Title: A Phase 1, Open-label, Single Intravenous Infusion Dose Study to Evaluate the Mass Balance, Pharmacokinetics, Metabolism, and Excretion of TAK-954 Containing Microtracer ([14C]-TAK-954) in Healthy Adult Male Subjects

NCT Number: NCT03500224

Protocol Approve Date: 26 March 2018

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

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

PROTOCOL

A Phase 1, Open-label, Single Intravenous Infusion Dose Study to Evaluate the Mass Balance, Pharmacokinetics, Metabolism, and Excretion of TAK-954 Containing Microtracer ([^{14}C]-TAK-954) in Healthy Adult Male Subjects

Study Identifier: TAK-954-1005

Compound: TAK-954

Date: 26 March 2018

Version/Amendment Number: Initial

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1.0 STUDY SUMMARY

Name of sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "sponsor," or "Takeda".	**Compound:** TAK-954
Study Identifier: TAK-954-1005	**Phase:** 1
Protocol Title: A Phase 1, Open-label, Single Intravenous Infusion Dose Study to Evaluate the Mass Balance, Pharmacokinetics, Metabolism, and Excretion of TAK-954 Containing Microtracer ([^{14}C]-TAK-954) in Healthy Adult Male Subjects	
Trial Design: This is a phase 1, open-label study in 6 healthy male subjects. The study will include a screening visit, a treatment period, and a follow-up period. At least 6 subjects will be dosed in the study. Subjects will complete the screening visit within approximately 28 days before study drug administration. Eligible subjects will be enrolled into the study and will receive a single 60-minute intravenous (IV) infusion of 0.5 mg TAK-954 containing a microtracer of [^{14}C]-TAK-954 (~1.5 μCi). Subjects will be confined from admission for a minimum of 7 days. If the recovery of radioactivity has not met the target conditions specified below, a subject's duration of confinement may be maximally extended to Day 15 (336 hours postdose). Should the duration of confinement be extended, clinical assessments planned at discharge will be rescheduled accordingly. An individual subject will be discharged from the clinic when at least 1 of the following criteria has been met for that subject: 1. ≥90% of the administered radioactivity has been recovered in excreta. 2. Excreta samples from 2 consecutive days contain <1% of the administered radioactivity. Safety will be assessed by monitoring for adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory results, and physical examinations.	
Trial Primary Objective: The primary objectives of the study are: • To determine the mass balance and routes of elimination of a single IV dose of TAK-954 containing microtracer ([^{14}C]-TAK-954). • To characterize the metabolic profiles following single-dose IV administration of TAK-954 containing microtracer ([^{14}C]-TAK-954) and identify major circulating and excreted metabolites. • To determine the single-dose pharmacokinetics (PK) of total radioactivity, TAK-954, THRX513466, and THRX 913682, where possible. **Secondary Objectives:** The secondary objective of the study is to evaluate the safety and tolerability of a single IV dose of TAK-954 containing microtracer ([^{14}C]-TAK-954) in healthy male subjects.	
Trial Subject Population: Healthy male subjects, aged 18 to 55 years, inclusive.	
Planned Number of Subjects: At least 6 subjects	**Planned Number of Sites:** 1 site

Dose Level:	**Route of Administration:**
0.5 mg TAK-954 IV containing a microtracer of [14C]-TAK-954 (~1.5 μCi).	IV
Duration of Treatment:	**Planned Trial Duration:**
Single dose	Up to approximately 6 to 7 weeks

Main Criteria for Inclusion:

To be eligible for study participation, subjects must:

- Be a man aged 18 to 55 years, inclusive, at the screening visit.
- Have a body mass index ≥18 and ≤30 kg/m^2 and a body weight >50 kg at the screening visit.
- Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before administration of the initial dose of trial drug.
- Be judged to be in good health by the investigator on the basis of clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of trial drug.
- Meet the following birth control requirements:
  - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom, from the first dose of study drug until 30 days after the last dose of study drug. No restrictions are required for a vasectomized male subject provided that the subject is at least 1 year postbilateral vasectomy procedure before the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year before the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
  - Is a male subject who agrees to not donate sperm from trial drug administration on the first day of the first dose until 30 days after the last dose of study drug.

Main Criteria for Exclusion:

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

- Has participated in another investigational trial within 4 weeks (or based on local regulations) before the pretrial visit (screening). This window will be derived from the date of the last trial procedure or AE related to the trial procedure in the previous trial to the pretrial/screening visit of the current trial.
- Has total ^{14}C radioactivity measured by accelerator mass spectrometry in plasma (during screening) exceeding $^{14}C/^{12}C$ ratio $1.1E^{-12}$.
- Participated in any study with a radiation dose above 0.1 MBq or radiation burden above 0.1 mSv within 1 year before screening.
- Was exposed to significant radiation (eg, serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring) within 12 months before check-in.
- Irregular defecation pattern (less than once per 2 days).

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study are:

1. Percentage of administered radioactive dose recovered in urine and feces and cumulative recovery in urine and feces combined.
2. TAK-954 and metabolites (if any) expressed as a percentage of total radioactivity in plasma and as a percentage of dose in urine and in feces.
3. Concentration of total radioactivity in whole blood and plasma.
4. PK parameters to describe the single-dose PK, postdose on Day 1, for a) total radioactivity in whole blood and plasma, b) TAK-954 in plasma, c) THRX513466 and THRX 913682 in plasma (where possible):

- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
- Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).
- Time of first occurrence of C_{max} (t_{max}).
- $t_{1/2z}$.
- Total clearance after IV administration (TAK-954 only).
- Volume of distribution during the terminal disposition phase after IV administration (V_z) (TAK-954 only).
- Amount of total radioactivity and TAK-954 excreted in urine and radioactivity only for feces from 0 to time t (A_{et}).
- Fraction of TAK-954 dose and total radioactivity excreted in urine and radioactivity only for feces from time 0 to time t (f_{et}).

Secondary endpoints include:

1. The ratio of total radioactivity in whole blood and plasma.
2. The ratio of plasma TAK-954 to total radioactivity in plasma.
3. Safety:
   - Percentage of subjects who experience at least 1 treatment-emergent AE.
   - Percentage of subjects who discontinue because of an AE.

