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

NCT Number: NCT04454918

Protocol Approve Date: 30 March 2020

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**TAKEDA PHARMACEUTICALS**

**PROTOCOL**

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

| | |
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| **Study Identifier:** | TAK-906-1007 |
| **Compound:** | TAK-906 |
| **Date:** | 30 March 2020 |
| **Version/Amendment Number:** | 1 |

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## 1.0 STUDY SUMMARY

| **Name of Sponsor:** | **Compound:** |
|---|---|
| Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd<br>40 Landsdowne Street<br>Cambridge, Massachusetts USA 02139<br>Telephone: +1 (617) 679-7000 | TAK-906 |
| **Study Identifier: TAK-906-1007** | **Phase:** 1 |
| **Protocol Title:** A Phase 1 Study to Assess Absolute Bioavailability of TAK-906 and to Characterize Mass Balance, Pharmacokinetics, Metabolism, and Excretion of [$^{14}$C]-TAK-906 in Healthy Male Subjects | |

**Trial Design:**

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

On Day 1 of Period 1 (absolute bioavailability [ABA] Study Period), after at least a 10-hour fast, 6 subjects will receive a single unlabeled oral 50 mg dose of TAK-906 as capsules. At approximately 45 minutes post oral dosing (0.75 hour) (ie, 15 minutes prior to the median $t_{max}$ for the oral unlabeled dose [~ 1.1 hours]), subjects will receive a 15-minute intravenous (IV) infusion of a microtracer dose of 100 µg (approximately equivalent to 1 microcurie ~[1 µCi]) [$^{14}$C]-TAK-906. Serial blood sampling will be performed to determine the pharmacokinetics (PK) of TAK-906 and its metabolite (M23) in the plasma for the oral dose and total radioactivity (TRA) and PK of [$^{14}$C]-TAK-906 in the plasma for the IV dose. Urine and fecal output will also be collected up to the morning of Day 5 (ie, Hour 96) to determine TRA levels and until a discharge criterion is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) but no less than Day 5 for [$^{14}$C]-TRA 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 discharge criterion is met or up to Day 7. Subjects will return to the clinic on Day -1 of Period 2 for Check-in procedures. There will be a washout period of at least 7 days between the dose in Period 1 and the dose in Period 2. As per site preference, subjects may be confined throughout the washout period.

On Day 1 of Period 2 (absorption, distribution, metabolism, and elimination [ADME] Study Period), after at least a 10-hour fast, the subjects will receive a single dose of 50 mg (~100 µCi) [$^{14}$C]-TAK-906 as an oral solution. Serial blood sampling and urine and feces output will be collected. PK of TAK-906 and its metabolite, M23, will be determined in plasma and urine; plasma, whole blood, urine, and feces will be collected for TRA determination; and plasma, urine, and feces will be collected to characterize the metabolite profiles of TAK-906. Complete urinary and fecal output will be collected until at least the morning of Day 6 (ie, Hour 120). Subjects will be confined in the clinic until at least this time and until a discharge criterion is met (ie, 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24 hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 14 days postdose (ie, Day 15). After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the CRU to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis. In each of the 2 consecutive intervals, both urine and fecal samples have to be collected and counted for TRA, ie, if only urine or feces is collected in a day, this day is not considered to be one of the 2 consecutive intervals. Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

In both Periods 1 and 2, any subject who experiences emesis within 3 hours post oral dose will be excluded in the final data analysis and will be replaced with a new subject. If a subject experiences emesis after dosing in Period 2, vomitus

will need to be collected as much as possible and assayed for TRA. For a subject who drops out in Period 2, the replacement subject will be required to complete Period 2 only.

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

| **Period 1 - ABA** | **Period 2 - ADME** |
|---|---|
| **Trial Primary Objective:**<br>• To determine the oral absolute bioavailability (F) of TAK-906 following single oral (capsule) administration of 50 mg of TAK-906 and single IV microtracer dose administration of 100 µg (~1 µCi) of [$^{14}$C]-TAK-906. | **Trial Primary Objective:**<br>• To determine the mass balance of TAK-906 in urine and feces following a single oral (solution) administration of 50 mg (~100 µCi) of [$^{14}$C]-TAK-906. |
| **Trial Secondary Objectives:**<br>• To determine the plasma PK parameters of TAK-906 and metabolite, M23, following single oral (capsule) administration of 50 mg of TAK-906.<br>• To determine plasma PK parameters of TRA following a single IV administration of 100 µg (~1 µCi) of [$^{14}$C]-TAK-906.<br>• To determine plasma PK parameters of [$^{14}$C]-TAK 906 following a single IV administration of 100 µg (~1 µCi) of [$^{14}$C]-TAK-906<br>CCI [redacted] | **Trial Secondary Objectives:**<br>• To determine the plasma PK parameters of TAK-906 and metabolite, M23, following a single oral (solution) administration of 50 mg (~100 µCi) of [$^{14}$C]-TAK-906.<br>• To determine plasma and whole blood PK parameters for TRA following a single oral (solution) administration of 50 mg (~100 µCi) of [$^{14}$C]-TAK-906.<br>CCI [redacted] |
| **Trial Safety Objective:**<br>• To evaluate the safety and tolerability of TAK-906, administered as a single oral dose (capsule) of TAK-906 followed by single IV microtracer dose administration of [$^{14}$C]-TAK-906. | **Trial Safety Objective:**<br>• To evaluate the safety and tolerability of TAK-906, administered as a single oral dose (solution) of [$^{14}$C]-TAK-906. |
| **Trial Subject Population:** Healthy adult male subjects | |
| **Planned Number of Subjects:**<br>6 | **Planned Number of Sites:**<br>1 |

| | |
|---|---|
| **Dose Levels:**<br>Period 1:<br>50 mg of TAK-906<br>100 µg (~1 µCi) [$^{14}$C]-TAK-906<br>Period 2:<br>50 mg (~100 µCi) [$^{14}$C]-TAK-906 | **Route of Administration:**<br>Period 1:<br>Oral (capsules)<br>IV infusion<br>Period 2:<br>Oral (solution) |
| **Duration of Treatment:**<br>Period 1:<br>On Day 1, subjects will receive a single oral dose followed by a 15 minute IV dose at ~0.75 hours post oral dose.<br>Period 2:<br>On Day 1, subjects will receive a single oral dose. | **Planned Trial Duration:**<br>Approximately 65 ± 2 days including the Screening Period and through follow-up. |

**Main Criteria for Inclusion:**

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

1. Healthy, adult, male, 19-55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to the first dosing and throughout the study.
3. Body mass index (BMI) ≥ 18.0 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 performed at the screening visit and before administration of the initial dose of trial drug, as deemed by the Investigator or designee.
5. A non-vasectomized male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days after the last dosing. (No restrictions are required for a vasectomized male provided his bilateral vasectomy procedure has been performed at least 1 year prior to the first dosing of study drug. A male who has been vasectomized less than 1 year prior to study first dosing must follow the same restrictions as a non-vasectomized male). Appropriate documentation of surgical procedures should be provided.
6. Male must agree not to donate sperm from the first dosing until 90 days after the last dosing (refer to Appendix E for detailed guidance on contraception and pregnancy avoidance procedures).
7. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

