposure limit for a single tissue specified by the FDA.

6.3.3 Rationale for Endpoints

NA

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this study, the blood, urine, and feces collection for radioactivity, plasma concentrations, and metabolite profiling for TAK-788 is the critical procedure and are required to be collected, as appropriate, as close to the scheduled times defined in this protocol as possible.

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

The dose and administration of the study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 6.5.5.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

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

6.5.2 Definition of End of the Trial

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

6.5.3 Definition of Trial Completion

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

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

6.5.4 Definition of Trial Discontinuation

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

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

6.5.5 Criteria for Premature Termination or Suspension of the Trial

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

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

6.5.6 Criteria for Premature Termination or Suspension of a Site

6.5.6.1 Criteria for Premature Termination or Suspension of a Site

NA

6.5.6.2 Procedures for Premature Termination or Suspension of a Site

NA

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 9.1.2.2. After the first dose, acetaminophen (up to 2 g per 24 hour period) may be administered at the discretion of the investigator or designee. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration.

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

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

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

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

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

Category	Between Screening and Randomization (Days -28 to predose [Day 1])	Post-Randomization (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from 48 hours prior to first dosing in each period and throughout the period of PK sample collection in each Treatment period.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing [a]	Prohibited from 24 hours prior to first dosing in each period and throughout the period of PK sample collection in each Treatment period [a].
Medications	See Sections 7.1 and 9.1.2.2	See Sections 7.1 and 9.1.2.2
Food substance		
Grapefruit/Seville orange	Prohibited from 14 days prior to first dosing	Prohibited until end of PK collection in Treatment Period 2.

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

7.2 Diet, Fluid, Activity

7.2.1 Diet and Fluid

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

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

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

7.2.2 Activity

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

7.3 Criteria for Discontinuation or Withdrawal of a Subject

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

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

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

Any subject who experiences emesis within 8 hours post the oral dose will be discontinued, excluded from the final data analysis, and may be replaced with a new subject. In Period 2, if a subject experiences emesis after dosing, vomitus will need to be collected as much as possible and assayed for total radioactivity.

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

7.4 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.3. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.5 Subject Replacement

Discontinued subjects may be replaced at the discretion of the Sponsor and the investigator.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

8.1.1 TAK-788 Capsule

A single unlabeled 160 mg dose of TAK-788 capsules will be administered in Period 1 of the study.

Oral dose of TAK-788 drug product is a nonsterile, oral, capsule dosage form, supplied in a hard gelatin capsule of TAK-788 succinate salt. TAK-788 succinate salt is the active pharmaceutical ingredient. The drug product is supplied as a hard gelatin capsule shell. No other ingredients are included in the drug product.

8.1.2 [^{14}C]-TAK-788 IV Sterile Solution

An IV dose of approximately 50 µg [^{14}C]-TAK-788 (~2 µCi) will be administered 3.75 hours after the TAK-788 oral dose (Section 6.1) in Treatment Period 1 of the study.

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

8.1.3 [^{14}C]-TAK-788 Oral Solution

A dose of 160 mg [^{14}C]-TAK-788 (~100 µCi) as oral solution will be administered in Treatment Period 2 of the study.

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

8.1.4 Clinical Study Drug Labeling

TAK-788 capsule containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.5 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of TAK-788 products to allow completion of this study.

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

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

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied. All TAK-788 products will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.1.6 Clinical Study Drug Blinding

This is an open-label study.

8.1.7 Randomization Code Creation and Storage

NA

8.1.8 Clinical Trial Blind Maintenance/Unblinding Procedure

NA

8.1.9 Accountability and Destruction of Sponsor-Supplied Drugs

At the conclusion of the study, any unused TAK-788 study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

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

9.1.1.2 Study Drug Assignment

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

9.1.2 Inclusion and Exclusion

9.1.2.1 Inclusion Criteria

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

1. Healthy, adult, male, 19 - 55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 20 years prior to the first dosing and throughout the study, based on subject self-reporting.
3. BMI ≥18 and <30.0 kg/m^2 at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the investigator or designee.
5. Normal baseline PFTs (≥80% of predicted normal for spirometry and lung volumes) within 7 days prior to the first dosing.
6. Subjects who are sexually active with a female partner of childbearing potential must use barrier contraception as indicated in Appendix D or abstain from sexual intercourse during the study until 94 days after the last dosing. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with your preferred and usual lifestyle.
7. Must agree not to donate sperm from the first dosing until 94 days after the last dosing.

8. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

9.1.2.2 Exclusion Criteria

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

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the investigator or designee.
3. History of any illness that, in the opinion of the investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of lung disease and current lung infection.
7. Positive urine drug or alcohol results at screening or first check-in.
8. Positive results at screening for HIV, HBsAg, or HCV.
9. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
10. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.
11. QTcF interval is >460 msec or ECG findings are deemed abnormal with clinical significance by the investigator or designee at screening.
12. Estimated creatinine clearance <80 mL/min at screening.
13. Has tattoo(s) or scarring at or near the site of IV infusion or any other condition which may interfere with infusion site examination, in the opinion of the investigator.
14. Subject has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
15. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks of first dosing.
16. Has received radiolabeled substances or has been exposed to radiation sources within 12 months of first dosing or is likely to receive radiation exposure or radioisotopes within 12 months of first dosing such that participation in this study would increase their total exposure beyond the recommended levels considered safe (ie, weighted annual limit recommended by the ICRP of 3000 mrem).

17. Unable to refrain from or anticipates the use of:

    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study, only after first dosing, if necessary to treat AEs. Milk of Magnesia (ie, magnesium hydroxide) (≤60 mL per day) may be administered approximately on Day 4 (Period 1) or Day 8 (Period 2) to ensure defecation, with agreement between the study investigator and Takeda physician. Additional administration of milk of Magnesia may be needed on other days at discretion of the study investigator and Takeda Physician.
    - Any drugs known to be significant inducers of CYP3A enzymes and/or P-gp, including St. John's Wort, within 28 days prior to the first dosing and throughout the study. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drug.

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

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.1 and in Section 9.1.2.2. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

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

For this study, the collection for blood, urine, and feces for total radioactivity, plasma concentrations, and metabolite profiling for TAK-788 are the critical parameter and need to be collected as close to the exact time point as possible. All other procedures should be completed as

close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

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

9.2.1 Full Physical Exam

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

9.2.2 Height and Weight

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

9.2.3 BMI

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

9.2.4 Vital Signs

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

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

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

9.2.5 12-Lead ECG

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

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

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

9.2.6 Pulmonary Function Test

9.2.6.1 Spirometry

Spirometry measures will be taken at screening (within 7 days prior to first dosing) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1 (forced expiratory volume);
- FVC (forced vital capacity);
- FEV_1/FVC.

9.2.7 Study Drug Administration

TAK-788 oral capsule and [^{14}C]-TAK-788 oral and IV solution will be provided as described in Section 8.1.

Subjects will be instructed not to crush, split, or chew the TAK-788 capsules.

Treatments A and B are described as:

Treatment A: 160 mg TAK-788 in capsules administered at Hour 0 on Day 1 followed by 50 µg (~2 µCi) [^{14}C]-TAK-788 IV solution administered at Hour 3.75 for 15 minutes.

Treatment B: 160 mg (~100 µCi) [^{14}C]-TAK-788 oral solution administered at Hour 0 on Day 1.

The oral doses of TAK-788 and [^{14}C]-TAK-788 will be administered following an overnight fast with approximately 240 mL of water. The exact clock time of oral dosing will be recorded.

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

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

9.2.8 AE Monitoring

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

9.2.9 Laboratory Procedures and Assessments

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

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

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

Chemistry

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

Chemistry evaluations will consist of the following standard chemistry panel:

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

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

Urinalysis

Urinalysis will consist of the following tests:

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

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

Other

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

9.3 PK Samples

Primary specimen collection parameters are provided in Table 9.a. Instructions for plasma, urine, fecal samples processing and handling will be provided in a separate document(s). Predose plasma samples from in Period 2 will also be used as Day 10 samples for Period 1.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Period 1				
Plasma for TAK-788 PK and metabolites	Plasma		PK analysis	Mandatory
Plasma for total radioactivity, [^{14}C]-TAK-788 PK and metabolites	Plasma		Total radioactivity and PK analysis	Mandatory
CCI [redacted]				
Blood for total radioactivity	Blood		Total radioactivity	Mandatory
Blood for TAK-788 and metabolites PK	Blood		PK analysis	Mandatory
Plasma for total radioactivity	Plasma		Total radioactivity	Mandatory
Plasma for TAK-788 and metabolites PK	Plasma		PK analysis	Mandatory
Plasma for TAK-788 Metabolic Profiling	Plasma		Metabolic profiling	Mandatory
CCI [redacted]				
Urine for TAK-788 PK	Urine		PK analysis	Mandatory
Urine for TAK-788 Metabolic Profiling	Urine		Metabolic profiling	Mandatory
Feces for total radioactivity	Feces		Total radioactivity	Mandatory
Feces for TAK-788 Metabolic Profiling	Feces		Metabolic profiling	Mandatory