Statistical Considerations:

Concentration Data:

Plasma concentration of TAK-954 and its metabolites and total radioactivity in whole blood and plasma at each scheduled timepoint will be summarized using descriptive statistics. Mass balance will be assessed by the percentage and cumulative percentage of administered radioactive dose recovered in urine and in feces and their combined total at appropriate intervals. Descriptive statistics will be used.

Mean and individual cumulative excretion of radioactivity in urine and in feces and their combined total by time curve will be displayed.

Individual percentage and cumulative percentage will be presented in data listings.

All concentration data will be listed.

PK:

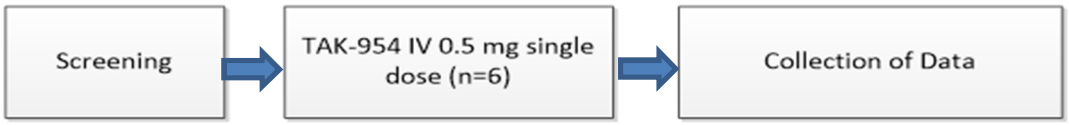
Descriptive statistics will be used to summarize the PK parameters. All PK parameter data will be listed. Statistical analyses will be performed if appropriate.

Circulatory and excretory metabolite profiles will be established for each subject. Metabolites will be presented as a mean percentage of total radioactivity and/or dose. Descriptive statistics will be used.

Sample Size Justification:

The sample size (n = 6) is based on the consideration that radioactivity is being administered to healthy subjects and that generally 6 subjects is sufficient to characterize the endpoints described in the protocol and is accepted by regulatory agencies.

2.0 STUDY SCHEMATIC



Abbreviation: IV, intravenous.

3.0 SCHEDULE OF STUDY PROCEDURES

Assessment	**Screening**	**Trial Days**										**Follow-up/ Early Termination**
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9-15**	**Day 15 ±2 Days**
Hours Postdose			**0**	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**192-336**	
Administrative Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Medication history	X											
Prior and concomitant medication review		----------Continuous monitoring----------										
Clinic Procedures/Assessments												
Full physical exam	X	X [a]										X
Semirecumbent vital signs (heart rate, systolic blood pressure, and diastolic blood pressure)	X		X [b]	X								X
Vital signs (respiratory rate and oral or tympanic temperature)	X		X [b]									X
Height	X											
Weight	X	X										
Body mass index	X											
Standard 12-lead electrocardiogram	X		X [b]	X								X
Adverse event monitoring	----------Continuous monitoring----------											
Laboratory Procedures/Assessments												
Serum chemistry	X	X [a]										X
Hematology	X	X [a]										X
Urinalysis	X	X [a]										X
Urine drug screen	X	X [a]										
Alcohol screen	X	X [a]										
HIV test	X											

Assessment	**Screening**	**Trial Days**										**Follow-up/ Early Termination**
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9-15**	**Day 15 ±2 Days**
Hours Postdose			**0**	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**192-336**	
Hepatitis panel	X											
Pharmacokinetics (PK) Evaluations												
Blood collection for total radioactivity in whole blood and plasma, TAK-954 in plasma, and metabolite profiling [c]			X----------									X
Urine collection for total radioactivity, TAK-954 concentrations, and metabolite profiling [d]		X	X----------									X
Emesis [e]			X									
Feces collection for total radioactivity and metabolite profiling [f]		X	X----------									X
Total ^{14}C radioactivity measured by accelerator mass spectrometry (AMS) in plasma.	X											
Drug Administration												
[^{14}C]-TAK-954 dosing			X									
Other												
Confinement		X	X	X	X	X	X	X	X	X [g]	X [g]	

[a] Within 24 hours before dosing on Day 1.
[b] Assessments predose (between waking up and the start of the infusion) and at the end of the infusion.
[c] PK blood samples (for total radioactivity in whole blood and plasma and TAK-954 in plasma) are collected predose (within 30 minutes) and at 0.5, 1 (at end of infusion), 1.5, 2, 3, 4, 6, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose and every 24 hours thereafter while the subject is confined. Blood samples for metabolite profiling will be collected predose and at 1 (at end of infusion), 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose and every 24 hours thereafter while the subject is confined.
[d] Urine will be collected predose (spot sample -12 to 0 hours) and at 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours and every 24 hours thereafter while the subject is confined.
[e] If emesis occurs within 8-10 hours after dosing, vomitus will be collected in a preweighed container assigned to each subject, reweighed, and submitted for analysis of total radioactivity.
[f] Feces will be collected predose (last stool before dosing), and all samples produced up to at least 168 hours postdose (to be pooled in 24-hour intervals) and every

24 hours thereafter will be collected while the subject is confined.
[g] Subjects will be confined only if requirements for discharge are not met.

4.0 INTRODUCTION

4.1 Background

TAK-954 is a small molecule, highly selective serotonin subtype 4 agonist being investigated for potential use in the treatment of gastrointestinal motility disorders. Takeda is developing TAK-954 for the treatment of reduced gastrointestinal motility, particularly in settings where an intravenous (IV) formulation is advantageous, such as critically ill patients within intensive care units who develop intolerance of enteral feeding support.

Nonclinical mass-balance studies in rats and dogs after 0.5 mg/kg IV dosing of [^{14}C]-TAK-954 (carbon-14-TAK-954) indicate that radioactivity was predominantly excreted in the feces (66.2% in rats and 79.4% in dogs), with urinary excretion being lower (32.7% in rats and 14.4% in dogs). The biliary excretion in rats constituted 40.4% of the IV dose.

TAK-954 was relatively stable when incubated in cryopreserved rat, dog, and human hepatocytes, with half-lives of 5.8, 8.8, and >17 hours, respectively. Furthermore, 2 active metabolites identified nonclinically (THRX513466 and THRX913682), were observed clinically following oral dosing, but mean maximum observed concentration (C_{max}) and area under the concentration-time curve from time 0 to 48 hours metabolite-to-parent ratios ranged from 0.0008 to 0.004. Renal excretion of these metabolites was also low, with concentrations in urine generally being below the limit of detection.