**Main Criteria for Exclusion:**

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

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiration, genitourinary, major neurological (including stroke and chronic seizures), or malignancy, or any other clinically significant abnormalities 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. Positive urine drug or cotinine, or alcohol results at screening or first check-in.
7. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
8. QTcF interval is >450 msec or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
9. Estimated creatinine clearance <90 mL/min at screening.
10. 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.
11. Subject has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
12. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks of first dosing.
13. 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 last 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).
14. 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. Acetaminophen (up to 2 g per 24 hr period) and Milk of Magnesia® (ie, magnesium hydroxide [≤ 60 mL per day after Day 3 in Period 1 and after Day 8 in Period 2]) may be permitted during the study, only after dosing, if necessary to treat AEs. Additional administration of Milk of Magnesia® may be administered on other days at discretion of the Investigator.
    - Any drugs known to significantly affect the absorption, distribution, metabolism or elimination of TAK-906 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.
15. 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.
16. Donation of blood or significant blood loss within 56 days prior to the first dosing.
17. Plasma donation within 7 days prior to the first dosing.
18. 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:** | **Main Criteria for Evaluation and Analyses:** |
|---|---|
| **Period 1 - ABA** | **Period 2 - ADME** |
| **The primary endpoint will be assessed through evaluation of the following:**<br>• Ratio of dose normalized $AUC_{\infty}$ of TAK-906 and [$^{14}$C]-TAK-906 in plasma (or $AUC_{last}$ in the case $AUC_{\infty}$ is incalculable). | **The primary endpoint will be assessed through evaluation of the following:**<br>• Cumulative recovery of radioactivity in urine (Cum%Dose[UR]) and feces (Cum%Dose[FE]) separately and both routes combined, expressed as a percent of total oral radioactive dose administered. |
| **The secondary endpoints will be assessed through evaluation of the following:**<br>• PK parameters for oral TAK-906 and M23 in plasma: $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC\%_{extrap}$, and $t_{1/2}$; for TAK-906 only in plasma: $V_z/F$, CL/F.<br>• PK parameters for IV TRA in plasma: $C_{eoi}$, $T_{max}$, | **The secondary endpoints will be assessed through evaluation of the following:**<br>• PK parameters for plasma TAK-906 and M23: $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{\infty}$, $AUC_{\%extrap}$, and $t_{1/2}$; |

| | |
|---|---|
| $AUC_{last}$, $AUC_{\infty}$, and $t_{1/2}$.<br>• PK parameters for IV [$^{14}$C]-TAK-906 in plasma: C, CL, $V_z$, $AUC_{\infty}$, $AUC_{last}$, and $t_{1/2}$.<br>CCI [redacted]<br>**The safety endpoint will be assessed through evaluation of the following:**<br>• AE reporting, laboratory tests, ECGs, and vital sign parameters after administration of a single oral dose (capsule) of TAK-906 followed by single IV microtracer dose administration of [$^{14}$C]-TAK-906. | for TAK-906 only: $V_z$/F and CL/F.<br>• PK parameters for plasma and whole blood TRA: $C_{max}$, $T_{max}$, time-matched $AUC_t$ (where t is the last common time point at which TRA and plasma TAK-906 are quantifiable in all subjects), $AUC_{\infty}$, $AUC_{last}$, and $t_{1/2}$.<br>CCI [redacted]<br>**The safety endpoint will be assessed through evaluation of the following:**<br>• AE reporting, laboratory tests, ECGs, and vital sign parameters after a single oral dose (solution) of [$^{14}$C]-TAK-906. |
| **Statistical Considerations:**<br>Descriptive statistics will be provided for the TRA (whole blood [Period 2], plasma, urine, feces [Periods 1 and 2], and if applicable, emesis [Period 2]), TAK-906 and metabolite concentrations and PK parameters (plasma and urine [Period 2]), and [$^{14}$C]-TAK-906 concentrations (plasma, urine, feces [Period 1]), and the metabolite profile of TAK-906 (plasma, urine, feces [Period 2]), using appropriate summary statistics to be fully specified in the SAP.<br>ABA of TAK-906 (Period 1) 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 $AUC_{\infty}$ between a single oral and the IV microtracer dose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose normalized $AUC_{\infty}$ geometric mean ratio (GMR); TAK-906 administered as oral dose / [$^{14}$C]-TAK-906 administered as IV microtracer dose. $AUC_{last}$ will be analyzed in a similar fashion if $AUC_{\infty}$ cannot be calculated.<br>Mass balance will be calculated as a sum of the percent of the TRA recovered in urine and feces 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 empirically without statistical considerations and is deemed adequate to meet the study objectives. In addition, this sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity. | |

## 2.0 STUDY SCHEMATIC

<table>
<tr><td>Screening</td><td colspan="4">Treatment Period 1 [a]</td></tr>
<tr><td rowspan="4">Within 28 days of first dosing on Period 1</td><td>Day -1</td><td colspan="2">Day 1</td><td>Days 2 - 7</td></tr>
<tr><td>Check-in</td><td>Oral Dosing at Hour 0</td><td>IV Dosing at Hour 0.75</td><td></td></tr>
<tr><td></td><td colspan="3">Plasma, urine, and fecal sampling for ABA and safety monitoring for at least 96 hours post oral dose [b]</td></tr>
<tr><td colspan="4">< - - - - - - - - - - - - confinement [b] - - - - - - - - - - - - ></td></tr>
<tr><td colspan="5">[a] Dosing in each period will be separated by at least 7 days.<br>[b] Subjects will be confined in the clinic until at least the morning of Day 5 (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until a discharge criterion is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to Day 7.</td></tr>
</table>

<table>
<tr><td colspan="3">Treatment Period 2 [c]</td><td>Follow-up</td></tr>
<tr><td>Day -1</td><td>Day 1</td><td>Days 2 – 15</td><td rowspan="4">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, whole blood, urine, and fecal sampling for PK, TRA, and metabolite profiling, and safety monitoring for at least 120 hours posdose, or up to approximately 336 hours postdose if discharge criteria are not met. Additional urine and feces samples may be taken in two blocks of Days 20, 21, 22 and Days 27, 28, and 29.</td></tr>
<tr><td colspan="3">< - - - - - - - - - - - - confinement [d] - - - - - - - - - - - - ></td></tr>
<tr><td colspan="4">[c] Day -1 of Period 2 may be the same day as Day 7 of Period 1.<br>[d] Subjects will be confined in the clinic until at least the morning of Day 6 and until discharge criterion is met (ie, 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 14 days postdose (ie, Day 15). After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the CRU to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 will be reviewed on a case-by-case basis. Since up to an approximate 24-hour time lag is anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.</td></tr>
</table>

## 3.0 SCHEDULE OF STUDY PROCEDURES

| Study Procedures [a] Days → | Screening [b] | Study Days in Period 1 [c] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | -1 (Check-In [d]) | 1 | 2 | 3 | 4 | 5 | 6-7 [e] |
| **Administrative Procedures** | | | | | | | | |
| Informed Consent | X | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | |
| Medical History | X | X | | | | | | |
| **Safety Evaluations** | | | | | | | | |
| Physical Examination [f] | X | X | | | | | | |
| Demographics | X | | | | | | | |
| Height | X | | | | | | | |
| Weight | X | | | | | | | |
| BMI | X | | | | | | | |
| 12-Lead Safety Electrocardiograms | X | | X [g] | | | | | X [o] |
| Vital Signs (pulse rate and blood pressure) | X | | X [g] | | | | | X [o] |
| Vital Signs (respiratory rate and temperature) | X | | X [g] | | | | | X [o] |
| Hematology, Serum Chemistry [h], and Urinalysis | X | X | | | X | | | X [o] |
| Urine Drug and Alcohol Screen | X | X | | | | | | |
| Urine cotinine screen | X | X | | | | | | |
| Human immunodeficiency virus /Hepatitis Screen | X | | | | | | | |
| Adverse Event Monitoring | X | | | | | | | X |
| Concomitant Medication Monitoring/Medication History | X | X | | | | | | X |
| **Study Drug Administration / Pharmacokinetics** | | | | | | | | |
| TAK-906 Administration (oral) | | | X [i] | | | | | |
| [$^{14}$C]-TAK-906 Administration (intravenous infusion) | | | X [j] | | | | | |
| Blood for TAK-906 and M23 Plasma pharmacokinetics [k] | | | X | X | X | X | X | |
| Blood for [$^{14}$C]-TAK-906 Plasma Pharmacokinetics and for Total | | | X | X | X | X | X | |

| **Study Procedures** [a] **Days →** | **Screening** [b] | **Study Days in Period 1** [c] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **-1 (Check-In** [d]**)** | **1** | **2** | **3** | **4** | **5** | **6-7** [e] |
| Radioactivity Plasma Pharmacokinetics [k] | | | | | | | | |
| Urine for [$^{14}$C]-TAK-906 Pharmacokinetics and for Total Radioactivity [l] | | X | | | | | | X |
| Feces for [$^{14}$C]-TAK-906 Pharmacokinetics and for Total Radioactivity [l] | | X | | | | | | X |
| **Other Procedures** | | | | | | | | |
| Confinement in the Clinical Research Unit [e, m] | | X | | | | | | X |
| Visit | X | | | | | | | |