9.3.1 PK Measurements

9.3.1.1 Plasma and Whole Blood PK Measurements

PK parameters for whole blood and plasma radioactivity concentration equivalents (Period 2) and for plasma TAK-788 concentrations and metabolites (Periods 1 and 2) will be calculated as follows, as appropriate, following oral administration:

AUC_{last}: The area under the concentration versus time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.

AUC_t: Area under the concentration versus time curve, from 0 to the time of the last common time point "t" at which plasma total radioactivity and plasma TAK-788 are quantifiable for all subjects *(plasma only)*.

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AUC_{∞}:	The area under the concentration versus time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_t plus the ratio of the last measurable blood concentration to the elimination rate constant.
$AUC_{\%extrap}$:	Percent of AUC_{∞} extrapolated, represented as $(1 - AUC_t/AUC_{\infty})*100$.
C_{max}:	Maximum observed concentration.
t_{max}:	Time to reach C_{max}. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
$t_{½}$:	Apparent first-order terminal elimination half-life will be calculated as $0.693/K_{el}$. Where K_{el} is the apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (eg, three or more non-zero plasma concentrations).

PK parameters for plasma concentrations of [^{14}C]-TAK-788 and metabolites following IV infusion (Period 1) will be calculated as follows, as appropriate:

AUC_{last}:	The area under the concentration versus time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC_t:	Area under the concentration versus time curve, from 0 to the time of the last common time point "t" at which plasma total radioactivity and plasma TAK-788 are quantifiable for all subjects *(plasma only)*.
AUC_{∞}:	The area under the concentration versus time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_t plus the ratio of the last measurable blood concentration to the elimination rate constant.
$AUC_{\%extrap}$:	Percent of AUC_{∞} extrapolated, represented as $(1 - AUC_t/AUC_{\infty})*100$.
C_{eoi}:	Concentration at the end of infusion.
$t_{½}$:	Apparent first-order terminal elimination half-life will be calculated as $0.693/K_{el.}$ Where K_{el} is the apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (eg, three or more non-zero plasma concentrations).

No value for K_{el}, AUC_{∞}, $AUC_{\%extrap}$, or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

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

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

The absolute bioavailability parameters for TAK-788 (Period 1) will be calculated as follows:

F:	Absolute bioavailability, calculated for plasma TAK-788.
%F:	Percent absolute bioavailability, calculated for plasma TAK-788 as [Dose (IV) x AUC_{∞} (oral)] / [Dose (oral) x AUC_{∞} (IV)] x 100.

CCI

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9.3.1.4 Additional PK Measurements

CCI [redacted]

9.3.2 Biomarker Measurements

NA

9.3.3 PGx Measurements

NA

9.3.4 Confinement

In Period 1, subjects will be housed on Day -1, at the time indicated by the CRU until at least after the 96-hour blood draw and/or study procedures and until a discharge criterion is met or up to Day 8. As per site preference, subjects may be confined throughout the washout period.

In Period 2, subjects will be housed on Day -1, at the time indicated by the CRU, until discharge criteria are met, or a maximum of 10 days (ie, Day 11).

All urine and fecal collections will be analyzed for radioactivity levels to determine if the discharge criteria are met. Subjects will be eligible for discharge if they meet either of the following discharge criteria from Day 5 (Period 1) and prior to Day 11 (Period 2):

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

It is expected that the majority (≥90%) of the administered radioactivity will be recovered within 96 hours post TAK-788 dose.

Release of subjects who do not meet criteria discharge criterion by Day 7 (Period 1) and/or Day 11 (Period 2) will be reviewed on a case-by-case basis.

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

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

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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 have occurred since the last study visit.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

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

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

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.7.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

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

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

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1.1 and 10.2.7.3).

10.1.2 Special Interest AEs

There are no AEs of Special Interest for TAK-788.