TAK-954 has been investigated in healthy subjects at single oral doses from 0.1 to 20 mg (maximum tolerated dose [MTD] 10 mg), multiple oral doses from 0.2 to 10 mg once daily (QD) for 10 days (MTD 5 mg), and multiple IV doses from 0.1 to 0.5 mg QD for 5 days. A single IV dose of 0.5 mg TAK-954 has also been investigated in critically ill patients with enteral feeding intolerance. After multiple IV infusion dosing in healthy subjects (0.1 and 0.5 mg over 1 hour), TAK-954 concentrations declined in a biphasic manner, with mean terminal disposition phase half-life ($t_{1/2z}$) values ranging from 18.0 to 18.9 hours on Day 5. TAK-954 steady state was achieved by Day 3, with minimal accumulation of TAK-954 after multiple IV doses of 0.5 mg. The increase in exposure from the 0.1 mg to 0.5 mg IV dose was approximately dose proportional, and the mean amount of TAK-954 excreted unchanged in urine on Day 5 ranged from 28% to 32%. In subjects who were critically ill and received 0.5 mg by IV infusion, the TAK-954 exposure was lower relative to that observed in healthy subjects. The average percentage of plasma protein binding was 56% in human plasma.

Following IV doses in healthy subjects, TAK-954 was generally well tolerated at doses ranging from 0.1 to 0.5 mg QD for 5 consecutive days. No serious adverse events (SAEs) were reported. The most common adverse events (AEs) (headache and postural dizziness) were not clinically significant and resolved spontaneously. Among the AEs reported, 3 subjects experienced modest and transient cardiovascular AEs upon standing following the first dose (postural tachycardia and postural dizziness); these resolved spontaneously and were not observed upon challenge. Following single infusions of TAK-954 of 0.5 mg in subjects who were critically ill with enteral feeding intolerance, no subject had an AE that led to study discontinuation or interruption of treatment. Vital sign changes from baseline noted over the course of treatment were minimal and

typical of critically ill subjects. No clinically relevant changes in electrocardiograms (ECGs) in either treatment group were observed.

4.2 Rationale for the Proposed Study

This radiolabeled human mass-balance study will characterize the overall disposition and biotransformation of TAK-954. The study design involves a microtracer ^{14}C dose, with sample analysis done primarily by highly sensitive accelerator mass spectrometry (AMS). The AMS technique will provide adequate sensitivity to assess quantitative disposition of TAK-954 in humans. The rationale for using a microtracer ^{14}C dose is as follows: Conducting a human mass-balance study with a traditional radioactive dose (100 μCi) requires [^{14}C]-TAK-954–specific activity of 200 μCi/mg. Preliminary stability results with radioactive material prepared at ~127 μCi/mg suggested a significant decrease in radiochemical purity, even after storing at -80°C over a 4-month period, and the instability is considered to be due to highly specific activity. Because the time required for completion of the human mass-balance and metabolite profiling/identification studies is approximately 6 to 9 months, the radiolabeled material would have to be stable until the analysis is complete. To avoid highly specific activity material and the ensuing radiochemical instability, for the human mass-balance study, a microtracer approach with approximately 3 μCi/mg has been adopted. The stability of the microtracer (approximately 3 μCi/mg) will be established before dosing human subjects.

4.3 Benefit-Risk Profile

As this trial will be conducted in healthy subjects, there is no expected clinical benefit to trial participants.

Potential risks of TAK-954 use include findings from prior studies. There were no SAEs or severe AEs observed in 2 oral dose studies in healthy subjects, Studies 0060 and 0061. Following multiple IV doses in healthy subjects in Study 0095, TAK-954 was generally well tolerated at doses ranging from 0.1 to 0.5 mg QD for 5 consecutive days. No SAEs were reported. The most common AEs (headache and postural dizziness) were not serious and resolved with treatment discontinuation. The radioactive burden due to approximately 1.5 μCi of total ^{14}C planned to be administered per subject is considered to pose negligible additional risk above the background cosmic radiation, so no dosimetry estimation is necessary.

Overall, the benefit-risk profile is considered appropriate for this study.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Trial Objectives

5.1.1 Trial Primary Objectives

The primary objectives of the study are:

- To determine the mass balance and routes of elimination of a single IV dose of TAK-954 containing microtracer ([^{14}C]-TAK-954).
- To characterize the metabolic profiles following single-dose IV administration of TAK-954 containing microtracer ([^{14}C]-TAK-954) and identify major circulating and excreted metabolites.
- To determine the single-dose pharmacokinetics (PK) of total radioactivity, TAK-954, THRX513466, and THRX 913682, where possible.

5.1.2 Trial Secondary Objective

The secondary objective of the study is to evaluate the safety and tolerability of a single IV dose of TAK-954 containing microtracer ([^{14}C]-TAK-954) in healthy male subjects.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints of the study are:

- Percentage of administered radioactive dose recovered in urine and feces and cumulative recovery in urine and feces combined.
- TAK-954 and metabolites (if any) expressed as a percentage of total radioactivity in plasma and as a percentage of dose in urine and in feces.
- Concentration of total radioactivity in whole blood and plasma.
- PK parameters to describe the single-dose PK, postdose on Day 1, for a) total radioactivity in whole blood and plasma, b) TAK-954 in plasma, and c) THRX513466 and THRX 913682 in plasma (where possible):
  - C_{max}.
  - Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Time of first occurrence of C_{max} (t_{max}).
  - $t_{1/2z}$.

- Total clearance after IV administration (CL) (TAK-954 only).
- Volume of distribution during the terminal disposition phase after IV administration (V_z) (TAK-954 only).
- Amount of total radioactivity and TAK-954 excreted in urine and radioactivity only for feces from 0 to time t (A_{et}).
- Fraction of TAK-954 dose and total radioactivity excreted in urine and radioactivity only for feces from time 0 to time t (f_{et}).

5.2.2 Secondary Endpoints

Secondary endpoints include:

- The ratio of total radioactivity in whole blood and plasma.
- The ratio of plasma TAK-954 to total radioactivity in plasma.
- Safety:
  - Percentage of subjects who experience at least 1 treatment-emergent AE.
  - Percentage of subjects who discontinue because of an AE.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 1, open-label study in 6 healthy male subjects. The study will include a screening visit, a treatment period, and a follow-up period. At least 6 subjects will be dosed in the study. The site should have alternate subjects available on the dosing day in case a subject is discontinued on Day 1.

Subjects will complete the screening visit within approximately 28 days before study drug administration.

Eligible subjects will be enrolled into the study and will receive a single 60-minute IV infusion of 0.5 mg TAK-954 containing a microtracer of [^{14}C]-TAK-954 (~1.5 μCi). For standardization purposes, study drug will be administered following at least 2 hours of fasting.