| **Study Procedures** [a] | **Study Days in Period 2** [c] | | | | | | | | | | | | **FU** [n] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **-1 (C-I** [d]**)** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11-15** | |
| **Safety Evaluations** | | | | | | | | | | | | | |
| Physical Examination [f] | X | | | | | | | | | | | | |
| 12-Lead Safety Electrocardiogram | | X [g] | | | | | | | | | | X [o] | |
| Vital Signs (pulse rate and blood pressure) | | X [g] | | | | | | | | | | X [o] | |
| Vital Signs (respiratory rate and temperature) | | X [g] | | | | | | | | | | X [o] | |
| Hematology, Serum Chemistry [h], and Urinalysis | X | | | X | | | | | | | | X [o] | |
| Urine Drug and Alcohol Screen | X | | | | | | | | | | | | |
| Adverse Event Monitoring | X | | | | | | | | | | | | |
| Concomitant Medication Monitoring | X | | | | | | | | | | | | |
| **Study Drug Administration / Pharmacokinetics** | | | | | | | | | | | | | |
| [$^{14}$C]- TAK-906 Administration (oral) | | X [e] | | | | | | | | | | | |
| Blood for Total Radioactivity whole blood Pharmacokinetics [p] | | X | X | X | X | X | X | | X | | | X | |
| Blood for Total Radioactivity Plasma Pharmacokinetics [p] | | X | X | X | X | X | X | | X | | | X | |
| Blood for TAK-906 and M23 Plasma Pharmacokinetics [p] | | X | X | X | X | X | X | | X | | | X | |
| Blood for TAK-906 Plasma Metabolite Profiling [p] | | X | X | X | X | X | X | | X | | | | |
| Urine for Total Radioactivity, Metabolite Profiling, and TAK-906 and M23 Pharmacokinetics [q] | X | | | | | | | | | | | | |
| Feces for Total Radioactivity and Metabolite Profiling [q] | X | | | | | | | | | | | | |
| **Other Procedures** | | | | | | | | | | | | | |
| Taste Questionnaire [r] | | X | | | | | | | | | | | |
| Confinement in the CRU [s] | X | | | | | | | | | | | | |
| Phone call | | | | | | | | | | | | | X |

[a] For details on Procedures, refer to Section 9.0.
[b] Within 28 days prior to the first dosing.
[c] There will be a washout period of at least 7 days between the dose in Period 1 and the dose in Period 2. Day -1 of Period 2 may be the same day as Day 7 of

Period 1.

[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, cotinine test, vital signs, and ECGs) may not be performed, following a decision by Investigator.

[e] Subjects who do not meet a discharge criterion in Period 1 (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) by Day 5, will remain confined and undergo study procedures until a discharge criterion is met or up to Day 7.

[f] A full physical examination will be conducted at screening. Abbreviated physical examinations are to be conducted on Day -1 of each period. These examinations will be repeated at the discharge day in Period 2 (ie, Day 15 or earlier). If the subject is required to return to the clinic facility to collect urine and fecal samples in two blocks of 24 hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 at the discretion of the Sponsor, those exams will be repeated at the applicable block discharge day. Symptom-driven physical examination may be performed at additional times, at the Investigator's or designee's discretion. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis.

[g] 12-Lead ECG and Vital signs (ie, pulse rate and blood pressure) are to be assessed within 24 hours prior to Day 1 oral dosing and at 1- and 4-hour post oral drug administration on Day 1; Vital signs (ie, respiratory rate and temperature) are to be assessed within 24 hours prior to Day 1 oral dosing, and at 4-hour post oral drug administration on Day 1. All ECG and vital sign assessments will be performed after the subjects have rested for at least 5 minutes.

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

[i] Oral drug administration will be performed at Hour 0 of Day 1.

[j] A 15 minute IV drug administration will begin at approximately 45 minutes post oral dose (Hour 0.75) on Day 1 of Period 1.

[k] For a detailed blood sampling schedule refer to Table 3.a.

[l] For a detailed urine and fecal sampling schedule refer to Table 3.b.

[m] As per site preference, subjects may be confined throughout the washout period. If subjects are confined throughout the washout period, some safety events at check-in of Period 2 (eg, clinical laboratory tests, urine drug and alcohol screen, cotinine test, vital signs, and ECGs) may not be performed, following a decision by the Investigator.

[n] The clinic will contact via phone call 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 subjects may be requested to return the site for further safety assessment, due to reported AEs, at the Investigator's discretion.

[o] To be performed at the end of Period 1 or Period 2 (prior to discharge) or prior to early termination from the study.

[p] For a detailed blood sampling schedule refer to Table 3.c.

[q] For a detailed urine and fecal sampling schedule refer to Table 3.d.

[r] A taste questionnaire will be completed within 5 minutes of [$^{14}$C]-TAK-906 administration.

[s] Subjects will remain confined to the CRU until at least the morning of Day 6 in Period 2. If discharge criteria are not met within 5 days post dose, the subject will continue to stay in the clinic until a discharge criterion is met (ie, ≥ 90% of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24-hour interval for at least 2 consecutive

intervals) or up to a maximum of 14 days postdose (ie, day 15) is reached, whichever occurs first. Subjects can be released after Day 15 collection of excreta. After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the clinic facility to collect urine and fecal samples in two blocks of 24-hour period on Days 20, 21, or 22 and Days 27, 28, or 29 at the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis.

Abbreviations: CRU = Clinical Research Unit, ECG = Electrocardiogram, IV = Intravenous.

## Table 3.a Blood and Plasma Sampling Schedule (Period 1 - ABA Study Period)

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

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

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

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

[a] Urine sample for TRA and [$^{14}$C]-TAK-906.
[b] Feces sample for TRA and [$^{14}$C]-TAK-906.
[c] Predose urine sample is to be obtained within 24 hours prior to IV infusion and prior to oral dosing. Predose samples should be stored separately away from the postdose samples to avoid cross contamination.
[d] Predose fecal sample is to be obtained within 48 hours prior to oral dosing. Subjects will be asked to bring a fecal sample at check-in (if produced within 48 hours prior to oral dosing). Feces produced between check-in and dosing will also be collected as a predose sample with the sample produced nearest to oral dosing to be retained as the only predose sample. Predose samples should be stored separately away from the postdose samples to avoid cross contamination.
[e] Including the urine and fecal sample collected on the morning of Day 5 (ie, Hour 96, as/when passed) prior to release.
[f] Collection only for subjects who have not met discharge criteria.

**Table 3.c Blood and Plasma Sampling Schedule (Period 2 - ADME Study Period)**

| Time (hour) (Relative to Oral Dosing) | Sample Collection | | |
|---|---|---|---|
| Matrix | Blood 1 [a] | Plasma 1 [b], Plasma 2 [b] | Plasma 3 [b] |
| 0 (predose) (c) | X | X | X |
| 0.5 hr postdose (±2 min) | X | X | X |
| 1 hr postdose (± 2 min) | X | X | X |
| 1.5 hr postdose (± 2 min) | X | X | |
| 2 hr postdose (± 2 min) | X | X | X |
| 3 hr postdose (± 2 min) | X | X | |
| 4 hr postdose (± 2 min) | X | X | X |
| 6 hr postdose (± 2 min) | X | X | |
| 8 hr postdose (± 2 min) | X | X | X |
| 12 hr postdose (± 5 min) | X | X | X |
| 24 hr postdose (± 5 min) | X | X | X |
| 48 hr postdose (± 10 min) | X | X | X |
| 72 hr postdose (± 10 min) | X | X | X |
| 96 hr postdose (± 15 min) | X | X | X |
| 120 hr postdose (± 15 min) | X | X | X |
| 168 hr postdose (± 1 hr) (d) | X | X | X |
| 240 hr postdose (± 1 hr) (d) | X | X | |
| 336 hr or before discharge (± 1 hr) (d) | X | X | |

[a] Blood sample for TRA (Blood 1).

[b] Plasma sample for TAK-906 PK and M23 metabolite (Plasma 1), Plasma sample for TRA (Plasma 2), and plasma sample for metabolite profiling (Plasma 3).

[c] Predose blood and plasma samples should be stored separately away from the postdose samples to avoid cross contamination.

[d] Collection only for subjects confined beyond the morning of Day 6 (ie, Hour 120) and not discharged at the collection time.

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

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

[a] Urine sample for TAK-906 and M23 PK (Urine 1); Urine sample for TRA and urine sample for metabolite profiling (Urine 2).