10.2 AE Procedures

10.2.1 Assigning Severity of AEs

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, dated 27 November 2017 [CTCAE 2017]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor

medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on subject/event outcome or action criteria described above and is usually associated with events that pose a threat to a subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to <2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

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

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Action Taken With Study Treatment

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

- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.6 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

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

10.2.7.1 Collection Period

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

10.2.7.2 Reporting AEs

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

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

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

10.2.7.3 Reporting SAEs

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

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

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

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

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

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

SAE Follow-Up

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

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

10.2.7.4 Reporting Special Interest AEs

NA

10.2.7.5 Reporting of Abnormal Liver Test Results

If a subject has elevated ALT ≥3x upper limit of normal (ULN) with concurrent elevated total bilirubin >2× ULN ***or*** elevated international normalized ratio (INR) >1.5, contact the sponsor's medical monitor within 24 hours.

For any subject with ALT ≥3x ULN and total bilirubin >2x ULN or INR >1.5x ULN for which an alternative etiology has not been found, report the event as an SAE (Section 10.2.7.3) and contact the sponsor immediately.

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

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

10.2.9 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided below.

Product	Call Center	Phone Number	Email	Fax
TAK-788	Dohmen Life Science Services, or DLSS (formerly known as MedComm)	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

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

11.1.1.2 PK Set

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

11.1.1.3 PD Set

NA

11.1.2 Analysis of Demography and Other Baseline Characteristics

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

11.1.3 PK Analysis

Descriptive statistics will be provided for the total radioactivity (whole blood, plasma, CCI and if applicable, emesis), TAK-788 and metabolites concentrations and PK parameters (blood, plasma and urine), [^{14}C]-TAK-788 plasma radioactivity concentrations equivalent, and the metabolic profile of TAK-788, using appropriate summary statistics to be fully specified in the SAP.

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

Absolute bioavailability of TAK-788 (Period 1) will be estimated using a ninety percent (90%) CI constructed for the difference in LS mean on the log scale for dose normalized AUC_{∞} between a single oral dose and the IV microdose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose normalized AUC_{∞} geometric mean ratio (TAK-788 administered as oral dose / [^{14}C]-TAK-788 administered as IV microdose). The AUC_{last}, AUC_t, and C_{max}, will be analyzed in a similar fashion.

11.1.4 Analysis of Mass Balance

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

11.1.5 Whole Blood to Plasma Partitioning Ratio

In Period 2, the change over time in percentage of [^{14}C]-radioactivity, TAK-788, and metabolites in whole blood relative to plasma will be estimated (eg, whole blood:plasma partitioning ratio).

11.1.6 Metabolite Profiling

In Period 2, TAK-788 metabolite profiling will be performed in plasma, urine, and feces containing sufficient amounts of radioactivity. The percent of 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.

11.1.7 PD Analysis

NA

11.1.8 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by subject.

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

11.1.8.1 AEs

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

11.1.8.2 Clinical Laboratory Evaluation

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

11.1.8.3 Vital Signs

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

11.1.8.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

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

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

11.2 Interim Analysis and Criteria for Early Termination

NA

11.3 Determination of Sample Size

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

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

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

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

12.2 Protocol Deviations

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

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

12.3 Quality Assurance Audits and Regulatory Agency Inspections

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

13.0 ETHICAL ASPECTS OF THE STUDY

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

13.1 IRB and/or IEC Approval

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

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

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

13.3 Subject Confidentiality

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

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

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

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

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

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

13.4.2 Clinical Trial Registration

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

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

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

13.4.3 Clinical Trial Results Disclosure

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	**SAE Reporting Contact Information** **Cognizant** **US and Canada** Toll-free fax #: 1-800-963-6290 E-mail: takedaoncocases@cognizant.com

Please refer to Safety Management Plan.

14.1.2 Investigator Agreement

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.8 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 Protocol Amendment 01 Summary of Changes

Rationale for Amendment No. 01

The purpose of this amendment is to to extend the period of feces collection in Period 1. Based on the extent of excreted radioactivity up to Day 5 of Period 1, excretion in urine is below level of quantification but excretion in feces is still ongoing for the majority of subjects. The sampling period for drug excretion in feces for subjects who do not meet the release criteria is therefore extended from up to Day 7 to up to Day 8. For specific descriptions of text changes and where the changes are located, see Appendix E.