Subjects will be confined from admission for a minimum of 7 days. If the recovery of radioactivity has not met the target conditions specified below, a subject's duration of confinement may be maximally extended to Day 15 (336 hours postdose). Should the duration of confinement be extended, clinical assessments planned at discharge will be rescheduled accordingly.

An individual subject will be discharged from the clinic when at least 1 of the following criteria has been met for that subject:

1. ≥90% of the administered radioactivity has been recovered in excreta.
2. Excreta samples from 2 consecutive days contain <1% of the administered radioactivity.

Discharge/stopping criteria will be assessed daily by liquid scintillation counting or using AMS until target conditions have been met, but ultimately, a subject's duration of confinement will not extend beyond Day 15 (336 hours postdose).

Specific measures should be taken to prevent the subject from missing a fecal or urine collection by strictly controlling and providing access to designated restrooms only.

Safety will be assessed by monitoring for AEs, vital signs, ECGs, clinical laboratory results, and physical examinations.

Follow-up visit procedures will be performed on the last possible day (15 days after the start of the infusion) of discharge; subjects who meet the stopping criteria before this day will be asked to return for a follow-up visit on Day 15 (±2 days).

6.2 Rationale for Trial Design, Dose, and Endpoints

6.2.1 Rationale for Trial Design

This trial has a standard design for assessing mass balance, metabolic profiles, and routes of elimination. The duration of sampling was chosen on the basis of the plasma elimination half-life for the parent drug (approximately 19 hours in healthy subjects), and observations from nonclinical tissue distribution and mass-balance studies.

6.2.2 Rationale for Dose

A single dose of 0.5 mg was chosen for the following reasons: a 0.5 mg IV dose is likely to be in the therapeutic range, and on the basis of previous clinical experience with this compound, this dose (and associated systemic exposure) has an acceptable safety profile in healthy subjects. The radioactive burden due to approximately 1.5 μCi of total ^{14}C planned to be administered per subject is considered to pose negligible additional risk above the background cosmic radiation, so no dosimetry estimation is necessary.

6.2.3 Rationale for Subject Population

The study involves a small amount of radioactivity; therefore, only adult males are included in the trial.

6.2.4 Rationale for Endpoints

6.2.4.1 Safety Endpoints

Key safety endpoints will be assessed through monitoring of AEs, vital signs, ECGs, laboratory assessments, and physical examinations.

6.2.4.2 PK Endpoints

The PK endpoints described are standard for this type of study.

6.2.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, the collections of the blood, urine, and feces samples are the critical procedures.

During the treatment period, where multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible:

- Vital signs and 12-lead EGC should be obtained as close as possible to the scheduled time but before any blood specimen collection.
- PK blood specimens should be obtained at scheduled time.
- All other procedures should be obtained as close as possible to the scheduled time but may be obtained before or after any blood specimen collection.
- The order of priority can be changed during the trial with joint agreement of the investigator and the sponsor.
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.3 Trial Design/Dosing/Procedure Modifications Permitted Within Protocol Parameters

This is a phase 1 assessment of TAK-954 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to

accommodate the inherent dynamic nature of phase 1 clinical trials. Modifications to the clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives or to ensure appropriate safety monitoring of the trial subjects.

Up to an additional 50 mL of blood may be drawn. The total blood volume withdrawn from any single subject will not exceed the total maximum allowable volume during the subject's participation in the trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the sponsor in a letter to the trial master file and forwarded to the investigator for retention. The letter may be forwarded to the institutional review board (IRB)/independent ethics committee (IEC) at the discretion of the investigator.

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

The overall trial begins when the first subject signs the trial informed consent form (ICF).

6.4.2 Definition of End of the Trial

The overall trial ends when the last subject completes the last planned or follow-up visit/ interaction associated with a planned visit (this can be a phone contact), discontinues from the trial, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.4.3 Definition of Trial Completion

The overall trial ends when the last subject completes the last planned or follow-up visit/ interaction associated with a planned visit (this can be a phone contact), discontinues from the trial, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.4.4 Definition of Trial Discontinuation

Trial discontinuation because of nonsafety reasons, such as:

- A finding (eg, PK, pharmacodynamics, efficacy, biologic targets) from another nonclinical or clinical trial using the trial treatment(s) results in the trial being stopped for a non–safety-related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this trial become available and result in the trial being stopped for a non–safety-related reason.
- The trial is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.

Trial discontinuation because of safety reasons: early trial termination because of unanticipated concerns about the safety of the trial subjects arising from clinical or nonclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial.

6.4.5 Criteria for Premature Termination or Suspension of the Trial

6.4.5.1 Criteria for Premature Termination or Suspension of Trial

A trial site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), the protocol, or a contractual agreement; is unable to ensure adequate performance of the trial; or as otherwise permitted by the contractual agreement.

6.4.5.2 Procedures for Premature Termination or Suspension of the Trial

If the sponsor, an IRB, or a regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during termination or trial suspension.

6.4.6 Criteria for Premature Termination or Suspension of a Site

6.4.6.1 Criteria for Premature Termination or Suspension of a Site

A trial site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, the protocol, or a contractual agreement; or is unable to ensure adequate performance of the trial; or as otherwise permitted by the contractual agreement.

6.4.6.2 Procedures for Premature Termination or Suspension of a Site

If the sponsor, an IRB/IEC, or a regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

To be eligible for study participation, subjects must:

1. Understand the trial procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all trial procedures and restrictions.
3. Be a man aged 18 to 55 years, inclusive, at the screening visit.
4. Have a body mass index (BMI) ≥18 and ≤30 kg/m^2 and a body weight >50 kg at the screening visit.
5. Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before administration of the initial dose of trial drug.
6. Be judged to be in good health by the investigator on the basis of clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of trial drug.
7. Meet the following birth control requirements:
   - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom, from the first dose of study drug until 30 days after the last dose of study drug. No restrictions are required for a vasectomized male subject provided that the subject is at least 1 year postbilateral vasectomy procedure before the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year before the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedures should be provided.
   - Is a male subject who agrees to not donate sperm from trial drug administration on the first day of the first dose until 30 days after the last dose of study drug.

7.2 Exclusion Criteria

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

1. Has participated in another investigational trial within 4 weeks (or based on local regulations) before the pretrial visit (screening). This window will be derived from the date of the last trial procedure or AE related to the trial procedure in the previous trial to the pretrial/screening visit of the current trial.
2. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of the sponsor or clinical site.
3. Has a history of cancer (malignancy).