[b] Feces sample for TRA and feces sample for metabolite profiling (Feces).

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

[d] Predose fecal sample is to be obtained within 48 hours prior to dosing. If applicable, for subject(s) who are released in Period 1 and return for Period 2, subjects will be asked to bring a fecal sample at check-in (if produced within 48 hours prior to dosing). Feces produced between check-in and dosing will also be collected as a predose sample with the sample produced nearest to dosing to be retained as the only predose sample. Predose fecal samples should be stored separately away from the postdose samples to avoid cross contamination.

(e) Including the urine and fecal sample collected on the morning of Day 6 (ie, Hour 120, as/when passed) prior to release.

(f) Collected for subjects who have not met the discharge criteria. Samples will continue to be collected in 24-hour intervals until a discharge criterion is met (ie, 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24 hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 14 days postdose (ie, Day 15). After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the CRU to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis.

# 4.0 INTRODUCTION

## 4.1 Background

The intended indication for TAK-906 is to treat patients with gastroparesis, a disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction. Symptoms are chronic and include nausea, vomiting, early satiety, abdominal pain, and postprandial fullness with episodic exacerbation [1]. The prevalence of gastroparesis in the United States (US) is estimated to be approximately 24.2 per 100,000 [2]. In cases of chronic gastroparesis, diabetic (29%), postsurgical (13%), and idiopathic (36%) etiologies comprise the majority of cases in the tertiary referral setting [3].

TAK-906 is a peripherally selective (eg, limited penetration of the blood brain barrier [BBB]) dopamine D2/D3 receptor antagonist. It has demonstrated suitable PK and pharmacodynamic (PD) activity in a phase 1 study and other completed studies. Therefore TAK-906 is expected to reduce nausea and vomiting, without the side effects which restrict the use of other D2/D3 antagonists. Because of its low BBB penetration and a weak human Ether-a-go-go-Related Gene channel affinity indicative of a low potential cardiac risk, TAK-906 is anticipated to have an improved safety profile, compared to other D2/D3 antagonists (eg, metoclopramide and domperidone).

To date, at least 259 subjects have been dosed in the completed and ongoing clinical studies in the TAK-906 program, of which approximately 149 subjects have received at least 1 dose of active treatment with TAK-906. The results from these clinical studies indicate that TAK-906 was well tolerated with no significant safety issues attributed to TAK-906 in healthy subjects, patients with diabetic gastroparesis, or with idiopathic gastroparesis.

To date, 5 clinical studies have been completed: a phase 1 randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study to evaluate the safety, PK, PD, effect of food, and optimal oral dose of TAK-906M in healthy subjects (Study AT-01C), a phase 1 itraconazole-interaction study in healthy subjects (Study TAK-906-1003), a phase 1 SAD and MAD study in Japanese healthy male subjects in Japan (Study TAK-906-1004), a phase 1 drug-drug interaction study with esomeprazole (Study TAK-906-1006), and a phase 2 randomized, double-blind and open-label, placebo- and active-comparator controlled study to evaluate the safety, PK, and PD of TAK-906 in subjects with diabetes mellitus and gastroparesis or idiopathic gastroparesis (TAK-906-1002).

**Preclinical Pharmacokinetics**

Following oral administration of [$^{14}$C]-TAK-906M at 3.66 mg/kg (3 mg/kg as TAK-906) to fasted male rats and dogs, the $t_{1/2z}$ values of TRA were 1.6 and 6.1 hours, respectively. TAK-906 radioactivity was almost completely eliminated from circulation by 24 and 120 hours in rats and dogs, respectively. Excretion of radioactivity in male rats was almost complete by 48 hours, with 6.0% and 94.7% of the dosed radioactivity excreted in urine and feces, respectively, and 0.0% excreted in expired air. In bile duct-cannulated rats, 86.0%, 5.1%, and 11.0% of the dosed radioactivity were excreted into bile, urine, and feces, respectively, by 24 hours. Thus, biliary excretion represented the major excretion route for TAK-906 and related substances in rats.

Similarly, in fasted male dogs, urinary and fecal excretion of TAK-906 were 8.0% and 91.3%, respectively, over 96 hours.

TAK-906 is a substrate of P-glycoprotein and organic anion transporting polypeptide (OATP) 1B1 and OATP1B3. Further uptake and kinetic studies using OATP1B1/1B3-expressing cells and human hepatocytes as a reference of pravastatin suggested that almost all the in vivo TAK-906 uptake into human hepatocytes is by a saturable process of transporters, not by a passive process and TAK-906 is taken up into the human hepatocytes predominantly by OATP1B1.

The in vitro metabolism showed that TAK-906 was mainly metabolized by cytochrome P450 (CYP)3A4/5 and CYP2C8. M23 (pharmacologically inactive) was the metabolite formed by human liver cytosol, but not formed by CYP-expressing microsomes. The relative contribution ratio of CYP and non-CYP toward in vitro metabolism of TAK-906 using human hepatic S9 with or without typical CYP inhibitor was 43.3% and 56.7%, respectively.

**Clinical Pharmacokinetics**

In Study AT-01C, TAK-906M was administered as a single oral dose (ranging from 5 to 300 mg) and repeated oral doses (ranging from 50 to 100 mg twice daily) for 5 days to healthy male and female non-Japanese subjects. Additionally, the effect of food on the PK of TAK-906 was evaluated at a single dose level of 25 mg TAK-906M in this study. TAK-906 showed rapid absorption and rapid elimination following oral administration. Median Tmax was ~1.1 hours postdose. The half-life (mean) following a single oral dose was ~4 hours when administered in the fasted state. Following administration of single oral doses of TAK-906 maleate between 5 and 300 mg, exposure to TAK-906 increased in a manner generally proportional to dose increment. Food had a significant impact on reducing the exposure to TAK-906 in healthy subjects. The ratio of geometric LS means for Cmax was 58.06% (90% CI: 38.97% to 86.51%) for the test (fed) to reference (fasting) doses. For $AUC_{\infty}$ and $AUC_{12}$, the ratios were 58.23% (90% CI: 45.08% to 75.21%) and 53.69% (90% CI: 42.79% to 67.37%), respectively. Confidence interval testing showed that all parameters were below and generally outside the comparison interval of 80% to 125%.

Drug-drug interaction potential of TAK-906 was evaluated. Coadministration of itraconazole, 200 mg for 5 days, with TAK-906 maleate increased TAK-906 mean $C_{max}$ by approximately 2.0-fold and $AUC_{\infty}$ by approximately 1.3-fold. TAK-906 is not classified as a sensitive CYP3A4 substrate. Following coadministration of esomeprazole (40 mg oral capsule) and TAK-906 (25 mg oral capsule) to healthy subjects, the $AUC_{last}$, $AUC_{\infty}$, and $C_{max}$ of TAK-906 decreased approximately 12 to 13% compared to TAK-906 administration alone. The $AUC_{last}$ and $AUC_{\infty}$ of M23 were similar, but the $C_{max}$ of M23 increased by approximately 20% when TAK-906 was coadministered with esomeprazole compared to TAK-906 administration alone.

Refer to the TAK-906 Investigator's Brochure for complete information on the investigational product [4].

## 4.2 Rationale for the Proposed Study

The primary purposes of the present study are to characterize the ABA (Period 1) and the absorption, distribution, metabolism, excretion, and mass balance of TAK-906 after single oral administration (Period 2) in healthy adult male subjects, by collecting plasma and urine samples for TAK-906 and M23 analysis, plasma, urine, whole blood, and fecal samples for TRA analysis and, plasma, urine, and fecal samples for metabolite profiling. The study will provide data required to evaluate the ABA, mass balance, and the metabolite profile of TAK-906 in humans.

## 4.3 Benefit/Risk Profile

The single dose of 50 mg TAK-906 is selected for this study and has been demonstrated to be safe and well tolerated in healthy subjects in studies conducted to date (IB, 2018).

The estimated radiation dose from a single IV administration of [$^{14}$C]-TAK-906 (~1 μCi) and a single oral dose of [$^{14}$C]-TAK-906 (~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, 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

Not applicable.