14.1.5 List of Abbreviations

µCi	Microcurie
µg	Microgram
%Dose(FE)	Percent of administered radioactive dose excreted in feces within a given collection interval
%Dose(UR)	Percent of administered radioactive dose excreted in urine within a given collection interval
%F	Percent absolute oral bioavailability
ABA	Absolute bioavailability
ADME	Absorption, distribution, metabolism, and elimination
AE	Adverse event
Aet_1-t_2	Amount of unchanged drug excreted in the urine collection interval from t_1 to t_2.
Ae(FE)	Amount of total radioactivity excreted in feces within a given collection interval
Ae(UR)	Amount of total radioactivity excreted in urine within a given collection interval
ALT	Alanine aminotransferase
AUC	Area under the concentration-time curve
$AUC_{\%extrap}$	Percent of AUC0-inf extrapolated
AUC_{last}	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration
AUC_t	Area under the concentration versus time curve, from 0 to the time of the last common time point "t" at which plasma total radioactivity and plasma TAK-788 are quantifiable for all subjects
AUC_∞	Area under the concentration-time curve, from time 0 extrapolated to infinity
BMI	Body mass index
bpm	Beats per minute
[^{14}C]	Carbon-14; radiocarbon
C_{eoi}	Concentration at end of infusion

CFR	Code of Federal Regulations
CI	Confidence interval
CLR	Renal clearance
cm	Centimeter
C_{max}	Maximum observed concentration
CO	Carbon monoxide
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome P450
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
F	Bioavailability
FVC	Forced vital capacity
FEV	Forced expiratory volume
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
He	Helium
HER2	Human epidermal growth factor 2
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICRP	Commission on Radiological Protection
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
Kel	Apparent first-order terminal elimination rate constant
kg	Kilogram
LFT	Liver function tests
LS	Least-squares
m^2	Meters squared
MBq	Megabecquerel
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
mrem	Millirem

msec	Millisecond
mSv	Millisievert
MTD	Maximum tolerated dose
NA	Not applicable
nCi	Nanocurie
NSCLC	Non–small cell lung cancer
oz	Ounce
P-gp	P-glycoprotein
PFT	Pulmonary function tests
PK	Pharmacokinetic(s)
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SRD	Single rising dose
SUSARs	Suspected unexpected serious adverse reactions
$t_{½}$	Apparent first-order terminal elimination half-life
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitors
t_{max}	Time to reach maximum observed concentration [C_{max}]
TRA	Total radioactivity
ULN	Upper limit of normal
US	United States
USA	United States of America
WT	Wild type

15.0 DATA HANDLING AND RECORD KEEPING

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

15.1 CRFs

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor or its designee will train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs must be completed in English.

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the investigator with use of change and modification records of the CRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

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

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.0 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6

(Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor.

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

16.0 REFERENCES

TAK-788. Millennium Pharmaceuticals, Inc. Global Investigator Brochure. Edition 2.0, January 2018.

Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. U.S. Department of Health and Human Services National Cancer Institute. 27 Nov 2017.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

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

10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

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

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

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 94 after the last dose of study drug.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

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

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

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

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 94 days after last dose of study drug, male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm throughout the duration of the study, and for 94 days after last dose of study drug. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with your preferred and usual lifestyle.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

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

The following procedures apply for contraception and pregnancy avoidance.

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

    - Non-Hormonal Methods:
        - Intrauterine device (IUD).
        - Bilateral tubal occlusion.
        - Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.
        - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 94 days after last dose.

- Hormonal Methods:
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
    - Oral.
    - Intravaginal (eg, ring).
    - transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
    - oral.
    - Injectable.
    - Implantable.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular {serum/urine} human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:

   a) contraceptive requirements of the study

   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners

c) assessment of subject compliance through questions such as

i. Have you used the contraception consistently and correctly since the last visit?

ii. Have you forgotten to use contraception since the last visit?

iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")

iv. Is there a chance you could be pregnant?

5. In addition to a negative {serum/urine} hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative {serum/urine} hCG pregnancy test prior to receiving any dose of study medication. In addition, subjects must also have a negative {serum/urine} hCG pregnancy test prior to receiving first dose of investigational drug as close as possible and prior to first dose of investigational drug, preferably on the same day.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Women will not be included in this study.

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

Any pregnancies in the partner of a male subject during the study or for 94 days after the last dose, should also be recorded following authorization from the subject's partner.

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

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

Appendix E Detailed Description of Amendments to Text

Change 1. Update of last day of confinement and feces sample collection in Period 1 for subjects who do not meet release criteria by Day 5, from Day 7 to Day 8.

The change occurs in Section 1.0 – Study Summary, under Study Design (first sentence in the third paragraph), and in Section 6.1 – Study Design (first sentence in the third paragraph).