4. Has a history of significant multiple or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
5. Has a positive alcohol or drug screen.
6. Has a positive test result for hepatitis B surface antigen, hepatitis C virus (HCV) antibody, or HIV antibody/antigen at the screening visit. Note: Subjects with positive hepatitis B virus (HBV) or HCV serology may be enrolled if quantitative polymerase chain reaction for HBV or HCV RNA is negative.
7. Had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 8 weeks before the first dose of study drug.
8. Has a known hypersensitivity to any component of the formulation of TAK-954 or related compounds.
9. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial, until the follow-up visit; see Section 7.3.
10. Has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to beer 354 mL/12 oz, wine 118 mL/4 oz, or distilled spirits 29.5 mL/1 oz).
11. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
12. Has a substance abuse disorder.
13. Has total ^{14}C radioactivity measured by AMS in plasma (during screening) exceeding $^{14}C/^{12}C$ ratio $1.1E^{-12}$.
14. Participated in any study with a radiation dose above 0.1 MBq or radiation burden above 0.1 mSv within 1 year before screening.
15. Was exposed to significant radiation (eg, serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring) within 12 months before check-in.
16. Irregular defecation pattern (less than once per 2 days).

7.3 Excluded Medications, Supplements, Dietary Products

7.3.1 Concomitant Medications

The use of concomitant medications (see Section 9.1.4) after enrollment (ie, Day 1) until the follow-up visit is not permitted. Subjects must be instructed not to take any medications without

first consulting the investigator. Any concomitant medication use must first be discussed with the sponsor, unless the investigator or designee believes that immediate administration is necessary.

The occasional use of acetaminophen (approximately <1 g/day) is allowed.

7.3.2 Fruit Juice

Subjects will refrain from consuming grapefruit juice, grapefruits, and products containing grapefruit beginning approximately 2 weeks before administration of the initial dose of study drug, throughout the trial, until the follow-up visit.

Subjects also will refrain from consuming all juices 24 hours before and after administration of the study drug. Consumption of all fruits other than grapefruit is allowed on all days of the trial.

7.3.3 Alcohol

Subjects will refrain from consuming alcohol 7 days before the screening visit and follow-up visit and starting 7 days before and until after the last PK blood sample has been collected. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 alcoholic beverage is approximately equivalent to beer 354 mL/12 oz, wine 118 mL/4 oz, or distilled spirits 29.5 mL/1 oz) per day.

7.3.4 Caffeine

Subjects will refrain from consuming caffeinated beverages starting 24 hours before and until after the last PK blood sample has been collected and for 24 hours before the screening visit and follow-up visit. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit = 120 mg of caffeine).

7.3.5 Smoking

Smoking is not permitted during the trial.

7.4 Diet, Fluid, and Activity

7.4.1 Diet and Fluid

Subjects will fast (no food or drink except water) for at least 2 hours before study drug dosing.

Water is permitted until 1 hour before TAK-954 administration. Water may be consumed without restrictions beginning 1 hour after TAK-954 dosing.

Lunch, dinner, and snacks will be provided on Day 1. Breakfast, lunch, dinner, and morning and afternoon snacks will be provided on all other domiciled days.

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (eg, weight lifting, running, bicycling) from the screening visit until administration of the study drug, throughout the trial, until the follow-up visit.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories.

1. Treatment discontinuation due to an AE: The subject has experienced an AE that requires early termination because continued participation poses an unacceptable risk to the subject's health or the subject is unwilling to continue in the study because of the AE.
2. Significant protocol deviation: The discovery that the subject did not meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up: The subject did not return to the clinic, and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal: The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
5. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (eg, withdrawal due to an AE should not be recorded in the voluntary withdrawal category).
6. Study termination: The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.5. In addition, a subject may discontinue participation without giving a reason at any time during the trial. 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 early termination visit.

7.7 Subject Replacement

If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Details regarding the composition and extemporaneous preparation of the active drug are found in the pharmacy manual. Clinical study drug will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the sponsor must be contacted before dosing.

8.1.1 Clinical Study Drug Labeling

Clinical study drug will be affixed with a clinical label in accordance with regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

Clinical study drug must be stored in a secure, limited-access location under the storage conditions specified on the label. Inventory (receipt and dispensing) of study drug must be recorded by an authorized, unblinded person at the trial site.

8.1.3 Clinical Study Drug Blinding

This is an open-label trial.

8.1.4 Clinical Trial Blind Maintenance/Unblinding Procedure

This is an open-label trial.

8.1.5 Accountability and Destruction of sponsor-Supplied Drugs

The investigator is responsible for keeping accurate records of the clinical study drug received from the sponsor or designee and the amount remaining at the conclusion of the trial. For all trial sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for clinical study drug accountability, return, and destruction.

9.0 STUDY PROCEDURES

The following sections describe the trial procedures to be performed and data to be collected as indicated in the schedule of study procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, at the investigator's discretion.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters the trial and before any protocol-directed procedures are performed. The requirements of informed consent are described in Appendix B.

9.1.1.1 Assignment of Screening and Subject Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur before enrollment. Each subject will be assigned only 1 screening number. Screening numbers must not be reused for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening event.

All eligible subjects will receive a subject number. The subject number identifies the subject for all procedures occurring after enrollment. Once a subject number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than 1 subject number.

9.1.1.2 Study Drug Assignment

On Day 1, subjects will be assigned a subject number in ascending numerical order at the clinical site. The subject number determines the order in which the subjects will receive TAK-954.

9.1.2 Inclusion and Exclusion

Each subject will be assessed according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Qualified site personnel will collect subject significant medical history (past and concurrent medical conditions), per the site's standard of care and appropriate clinical judgment, and subject demographics.

9.1.4 Concomitant Medications

Qualified site personnel will review each subject's prior and concomitant medication use. Medications are defined as prescription and over-the-counter drugs, vaccines, supplements, nutraceuticals, and oral herbal preparations.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

Qualified site personnel will conduct full physical examinations.

A neurological assessment will be part of the physical examination and mainly will consist of tests of sensory and motor functions (eg, reflexes, coordination, and gait).

9.2.2 Height and Weight

Body weight and height will be obtained with the subject's shoes off and jacket or coat removed.

9.2.3 BMI

BMI equals a subject's weight in kilograms divided by height in meters squared (BMI = kg/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4, round down, and 0.5 to 0.9, round up.