## 5.2 Trial Objectives

### 5.2.1 Trial Primary Objectives

**Trial Primary Objective – Period 1 (ABA):**

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

**Trial Primary Objective – Period 2 (ADME):**

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

### 5.2.2 Trial Secondary Objectives

**Trial Secondary Objectives – Period 1 (ABA):**

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

**Trial Secondary Objectives – Period 2 (ADME):**

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

CCI

[redacted]

CCI

[redacted]

### 5.2.4 Trial Safety Objectives

**Trial Safety Objective - Period 1 (ABA):**

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

**Trial Safety Objective - Period 2 (ADME):**

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

## 5.3 Endpoints

### 5.3.1 Primary Endpoints

**Period 1 (ABA)**:

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

**Period 2 (ADME):**

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

### 5.3.2 Secondary Endpoints

**Period 1 (ABA):**

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

**Period 2 (ADME):**

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

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[redacted]

### 5.3.4 Safety Endpoints

**Period 1 (ABA):**

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

**Period 2 (ADME):**

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

# 6.0 TRIAL DESIGN AND DESCRIPTION

## 6.1 Trial Design

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

On Day 1 of Period 1 (ABA Study Period), after at least a 10-hour fast, 6 subjects will receive a single unlabeled oral 50 mg dose of TAK-906 as capsules. At approximately 45 minutes post oral dosing (0.75 hour) (ie, 15 minutes prior to the median $t_{max}$ for the oral unlabeled dose [~ 1.1 hours]), subjects will receive a 15-minute IV infusion of a microtracer dose of 100 µg (approximately equivalent to 1 µCi ~[1 µCi]) [$^{14}$C]-TAK-906. Serial blood sampling will be performed to determine the PK of TAK-906 and its metabolite (M23) in the plasma for the oral dose and TRA and PK of [$^{14}$C]-TAK-906 in the plasma for the IV dose. Urine and fecal output will also be collected up to the morning of Day 5 (ie, Hour 96) to determine TRA levels and [$^{14}$C]-TAK-906 PK and until a discharge criterion is met (ie, 80% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24-hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) but no less than Day 5 for [$^{14}$C]-TRA excretion in urine and feces.

In Period 1, subjects will be confined in the CRU for at least 5 days (until after the last PK sample and morning urine and fecal sample [when passed] are collected) and until discharge criterion is met or up to Day 7. Subjects will return to the clinic on Day -1 of Period 2 for Check-in procedures. There will be a washout period of at least 7 days between the dose in Period 1 and the dose in Period 2. As per site preference, subjects may be confined throughout the washout period.

On Day 1 of Period 2 (ADME Study Period), after at least a 10-hour fast, the subjects will receive a single dose of 50 mg (~100 µCi) [$^{14}$C]-TAK-906 as an oral solution. Serial blood sampling and urine and feces output will be collected. PK of TAK-906 and its metabolite, M23, will be determined in plasma and urine; plasma, whole blood, urine, and feces will be collected for TRA determination; and plasma, urine, and feces will be collected to characterize the metabolite profiles of TAK-906. Complete urinary and fecal output will be collected until at least the morning of Day 6 (ie, Hour 120). Subjects will be confined in the clinic until at least this time and until a discharge criterion is met (ie, 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples or the excretion of radioactivity in the urine and feces combined has declined to ≤1% of the total administered radioactivity per 24 hour interval for at least 2 consecutive intervals where both a urine and fecal sample are collected) or up to 14 days postdose (ie, Day 15). After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the CRU to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis. In each of the 2 consecutive intervals, both urine and fecal samples have to be collected and counted for TRA, ie, if only urine or feces is collected in a day, this day is not considered to be one of the 2 consecutive intervals. Since up to an approximate 24-hour time lag is

anticipated for radioactivity counting of samples, actual subject release from the CRU may occur 1 day after discharge criteria are met.

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

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

The planned dose levels of TAK-906 to be evaluated are outlined in Table 6.a.

**Table 6.a Planned TAK-906 and [$^{14}$C]-TAK-906 Doses**

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

## 6.2 Dose Escalation

Not applicable.

## 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-906 will be estimated using a labeled IV microtracer administered at ~0.75 hours ie, approximately 45 min post oral dose (over approximately 15 minutes) after an unlabeled oral dose in order to characterize the disposition properties of TAK-906. In order to determine ABA accurately and reliably, a healthy adult population is chosen.

Characterization of the disposition of a drug following IV administration facilitates the understanding of fundamental aspects of TAK-906'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-906.

In Period 2 of the study, characterization of the absorption, distribution, metabolism, excretion, and mass balance of TAK-906 after oral administration of a single 50 mg (~100 µCi) [$^{14}$C]-TAK-906 will be achieved by collecting plasma and urine samples for drug concentration analysis; plasma, whole blood, urine, and fecal samples for TRA analysis; and plasma, urine, and

feces for metabolite profiling The study will provide data required to evaluate the mass balance and the metabolite profile of TAK-906 in humans.

### 6.3.2 Rationale for Dose

A single oral dose of 50 mg of unlabeled and [$^{14}$C]-TAK-906 will be used in the study in Periods 1 and 2. This is the highest dose of TAK-906 which is being evaluated in a dose range phase-IIb trial in gastroparesis patients. Safety and tolerability of TAK-906 were studied up to a single dose of 300 mg and 100 mg twice daily for 4 days via the oral route in healthy subjects and found to be safe and tolerable.

Radiolabeled doses [$^{14}$C] were administered to male Sprague-Dawley and Long-Evans rats (blood and pigmented skin only). Tissue concentration versus time profiles showed that elimination/tissue release of radioactivity from all tissues was generally very rapid and concentrations for many tissues were below the limit of quantitation (BLQ).

The calculated radiation absorbed doses were relatively low (< 2.000 mrem and < 0.020 mSv) for most tissues (except bladder) for male human subjects following a single oral dose of [$^{14}$C]TAK-906 of 100 μCi. The highest estimated absorbed dose was in the bladder, which had a value of 4.854 mrem (0.049 mSv) and represented 0.097% of the allowable 5000 mrem United States (US)-Food and Drug Administration (FDA) exposure limit for a single tissue. In descending order, the next highest radiation absorbed doses (> 0.200 mrem) were in the small intestine (1.270 mrem, 0.013 mSv), the liver (0.917 mrem, 0.009 mSv), the mesenteric lymph node (0.221 mrem, 0.002 mSv), and the kidney (0.219 mrem, 0.002 mSv). Blood, blood-forming organs, and lymph nodes each had an estimated dose of ≤ 0.221 mrem (0.002 mSv), which represented 0.0074% of the allowable 3000 mrem US-FDA exposure limit. Radioactive concentrations in the eyes and testis (gonads) were BLQ at all sampled time-points, which represented 0% of the allowable 3000 mrem exposure limit. The overall human male whole-body exposure was calculated to be 0.3143 mrem (0.0031 mSv), which represented approximately 0.010% of the allowable 3000 mrem US-FDA exposure limit, and 0.31% of the allowable 1 mSv ICRP (International Committee on Radiation Protection) limit and is considered to be safe. A single oral dose of up to 100 μCi (3.70 MBq) of [$^{14}$C]-TAK-906 is not expected to represent a major whole-body radiation exposure risk to human male subjects as defined in the US-FDA and ICRP guidelines.

### 6.3.3 Rationale for Endpoints

Not applicable

### 6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this study, the blood, plasma, urine, and feces collections for total radioactivity, plasma and urine concentrations, and plasma, urine, and feces for metabolite profiling for TAK-906 and M23, as appropriate, are the critical procedures and are required to be collected, as appropriate, as close to the scheduled times defined in this protocol as possible.

## 6.4 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 subjects must be discontinued for the reasons described in Section 7.5.

## 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*

Not Applicable.

*6.5.6.2 Procedures for Premature Termination or Suspension of a Site*

Not Applicable.