Initial wording:

In Period 1, subjects will be confined in the clinical research unit (CRU) for at least 5 days (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until a discharge criterion is met or up to Day 7.

Amended or new wording:

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

Section 2.0 – Study Schematics, under Treatment Period 1 (column header for Study Days and footnote 'b'),

Initial wording:

Screening	Treatment Period 1		
	Day -1	Day 1	Days 2 - 7

[b] Subjects will be confined in the clinic 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 (i.e., 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 day for at least 2 consecutive intervals where both a urine and fecal sample is collected) or up to Day 7.

Amended or new wording:

Screening	Treatment Period 1		
	Day -1	Day 1	Days 2 - 8

[b] Subjects will be confined in the clinic 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 (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 day for at least 2 consecutive intervals where both a urine and fecal sample is collected) or up to Day 8.

Section 3.0 – Schedule of Study Procedures (column header for Study Days 6-7 and footnote 'e')

Initial wording:

Study Procedures [a] **Days →**	**S** [b]	**Study Days in Period 1** [c]						
		-1 (C-I[d]**)**	**1**	**2**	**3**	**4**	**5**	**6-7** [e]

[e] Subjects who do not meet a discharge criterion (i.e., 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 day for at least 2 consecutive intervals where both a urine and fecal sample are collected) by Day 5, will remain confined and undergo study procedures until a discharge criterion is met or up to Day 7.

Amended or new wording:

Study Procedures [a] **Days →**	**S** [b]	**Study Days in Period 1** [c]						
		-1 (C-I[d]**)**	**1**	**2**	**3**	**4**	**5**	**6-8** [e]

[e] Subjects who do not meet a discharge criterion (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 day for at least 2 consecutive intervals where both a urine and fecal sample are collected) by Day 5, will remain confined and undergo study procedures until a discharge criterion is met or up to Day 8.

Section 3.0 – Schedule of Study Procedures, under Table 3.b - Urine and Fecal Sampling Schedule (Period 1 – ABA Study Period), a row was added for feces collection on study Days 7 to 8.

Amended or new wording:

Added row:

	Time Interval (hours) (Relative to Oral Dosing)	Urine Sample Collection	Feces Sample Collection
Study Day	Matrix	Urine [a]	Feces [b]
(…)			
Day 7 to 8	144-168 hours		X [g]

Section 3.0 – Schedule of Study Procedures, under Table 3.b - Urine and Fecal Sampling Schedule (Period 1 – ABA Study Period) (footnote 'g')

Initial wording:

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 per day 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 7.

Amended or new wording:	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 per day 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.

Section 9.0 – Confinement (first paragraph)

Initial wording:	In Period 1, subjects will be housed on Day -1, at the time indicated by the CRU until at least after the 96-hour blood draw and/or study procedures and until a discharge criterion is met or up to Day 7. As per site preference, subjects may be confined throughout the washout period.
Amended or new wording:	In Period 1, subjects will be housed on Day -1, at the time indicated by the CRU until at least after the 96-hour blood draw and/or study procedures and until a discharge criterion is met or up to Day 8. As per site preference, subjects may be confined throughout the washout period.

Rationale for Change:

Based on the extent of excreted radioactivity up to Day 5, excretion in urine is below level of quantification but excretion in feces is still ongoing for the majority of subjects. The sampling period for drug excretion in feces for subjects who do not meet the release criteria is therefore extended from up to Day 7 to up to Day 8.

Change 2. Clarification of the duration of blood sample collection for TRA and PK in Period 1.

The change occurs in Section 3.0 - Schedule of Study Procedures, under Table 3.a - Blood Collection Schedule after the Oral and Intravenous Doses of TAK-788 (Period 1 - ABA Study Period), footnote d.

Initial wording:	For subjects who do not meet the discharge criteria 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 per day 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 7.
Amended or new wording:	For subjects who do not meet the discharge criteria by Day 5, blood samples will continue to be collected in 24-hour intervals until radioactivity in urine and feces combined is ≤1% of the total administered radioactivity per day 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 7.

Rationale for Change:

Clarification was added to make sure blood samples are not collected on Day 8 following the extension of fecal sample collection from Day 7 to Day 8.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	01-Mar-2019 16:14 UTC
	Biostatistics Approval	04-Mar-2019 00:58 UTC
	Clinical Pharmacology Approval	06-Mar-2019 14:56 UTC