9.2.4 Vital Signs

Body temperature will be measured with an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (ie, oral or tympanic) must be used for all subsequent measurements for each subject and should be the same for all subjects.

Subjects should rest in a semirecumbent position for at least 5 minutes before vital signs are measured. Vital signs will include heart rate, respiratory rate, and systolic and diastolic blood pressure. The same method (eg, same size cuff, manual or automated) must be used for all measurements for each subject and should be the same for all subjects.

Subjects should continue to rest in a semirecumbent position from the time of dosing until 4 hours postdose, except to stand for the measurement of standing vital signs (if needed) or other trial-related procedures.

9.2.5 12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Subjects may need to be shaved to ensure proper lead placement.

Subjects should be resting in a semirecumbent position for at least 5 minutes before each ECG measurement.

QT intervals with Fridericia correction method (QTcF intervals) will be calculated in this trial.

An ECG will be obtained at screening. This measurement will be used as the baseline assessment. The principal investigator should arrange to have a trial cardiologist available as needed to review ECG tracings with abnormalities.

During the treatment period, if a subject demonstrates an increase in QTcF interval ≥40 milliseconds compared with a predose baseline measurement, the ECG will be repeated

within 5 minutes. The average value of the QTcF interval from the 2 ECGs will represent the value at that time point. If the average QTcF interval increase from baseline for any postdose time point is ≥40 milliseconds, the subject will continue to be monitored by repeat 12-lead ECGs every 60 minutes for at least 4 hours or until the QTcF interval is within 40 milliseconds of the baseline value. If prolongation of the QTcF interval ≥40 milliseconds persists, a consultation with a trial cardiologist may be appropriate, and the sponsor should be notified.

If the QTcF interval is ≥500 milliseconds, the sponsor should be notified, and the ECGs should be reviewed by a cardiologist. The subject should be monitored by telemetry (until the QTcF interval is <500 milliseconds) or should be considered for transfer to a location where closer monitoring is available.

If the subject has unstable hemodynamics or any clinically significant dysrhythmias noted by telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker to ensure reproducible electrode placement.

The following ECG parameters will be recorded: heart rate, PR interval, QRS interval, QT interval, QTcF interval, and the interpretation of the ECG profile by the principal investigator.

9.2.6 Study Drug Administration

On Day 1 of the treatment period, study drug (a single dose of TAK-954) will be administered as described in Section 6.1.

9.2.7 AE Monitoring

AE monitoring begins after signing of the ICF. Changes in subject health status from the baseline assessment until study drug administration should be captured in the subject's medical history. A complete description of AE collection and procedures is provided in Section 10.0.

9.2.8 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be taken on the days indicated in the schedule of study procedures (Section 3.0).

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells [RBCs])	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells [WBCs]) with absolute differential	

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatinine	Glucose
γ-glutamyl transferase (GGT)	Sodium
Potassium	Bilirubin (total), if above ULN total bilirubin will be fractionated
Protein (total)	

Abbreviations: ULN, upper limit of normal.

If subjects experience ALT or AST >3 × the upper limit of normal (ULN), follow-up laboratory tests (at a minimum, serum alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and γ-glutamyl transferase) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

If ALT or AST remains elevated >3 × ULN on these 2 consecutive occasions, the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE.

Refer to Section 7.5 for subject discontinuation criteria regarding abnormal liver function tests (LFTs) and Section 10.2.8.4 for guidance on reporting abnormal LFTs.

Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrite

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of red blood cells/high-power field, white blood cells/high-power field, and casts.

9.2.8.2 Diagnostic Screening

The serum diagnostic screening assessment will include the following tests:

HIV	Hepatitis screen (HBsAg, HCV antibody)

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Alcohol Screen

Subjects will undergo an alcohol breath test. A urine alcohol test may be performed at the discretion of the investigator.

Urine

The urine drug screening assessment will include the following tests:

Amphetamines	MDMA
Barbiturates	Methadone/metabolite
Benzodiazepines	Opiates
Buprenorphine/metabolite	Oxycodone/oxymorphone
Cannabinoids	Phencyclidine
Cocaine/metabolites	

Abbreviations: MDMA, 3,4-methylenedioxy-methamphetamine.

9.3 PK Samples

Samples for total radioactivity concentration determination in whole blood, plasma, urine, and feces, and the determination of concentration of TAK-954 in plasma and urine will be collected as specified in the schedule of study procedures (Section 3.0). Refer to the laboratory manual for information on collecting, processing, and shipping samples to the central laboratory.

A detailed PK analysis plan will be prepared before PK parameter computation.

It is anticipated that the total blood volume drawn in this trial will be approximately 400 mL.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Plasma sample for TAK-954 PK	Plasma	PK measurement	Mandatory
Urine sample for TAK-954 PK	Urine	PK measurements	Mandatory
Plasma, urine, and feces for metabolite profiles	Plasma/urine/feces	Metabolic profiling	Mandatory
Blood and plasma sample for total radioactivity	Blood and plasma	Total radioactivity	Mandatory
Feces samples for total radioactivity	Feces	Total radioactivity	Mandatory

Abbreviation: PK, pharmacokinetics.

9.3.1 PK Evaluations

The following parameters for TAK-954 and/or total radioactivity will be calculated. The PK parameters for TAK-954 and/or total radioactivity will be derived using noncompartmental analysis methods and will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times. A more detailed description will be given in the clinical pharmacology analysis plan.

The following plasma PK parameters for TAK-954 and both plasma and whole blood PK parameters for radioactivity will be calculated:

- C_{max}.
- AUC_{last}.
- AUC_{∞}.
- t_{max}.
- $t_{1/2z}$.
- CL (TAK-954 only).
- V_z (TAK-954 only).

The following urinary PK parameters will be calculated for both TAK-954 and radioactivity:

- A_{et}.
- f_{et}.

The following fecal parameter will be calculated for total radioactivity:

- f_{et}.

The following radioactivity parameters/profiles will be calculated:

- Cumulative recovery (% urine, % feces, and percentage of total radioactivity in urine and feces over the entire period of collection).
- TAK-954 metabolite profiles in plasma, urine, and feces.

Other PK parameters may be calculated if deemed necessary for the interpretation of the data including PK parameters for the metabolites THRX513466 and THRX 913682, if possible.