# 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

## 7.1 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 3 months prior to the first dosing and throughout the study.
3. BMI $\geq$ 18.0 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 performed at the screening visit and before administration of the initial dose of trial drug, as deemed by the Investigator or designee.
5. A non-vasectomized male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days after the last dosing. (No restrictions are required for a vasectomized male provided his bilateral vasectomy procedure has been performed at least 1 year prior to the first dosing of study drug. A male who has been vasectomized less than 1 year prior to study first dosing must follow the same restrictions as a non-vasectomized male). Appropriate documentation of surgical procedures should be provided.
6. Male must agree not to donate sperm from the first dosing until 90 days after the last dosing (refer to Appendix E for detailed guidance on contraception and pregnancy avoidance procedures).
7. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

## 7.2 Exclusion Criteria

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

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiration, genitourinary, major neurological (including stroke and chronic seizures), or malignancy, or any other clinically significant abnormalities 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. Positive urine drug or cotinine, or alcohol results at screening or first check-in.
7. Positive results at screening for HIV, HBsAg, or HCV.
8. QTcF interval is >450 msec or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
9. Estimated creatinine clearance <90 mL/min at screening.
10. 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.
11. Subject has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
12. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks of first dosing.
13. 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 last 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).
14. 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. Acetaminophen (up to 2 g per 24 hr period) and Milk of Magnesia® (ie, magnesium hydroxide [≤ 60 mL per day after Day 3 in Period 1 and after Day 8 in Period 2]) may be permitted during the study, only after dosing, if necessary to treat AEs. Additional administration of Milk of Magnesia® may be administered on other days at discretion of the Investigator.
    - Any drugs known to significantly affect the absorption, distribution, metabolism or elimination of TAK-906 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.
15. 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.
16. Donation of blood or significant blood loss within 56 days prior to the first dosing.
17. Plasma donation within 7 days prior to the first dosing.

18. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

## 7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2.

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

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

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

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

| Category | Between Screening and First Dosing (Days -28 to predose [Day 1 Period 1]) | Post-First Dosing (Day 1 Period 1) to Follow-Up |
|---|---|---|
| **Alcohol** | Prohibited from 48 hours prior to first dosing. | Prohibited until end of PK collection in Period 2 |
| **Xanthine and/or caffeine** | Prohibited from 24 hours prior to first dosing [a] | Prohibited 24 hours prior to each dosing until end of PK collection in each period [a] |
| **Medications** | See Sections 7.2 and 7.3 [b] | See Sections 7.2 and 7.3 [b] |
| **Food substance** | | |
| **Grapefruit/Seville orange** | Prohibited from 14 days prior to first dosing | Prohibited until end of PK collection in Period 2 |

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

[b] Acetaminophen (up to 2 g per 24 hr period) and Milk of Magnesia® (ie, magnesium hydroxide [≤ 60 mL per day after Day 3 in Period 1 and after Day 8 in Period 2]) may be permitted during the study, only after dosing, if necessary to treat AEs. Additional administration of Milk of Magnesia® may be administered on other days at discretion of the Investigator.

## 7.4 Diet, Fluid, Activity

### 7.4.1 Diet and Fluid

Water (except water provided with each oral dosing) will be restricted 1 hour prior to and 1 hour after each oral study drug administration, but will be allowed *ad libitum* at all other times, 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 following the oral study drug administration.

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

### 7.4.2 Activity

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

## 7.5 Criteria for Discontinuation or Withdrawal of a Subject

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

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

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

Any subject who experiences emesis within 3 hours post the oral dose 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 TRA.

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

## 7.6 Procedures for Discontinuation or Withdrawal of a Subject

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

## 7.7 Subject Replacement

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

# 8.0 CLINICAL STUDY MATERIAL MANAGEMENT

## 8.1 Clinical Study Drug

### TAK-906 Capsule

A single unlabeled 50 mg dose of TAK-906 capsules will be administered in Period 1 of the study.

The drug product, TAK-906 capsules, for oral administration consists of TAK-906 maleate (TAK-906M), nominally 50 mg of TAK-906 (free base) per capsule, along with microcrystalline cellulose.

### [$^{14}$C]-TAK-906 IV Sterile Solution

An IV dose of approximately 100 µg [$^{14}$C]-TAK-906 (~1 µCi) will be administered at ~0.75 hours (ie, ~45 min) after the TAK-906 oral dose in Period 1 of the study.

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

### [$^{14}$C]-TAK-906 Oral Solution

A dose of 50 mg [$^{14}$C]-TAK-906 (~100 µCi) as an oral solution will be administered in 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.

### 8.1.1 Clinical Study Drug Labeling

All study drug preparations will be affixed with a clinical label in accordance with local regulatory requirements.

### 8.1.2 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of TAK-906 products to allow completion of this study.

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

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

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied. All TAK-906 products will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

### 8.1.3 Clinical Study Drug Blinding

This is an open-label study.

### 8.1.4 Randomization Code Creation and Storage

Not applicable.

### 8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

Not applicable.

### 8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Not applicable.

# 9.0 STUDY PROCEDURES

## 9.1 Administrative Procedures

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 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.

### 9.1.2 Study Drug Assignment

This is a fixed-sequence study. All subjects will receive the same treatments as detailed in Table 6.a.

### 9.1.3 Inclusion and Exclusion

Please refer to Sections 7.1 and 7.2.

### 9.1.4 Medical History/Demography

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

### 9.1.5 Concomitant Medications

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

## 9.2 Clinical Procedures and Assessments

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

For this study, the collection for blood, plasma, urine, and feces for TRA, TAK-906, M23, and [$^{14}$C]-TAK-906 concentrations, and for metabolite profiling, as appropriate, 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

Full and abbreviated physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). An abbreviated physical examination will include at the minimum, examination of respiratory, cardiovascular, and gastrointestinal systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

### 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 pulse 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 pulse 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. All vital sign assessments will be performed after the subjects have rested for at least 5 minutes.

Blood pressure, pulse rate, respiratory rate, and temperature will be measured within 24 hours prior to Day 1 oral 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 assessments will be performed after the subjects have rested for at least 5 minutes. All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within 24 hours prior to Day 1 oral 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 Taste Questionnaire

Subjects will complete a taste questionnaire (Appendix A) evaluating the taste of the TAK-906 oral solution administered in Period 2. The questionnaire will be completed within 5 minutes of dosing.

### 9.2.7 Study Drug Administration

TAK-906 oral capsule and [$^{14}$C]-TAK-906 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-906 capsules.

Treatments A and B are described as follows:

Treatment A: 50 mg TAK-906 capsules administered at Hour 0 on Day 1 followed by a 100 µg (~1 µCi) [$^{14}$C]-TAK-906 IV infusion administered at Hour 0.75 for approximately 15 minutes (Period 1).

Treatment B: 50 mg (~100 µCi) [$^{14}$C]-TAK-906 oral solution administered at Hour 0 on Day 1 (Period 2).

The oral doses of TAK-906 and [$^{14}$C]-TAK-906 will be administered following an overnight fast with approximately 240 mL of water. The total volume of liquid administered will not exceed 240 mL. The exact clock time of oral dosing will be recorded.

The start and end time of the IV infusion will be recorded.

The pharmacy at the CRU will provide for each subject, the IV dose and the oral capsule dose (in individual unit dose containers) for dosing in Period 1, and the oral solution dose (prepared in a dosing container) for dosing in Period 2.

### 9.2.8 AE Monitoring

Subjects will be monitored throughout the study for AEs 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**

Chemistry evaluations will consist of the following standard chemistry panel:

| | |
|---|---|
| Total protein | Sodium |
| Blood urea nitrogen | Potassium |
| Bilirubin (total and direct) | Chloride |
| Alkaline phosphatase | Glucose |
| Aspartate aminotransferase *** | Creatinine** |
| Alanine aminotransferase*** | |
| Albumin | |

* Serum chemistry tests will be performed after at least a 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.

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

*** Coagulation tests (prothrombin/international normalized ratio) will be performed if subjects have on-study aspartate aminotransferase or alanine aminotransferase elevated ≥3x the upper limit of normal.

*Urinalysis*

Urinalysis will consist of the following tests:

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

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

## 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).

**Table 9.a Primary Specimen Collections**

| Specimen Name | Primary Specimen | Primary Specimen Derivative | Description of Intended Use | Sample Collection |
|---|---|---|---|---|
| **Period 1** | | | | |
| Plasma for TAK-906 and M23 PK | Plasma | | PK analysis | Mandatory |
| Plasma for TRA and [$^{14}$C]-TAK-906 PK | Plasma | | TRA and PK analysis | Mandatory |
| Urine for TRA and [$^{14}$C]-TAK-906 PK | Urine | | TRA recovery and PK analysis | Mandatory |
| Feces for TRA and [$^{14}$C]-TAK-906 PK | Feces | | TRA recovery and PK analysis | Mandatory |
| **Period 2** | | | | |
| Blood for TRA | Whole Blood | | TRA | Mandatory |
| Plasma for TRA | Plasma | | TRA | Mandatory |
| Plasma for TAK-906 and M23 PK | Plasma | | PK analysis | Mandatory |
| Plasma for TAK-906 Metabolite Profiling | Plasma | | Metabolite profiling | Mandatory |
| Urine for TRA | Urine | | TRA | Mandatory |
| Urine for TAK-906 and M23 PK | Urine | | PK analysis | Mandatory |
| Urine for TAK-906 Metabolite Profiling | Urine | | Metabolite profiling | Mandatory |
| Feces for TRA | Feces | | TRA | Mandatory |
| Feces for TAK-906 Metabolite Profiling | Feces | | Metabolite 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-906 and metabolite concentrations (Periods 1 and 2) following oral administration will be calculated as follows, as appropriate and not limited to:

| | |
|---|---|
| $AUC_{last}$: | 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. |
| $AUC_{\infty}$: | The area under the concentration versus time curve, from time 0 extrapolated to infinity. $AUC_{\infty}$ is calculated as $AUC_t$ plus the ratio of the last measurable blood concentration to the elimination rate constant. |
| $AUC_t$: | The area under the concentration-time curve from time 0 to time of the last common time point "t" at which total radioactivity and TAK-906 are quantifiable for all subjects. |
| $AUC_{\%extrap}$: | Percent of $AUC_{\infty}$ extrapolated, represented as $(1 - AUC_t/AUC_{\infty})*100$. |
| CL/F: | Apparent total plasma clearance after oral (extravascular) administration, calculated as $Dose/AUC_{0-\infty}$ (parent only) |
| $C_{max}$: | 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 $0.693/K_{el}$. |
| $V_z/F$: | Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as $Dose/(AUC_{0-\infty} \times Kel)$ (parent only) |
| $K_{el}$: | $K_{el}$ 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-906 and plasma radioactivity concentration equivalents following IV infusion (Period 1) will be calculated as follows, as appropriate and not limited to:

$AUC_{last}$: 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.

$AUC_{\infty}$: The area under the concentration versus time curve, from time 0 extrapolated to infinity. $AUC_{\infty}$ is calculated as $AUC_t$ plus the ratio of the last measurable blood concentration to the elimination rate constant.

$AUC_{\%extrap}$: Percent of $AUC_{\infty}$ extrapolated, represented as $(1 - AUC_t/AUC_{\infty})*100$.

$C_{eoi}$: Concentration at the end of infusion.

CL: Total clearance after intravenous administration.

$t_{½}$: Apparent first-order terminal elimination half-life will be calculated as $0.693/K_{el.}$

$K_{el}$: 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).

$V_{ss}$: Volume of distribution during the terminal disposition phase after intravenous administration.

In all above-listed PK parameter calculations, no value for $K_{el}$, $AUC_{\infty}$, $AUC_{\%extrap}$, $t_{½}$, CL/F, $V_z$/F, CL, or $V_{ss}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile and $AUC_{last}$ would be used for the further calculations, wherever necessary if $AUC_{\infty}$ would not be available.

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-906 (Period 1) will be calculated as follows:

F: Absolute bioavailability, calculated for plasma TAK-906, calculated as:

Dose (IV) x $AUC_{\infty}$ (oral) / Dose (oral) x $AUC_{\infty}$ (IV).

%F: Percent absolute bioavailability, calculated for plasma TAK-906 as [Dose (IV) x $AUC_{\infty}$ (oral)] / [Dose (oral) x $AUC_{\infty}$ (IV)] x 100.

If $AUC_{\infty}$ cannot not be calculated, $AUC_{last}$ will be used for the F determination.

*9.3.1.2 Urine for PK Measurements*

PK parameters for urine concentrations of [$^{14}$C]-TAK-906 (Period 1; IV dose), for urine TAK-906 and metabolite concentrations (Period 2), and for urine TRA (Periods 1 and 2) will be calculated as follows, as appropriate:

| | |
|---|---|
| $Ae_{t1-t2}$: | Amount of unchanged drug excreted in the urine collection interval from $t_1$ to $t_2$. |
| Ae(UR): | Cumulative amount of TRA excreted in urine. |
| %Dose(UR): | Percent of administered radioactive dose excreted in urine within a given collection interval. |
| Cum%Dose(UR): | Cumulative percent of administered dose excreted in urine. |

CCI [redacted]

TRA excreted in urine will be presented in mass equivalent units.

*9.3.1.3 Feces for PK Measurements*

PK parameters for fecal concentrations of [$^{14}$C]-TAK-906 (Period 1; IV dose) and for fecal TRA (Periods 1 and 2) will be calculated as follows:

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

TRA excreted in feces will be presented in mass equivalent units.

*9.3.1.4 Additional PK Measurements*

PK parameter for combined urine and fecal [$^{14}$C]-TAK-906 concentrations (Period 1; IV dose) and for urine and fecal TRA (Periods 1 and 2) will be calculated as follows:

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

If technically feasible, cumulative [$^{14}$C]-M23 excreted in urine and feces in Period 1 will be measured.

### 9.3.2 Biomarker Measurements

Not applicable.

### 9.3.3 PGx Measurements

Not applicable.

### 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 morning urine and fecal sample [when passed] (Day 5) and/or study procedures and if a discharge criterion is met, or up to Day 7. 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, and confined until at least after the 120-hour blood draw and morning urine and fecal sample [when passed] (Day 6) and/or study procedures and if a discharge criterion is met, or up to Day 15.

All urine and fecal collections will be analyzed for radioactivity levels in both periods to determine if the discharge criteria are met. In each of the 2 consecutive periods, both urine and fecal samples have to be collected and counted for TRA, ie, if only urine or feces is collected in a day, this day is not considered to be one of the 2 consecutive intervals. Subjects will be eligible for discharge if they meet either of the following discharge criteria on Day 5 (Period 1) or Day 6 (Period 2):

- ≥80% (following Period 1 dose) and ≥90%* (following Period 2 dose) 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.

*The specified discharge criteria (ie, ≥90%) for Period 2 is implemented to maximize the radioactive dose recovered in the ADME period.

Subjects can be released after Day 15 collection of excreta in Period 2. After Day 15, if subjects have not met the discharge criteria, the subject may need to return to the clinic facility to collect urine and fecal samples in two blocks of 24-hour periods on Days 20, 21, or 22 and Days 27, 28, or 29 based on the discretion of the Sponsor. Release of subjects who do not meet a discharge criterion by Day 15 in Period 2 will be reviewed on a case-by-case basis.

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

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

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

# 10.0 ADVERSE EVENTS

## 10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

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

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

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

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

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

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

### 10.1.1 SAEs

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

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

**Table 10.a Takeda Medically Significant AE List**

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

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

### 10.1.2 Special Interest AEs

There were no AEs of special interest defined for reporting in this study.

## 10.2 AE Procedures

### 10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

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

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

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

### 10.2.2 Assigning Causality of AEs

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

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

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

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

### 10.2.3 Start Date

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

### 10.2.4 End Date

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

### 10.2.5 Pattern of Adverse Event (Frequency)

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

### 10.2.6 Action Taken With Study Treatment

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

### 10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed

study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."

- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

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

#### *10.2.8.1 Collection Period*

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

#### *10.2.8.2 Reporting AEs*

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

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

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.

- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with trial drug.
- Outcome of event.
- Seriousness.

*10.2.8.3 Reporting SAEs*

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

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

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

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

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

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

*SAE Follow-Up*

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

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

*10.2.8.4 Reporting Special Interest AEs*

There are no AEs of Special Interest defined for reporting in this study.

*10.2.8.5 Reporting of Abnormal LFTs*

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN, concurrently with total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The Investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.9 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

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

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

# 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. A clinical pharmacology analysis plan will also be generated for the study.

### 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*

Not applicable

### 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 TRA (whole blood [Period 2], plasma, urine, feces [Periods 1 and 2], and if applicable, emesis [Period 2]), TAK-906 and metabolite concentrations and PK parameters (plasma and urine [Period 2]), and [$^{14}$C]-TAK-906 concentrations (plasma, urine, feces [Period 1]), and the metabolite profile of TAK-906 (plasma, urine, feces [Period 2]), using appropriate summary statistics to be fully specified in the SAP.