Radioactivity in plasma will be measured and reported in unchanged drug equivalents per volume of plasma (eg, ng-eq/mL). Noncompartmental PK parameters (t_{max}, C_{max}, AUC_{last}, AUC_{∞}, $t_{1/2z}$) will be calculated from the plasma radioactivity concentration-time data.

Unchanged drug and metabolite concentrations in plasma will be measured and reported in mass per volume of plasma (eg, ng/mL), and the percentage of total radioactivity associated with TAK-954 and metabolites will be calculated. Noncompartmental PK parameters (including t_{max}, C_{max}, AUC_{last}, AUC_{∞}, CL (TAK-954 only), V_z (TAK-954 only), $t_{1/2z}$) will be calculated from the plasma concentration-time data.

Radioactivity in whole blood will be measured and reported in unchanged drug equivalents per volume of blood (eg, µg-eq/mL). The total radioactivity ratio of whole blood to plasma will be calculated.

Radioactivity in urine will be measured and reported as the percentage of the administered radioactivity excreted at each time interval and the total percentage of dose excreted in urine.

The percentage of total radioactivity associated with TAK-954 and metabolites (where possible) will be calculated. Renal clearance of unchanged drug may also be calculated (if appropriate).

Radioactivity in feces will be measured and reported as the percentage of the administered radioactivity excreted at each time interval and the total percentage of dose excreted in feces.

The percentage of total radioactivity associated with TAK-954 and metabolites (where possible) will be calculated.

For metabolite profiling of urine and feces, samples collected at different time intervals for each subject will be pooled. Pooling will occur in proportion to the amount (weight or volume) of excreta collected in each sampling period.

PK Assessments

It is extremely important to quantitatively collect all scheduled blood, urine, and feces samples. The separate collection of urine and feces is critical to the success of this study. If urine and feces become mixed at any collection, note the weight and add the feces-contaminated urine to the feces collection. Samples missed or lost for any reason should be documented.

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be recorded as a protocol deviation. The exact collection time of all samples must be noted on the source document and data collection tool (eCRF).

Detailed instructions for processing plasma samples will be provided to the site before the initiation of the study. Samples will be analyzed for TAK-954 and 2 of the standard metabolites using a validated analytical method.

Detailed instructions for processing plasma radioactivity samples will be provided to the site before the initiation of the study. Samples will be assayed for radioactivity using the clinical research unit's standard operating procedures.

9.3.1.1 Blood Collection for Total Radioactivity and TAK-954 PK

More detailed sample handling information can be found in the TAK-954-1005 laboratory manual for all the following sections.

9.3.1.2 Blood Collection for Metabolite Profiling

More detailed sample handling information can be found in the TAK-954-1005 laboratory manual for all the following sections.

9.3.1.3 Urine Collection for Total Radioactivity and Metabolic Profiling

More detailed sample handling information can be found in the TAK-954-1005 laboratory manual for all the following sections.

9.3.1.4 Fecal Collection for Total Radioactivity and Metabolic Profiling

More detailed sample handling information can be found in the TAK-954-1005 laboratory manual for all the following sections.

9.3.1.5 Unscheduled Sample Collection

More detailed sample handling information can be found in the TAK-954-1005 laboratory manual for all the following sections.

9.3.1.6 Emesis

More detailed sample handling information can be found in the TAK-954-1005 laboratory manual.

9.3.2 Confinement

Subjects will be confined from admission for a minimum of 7 days. If the recovery of radioactivity has not met the target conditions specified below, a subject's duration of confinement may be maximally extended to Day 15 (336 hours postdose). Should the duration of confinement be extended, clinical assessments planned at discharge will be rescheduled accordingly.

A subject will be discharged from the clinic when at least 1 of the following criteria has been met for that subject:

- ≥90% of the administered radioactivity has been recovered in excreta.
- Excreta samples from 2 consecutive days contain <1% of the administered radioactivity.

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 preexisting 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) and symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs and symptoms should be recorded appropriately as an AEs.

Laboratory values and ECG findings:

- Changes in laboratory values and 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). Laboratory retests and continued monitoring of an abnormal value are not considered interventions. 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), only the diagnosis should be reported appropriately as an AE.

Preexisting conditions:

- A preexisting 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) 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 preexisting episodic condition (eg, asthma, epilepsy), any occurrence of an episode should be captured as an AE only if the episodes become more frequent, serious, or severe in nature, and 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 be captured as an AE only if occurring to a greater extent than 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 and procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of worsening of the preexisting 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 and 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 eCRF to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE eCRFs according to Section 10.0.
- 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.

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).

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

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

Severe: An AE 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 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 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 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 AE (Frequency)

Episodic AEs (eg, headache) or those that 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 because of the particular AE.
- Dose not changed: The particular AE did not require stopping a study medication.
- Unknown: To be used only if it is not possible to determine what action has been taken.
- Not applicable: A study medication was stopped for a reason other than the particular AE; eg, the study has been terminated, the subject died, dosing with study medication had not yet started, or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced: The dose was reduced because of the particular AE.
- Dose increased: The dose was increased because of the particular AE.
- Drug interrupted: The dose was interrupted because of the particular AE.

10.2.7 Outcome

- Recovered/resolved: The subject returned to first assessment status with respect to the AE.

- Recovering/resolving: The intensity is lowered by one or more stages: The diagnosis 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 because of 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, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (AEs, SAEs, and abnormal LFTs) will commence when the subject signs the informed consent. Routine collection of AEs will continue until the follow-up visit on day 15 (±2 days). For subjects who discontinue before 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 before 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 until there is a satisfactory explanation for the change. Nonserious AEs that begin before 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 eCRF, 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).
- Action taken with trial drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs during 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 after first onset or notification of the event. The information should be completed as fully as possible but must contain, at a minimum:

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

The SAE form should be transmitted within 24 hours.

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 the first administration of investigational product will follow the same procedure as SAEs occurring on treatment.

SAE Follow-up

If information not available at the time of the first report later becomes available, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours after 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 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 eCRF 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 and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported per Section 10.2.8.3. The investigator must contact the sponsor's 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 9.2.8 must also be performed. In addition, an LFT increases eCRF must be completed and transmitted with the Takeda SAE form.

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 that 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 product administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to the site's IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

The safety analysis set will include subjects who are enrolled in the study and receive at least 1 dose of study drug. Subjects in this analysis set will be used for demographic and safety summaries.