PK parameters for whole blood, plasma, and TRA concentrations will be calculated as described in Section 9.3.1.1 and for urine and feces, as described in Sections 9.3.1.2 and 9.3.1.3, respectively. Further details would be specified in the Clinical Pharmacology Analysis Plan.

ABA of TAK-906 (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 $AUC_{\infty}$ between a single oral and the IV microtracer dose. Exponentiating the log-scale 90% CI will provide a 90% CI for the dose normalized $AUC_{\infty}$ GMR; TAK-906 administered as oral dose / [$^{14}$C]-TAK-906 administered as IV microtracer dose. $AUC_{last}$ will be analyzed in a similar fashion if $AUC_{\infty}$ cannot be calculated.

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

### 11.1.4 Analysis of Mass Balance

In Period 2, mass balance will be calculated as a sum of the percent of the TRA 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 fraction of [$^{14}$C]-radioactivity associated with red blood cells and other cellular components of whole blood will also be determined by using the concentration of [$^{14}$C]-radioactivity in whole blood and plasma to calculate the whole blood:plasma partitioning ratio.

### 11.1.6 Metabolite Profiling

In Period 2, TAK-906 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

Not applicable.

### 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 ECG Assessment*

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

*11.1.8.5 Other Safety Parameters*

Physical examination findings will be presented in the data listings.

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 empirically without statistical considerations and is deemed adequate to meet the study objectives. In addition, this sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity.

# 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 (CRO) 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 Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

### 13.1 IRB and/or IEC Approval

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

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, 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 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.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify Sponsor of consent withdrawal.

### 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 Americas Investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting 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 | PPD |

### 14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert, as appropriate, 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 Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

### 14.1.3 Study-Related Responsibilities

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

### 14.1.4 List of Abbreviations

| | |
|---|---|
| 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 |
| Ae | Amount excreted |
| $Aet_1$-$t_2$ | 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 $AUC_\infty$ 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 |
| $AUC_\infty$ | Area under the concentration-time curve, from time 0 extrapolated to infinity |
| $AUC_{12}$ | Area under the concentration-time curve, from time 0 to Hour 12 concentration |
| BBB | Blood brain barrier |
| BLQ | Below the limit of quantitation |
| 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 |
| CL/F | Apparent total plasma clearance after oral (extravascular) administration |
| CCI [redacted] | |
| $C_{max}$ | Maximum observed concentration |

| | |
|---|---|
| CRF | Case report form |
| CRU | Clinical Research Unit |
| Cum%Dose(FE): | Cumulative percent of administered dose excreted in feces. |
| Cum%Dose(UR): | Cumulative percent of administered dose excreted in urine. |
| CYP | Cytochrome P450 |
| ECG | Electrocardiogram |
| F | Bioavailability |
| FDA | Food and Drug Administration |
| g | Gram |
| GCP | Good Clinical Practice |
| GMR | Geometric mean ratio |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| ICRP | Commission on Radiological Protection |
| IEC | Independent Ethics Committee |
| 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 |
| MAD | Multiple ascending dose |
| MBq | Megabecquerel |
| MedDRA® | Medical Dictionary for Regulatory Activities® |
| mg | Milligram |
| min | Minute |
| mL | Milliliter |
| mrem | Millirem |
| msec | Millisecond |
| mSv | Millisievert |
| OATP | Organic anion transporting polypeptide |
| Oz | Ounce |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| SAD | Single ascending dose |

| | |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SUSARs | Suspected unexpected serious adverse reactions |
| $t_{½}$ | Apparent first-order terminal elimination half-life |
| TEAE | Treatment-emergent adverse event |
| $t_{max}$ | Time to reach maximum observed concentration [$C_{max}$] |
| TRA | Total radioactivity |
| ULN | Upper limit of normal |
| US | United States |
| USA | United States of America |
| $V_z/F$ | Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration |

## 15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

### 15.1 CRFs (Electronic and Paper)

Completed CRFs are required for each subject who signs an informed consent.

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor will make arrangements to 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. Data are transcribed directly onto CRFs.

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 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic 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

1. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological A. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology 2004;127(5):1592-622.
2. Camilleri M, Parkman HP, Shafi MA, Abell TL. Gerson L, American College of G. Clinical guideline: management of gastroparesis. Am J Gastroenterol 2013;108(1):18-37.
3. Hyett B, Martinez FJ, Gill BM, Mehra S, Lembo A, Kelly CP, et al. Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis. Gastroenterology 2009;137(2):445-52.
4. Takeda Pharmaceuticals, Inc. Global Investigator Brochure. Edition 3.0, Dec 2018.

# 17.0 APPENDICES

## Appendix A Taste Questionnaire

This assessment would be done within 5 minutes of completion of dosing in Period 2. Subjects will be isolated from other subjects during the evaluation session in such a way that they do not see each other's facial impression or body gestures. Subjects will be asked to refrain from communicating their opinions in a manner that could bias other subjects. Talking will be restricted. The taste area will be monitored for compliance by the site personnel.

| | | | | | | |
|---|---|---|---|---|---|---|
| Subject Number: _____<br>Treatment Period: _____ | | | | | | |
| Please evaluate the following attributes by circling the number that best represents your response | | | | | | |
| **TASTE:** | | | | | | |
| 1<br>Definitely disliked | 2<br>Disliked moderately | 3<br>Disliked slightly | 4<br>Neither dislike or liked | 5<br>Liked slightly | 6<br>Liked moderately | 7<br>Definitely liked |
| **AFTERTASTE:** | | | | | | |
| 1<br>Definitely disliked | 2<br>Disliked moderately | 3<br>Disliked slightly | 4<br>Neither dislike or liked | 5<br>Liked slightly | 6<br>Liked moderately | 7<br>Definitely liked |
| Do you have any additional comments regarding this formulation? No ___ Yes __<br>If yes, please print your comments here: _____<br>_____<br>_____<br>_____ | | | | | | |
| **What is the taste of the product? Please use the following scale and circle all that applies** | | | | | | |
| Sweetness | 0 (nothing) | 1 | 2 | 3 | 4 | 5 (Very strong) |
| Bitterness | 0 (nothing) | 1 | 2 | 3 | 4 | 5 (Very strong) |
| Sourness | 0 (nothing) | 1 | 2 | 3 | 4 | 5 (Very strong) |
| Saltiness | 0 (nothing) | 1 | 2 | 3 | 4 | 5 (Very strong) |
| Other | 0 (nothing) | 1 | 2 | 3 | 4 | 5 (Very strong) |
| Please describe other taste: | | | | | | |
| | | | | | | |

## Appendix B Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the Investigator/institution retains the services of any individual or party to perform 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 C Elements of the Subject Informed Consent

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

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

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

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

25. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 90 days 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 D 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 E 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 90 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 spermicide). In addition, they must be advised not to donate sperm throughout the duration of the study, and for 90 days after last dose of study drug. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below. Total abstinence (no sexual intercourse) may be considered an acceptable method of birth control if it agrees with the subject's preferred and usual lifestyle.

*Definitions and Procedures for Contraception and Pregnancy Avoidance*

*The following definitions apply for contraception and pregnancy avoidance procedures.*

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

*The following procedures apply for contraception and pregnancy avoidance.*

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). Acceptable methods of contraception are:
    - Non-Hormonal Methods:
        - Intrauterine device (IUD).
        - Bilateral tubal occlusion.
        - Vasectomised subject (has received medical assessment of the surgical success).
        - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 90 days after the last dose.
    - Hormonal Methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
            - Oral.

- Intravaginal (eg, ring).
- transdermal.

– Progestogen-only hormonal contraception associated with inhibition of 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 shorter till she has been on contraceptive for 3 months;

- oral.
- Injectable.
- Implantable.

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

*General Guidance With Respect to the Avoidance of Pregnancy*

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.

- reasons for use of barrier methods (ie, condom) in subjects with pregnant partners.
- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?

**Procedures for Reporting Drug Exposure During Pregnancy and Birth Events**

Women will not be included in this study.

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

Any pregnancies in the partner of a male subject during the study or for 90 days after the last dose, should also be recorded following authorization from the subject's partner.

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

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

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| PPD | Biostatistics Approval | 01-Apr-2020 16:01 UTC |
| | Clinical Science Approval | 03-Apr-2020 00:52 UTC |
| | Clinical Pharmacology Approval | 03-Apr-2020 02:25 UTC |