11.1.1.2 PK Set

The PK analysis set will consist of all subjects in the safety analysis set with sufficient concentration data to facilitate the derivation of at least 1 PK parameter from the concentration-time data. All subjects who have a valid PK parameter estimated will be included in the analyses and summary statistics for that parameter.

All subjects who have valid concentration data at a scheduled sample collection time will be included in the summary statistics.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using the safety analysis set. Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age and weight), and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, ethnicity, and race).

The number and percentage of subjects who are enrolled, complete the study visit, those who discontinue early, and each reason for discontinuation will be summarized.

11.1.3 PK and Radioactivity Analysis

11.1.3.1 Concentration Data

Plasma concentration of TAK-954 and its metabolites and total radioactivity in whole blood and plasma at each scheduled time point will be summarized using descriptive statistics.

Mass balance will be assessed by the percentage and cumulative percentage of administered radioactive dose recovered in urine and in feces and their combined total at appropriate intervals. Descriptive statistics will be used.

Mean and individual cumulative excretion of radioactivity in urine and in feces and their combined total by time curve will be displayed.

Individual percentage and cumulative percentage will be presented in data listings.

All concentration data will be listed.

11.1.3.2 PK Parameters

Descriptive statistics will be used to summarize the PK parameters. All PK parameter data will be listed. Statistical analyses will be performed if appropriate.

11.1.3.3 Metabolites

Circulatory and excretory metabolite profiles will be established for each subject. Metabolites will be presented as a mean percentage of total radioactivity and/or dose. Descriptive statistics will be used.

11.1.4 Safety Analysis

All safety assessments, including AEs, clinical laboratory evaluations, vital signs, and ECG findings, will be presented in the data listings and summarized using descriptive statistics for all subjects in the safety analysis set, where appropriate.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Data will be summarized using Preferred Term and primary System Organ Class.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 Determination of Sample Size

No formal sample size calculations have been performed. The sample size (n = 6) is based on the consideration that radioactivity is being administered to healthy subjects and that generally 6 subjects is sufficient to characterize the endpoints described in the protocol and is accepted by regulatory agencies.

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 eCRFs. 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 (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized) including, but not limited to, the investigator's binder, trial drug, subject medical records, informed consent documentation, and review of eCRFs 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 when necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that require deviation from protocol-specified procedures, the investigator should consult the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (prospectively approved deviations) 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 United States [US] Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). The sponsor should be notified immediately if the study site is contacted for an inspection by a regulatory body. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council 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 listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB/IEC Approval

This study will be conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS (Council for International Organizations of Medical Sciences) International Ethical Guidelines, ICH GCP guidelines, and laws and regulations applicable to clinical studies (including US 21 Code of Federal Regulations [CFR] and European Union Clinical Trials Directive 2001/20/EC).

- The protocol, ICFs, investigator's brochure, and other relevant supporting documents (eg, advertisements, information on payments and compensation available to subjects) must be submitted to an IRB/IEC by the investigator. Written approval of the protocol from the IRB/IEC must be obtained before the study is initiated, ie, the first subject signs the study ICF.
- The study cannot be initiated until notification is received from the sponsor.
- Any amendment to the protocol, except when necessary to eliminate an immediate hazard to study participants, requires IRB/IEC written approval before implementation.
- If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of an amendment.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

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 ICF, 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 ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that participants are free to withdraw at any time without giving a reason and without prejudice to further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, 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 ICF, 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. If 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 to participate in the study. If the subject, or the subject's legally acceptable representative, determines that the subject will participate in the study, then the ICF 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 before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a blue or black ballpoint pen. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters 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 ICF, 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 ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs 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 ICF.

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 be linked only 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, 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, US 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 by 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 (subject name, address, and other identifier fields not collected on the subject's eCRF).

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 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

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 or other publicly accessible websites before the start of the study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers with 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 to request 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, the caller should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with 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 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 clinical study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. The investigator should contact the sponsor or sponsor's designee with any questions regarding this policy.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

Trial contact numbers can be found in the study manual, the communication plan, or other similar documents provided to the site.

14.1.1 Investigator Agreement

I confirm that I have read and that I understand this protocol, the investigator's brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and 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.
- ICH E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.9 of this protocol.
- Terms outlined in the clinical 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 C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

14.1.2 List of Abbreviations

^{14}C	carbon-14
AE	adverse event
A_{et}	Amount of total radioactivity and/or TAK-954 excreted in urine/feces from 0 to time t
ALT	alanine aminotransferase
AMS	accelerator mass spectrometry
AST	aspartate aminotransferase

AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BMI	body mass index
CFR	Code of Federal Regulations
CL	total clearance after intravenous administration
C_{max}	maximum observed concentration
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
f_{et}	fraction of TAK-954 dose and/or total radioactivity excreted in urine/feces from time 0 to time t
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
PK	pharmacokinetics
QD	once daily
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of maximum observed concentration
ULN	upper limit of normal
US	United States
V_Z	volume of distribution during the terminal disposition phase after intravenous 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 MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

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

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the data 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 eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

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

eCRFs 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 eCRFs. The completed eCRFs 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 ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), eCRFs 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

Not applicable

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on 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 before 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. A valid ICF is the most current version approved by the IRB/IEC. Each ICF 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 ICF 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 eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or

that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

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

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. 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 description of the possible side effects of the treatment that the subject may receive.
10. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
11. 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.
12. 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.
13. 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, auditors, IRBs/IECs, and the medical monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
14. 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.
15. The anticipated prorated payments, if any, to the subject for participating in the study.
16. The anticipated expenses, if any, to the subject for participating in the study.
17. 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.
18. 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.

19. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
20. 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.
21. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
22. A written subject authorization (either contained within the ICF 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) 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, 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) 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) 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.
    e) The subject's identity will remain confidential if study results are published.
23. Male subjects must use highly effective contraception (as defined in the informed consent) and avoid sperm donation from signing the informed consent throughout the duration of the study and for 30 days after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive treatment information.
24. A statement that clinical trial information from this trial will be disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

A Phase 1, Open-label, Single Intravenous Infusion Dose Study to Evaluate the Mass Balance, Pharmacokinetics, Metabolism, and Excretion of TAK954 Containing Microtracer ([14C]-TAK-954) in Healthy Adult Male Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	28-Mar-2018 13:13 UTC
	Clinical Science Approval	28-Mar-2018 19:49 UTC
	Clinical Pharmacology Approval	28-Mar-2018 23:25 UTC