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

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-954-1005

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

PHASE 1

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CV	coefficient of variation
CRF	case report form
ECG	electrocardiogram
HR	heart rate
LLN	lower limit of normal
MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 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.

4.2 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.

4.3 Study 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).

5.0 ANALYSIS ENDPOINTS

5.1 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 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 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Continuous data will be summarized using number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, percent of coefficient of variation (%CV) and geometric mean, will also be included in the summary of continuous data. Categorical data will be summarized using the number and percent of subjects (N [%]) for each category where appropriate.

Unless otherwise stated, Baseline will be defined as last observation prior to administration of the study drug.

In general, the presentation of decimal points will follow the following rules as appropriate: minimum and maximum values will be presented using the same number of decimal places as the recorded data. Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data.

All statistical analyses will be performed using the SAS System® Version 9.4 or higher.

7.1.1 Study Definitions

There are no study-specific definitions.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the electronic case report form (eCRF) dosing page. Other study days are defined relative to Study Day 1, with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug}. Study days on or after the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug + 1}.

7.1.3 Definition of Study Visit Windows

All data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

7.1.4 Conventions for Missing Adverse Event Dates

When calculating the duration/ onset of adverse events (AE), any AEs with start and/ or end times that are partially or completely missing will be imputed as follows:

- If start time is missing, then impute to 00:01.
- If end time is missing, then impute to 23:59.

There will be no imputation of incomplete or missing adverse event dates.

7.1.5 Conventions for Missing Data

There will be no imputation of incomplete or missing data. Inclusion of subjects who are noncompliant with the dosing or who have incomplete data, will be made on a case-by-case basis.

Plasma or urine concentrations that are below the limit of quantification (< BLQ) will be treated as zero in the summarization of concentration values and derivation of PK parameters. They will be flagged in the data listings; however, deviations from this convention may be considered on a case-by-case basis.

7.2 Analysis Sets

Safety Set

The Safety Analysis Set will include subjects who are enrolled in the study and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristic and safety summaries.

Pharmacokinetic (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.

7.3 Disposition of Subjects

The number and percentage of subjects who are enrolled, complete the study drug and study visits, who prematurely discontinue study drug and/or study visits and each reason for discontinuation will be summarized. Subjects' study completion data, including reasons for premature termination, will be listed.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for subjects in the safety set. Descriptive statistics (number of subject (N), mean, SD, median, minimum and maximum) will be generated for continuous demographic variables and baseline characteristics variables (e.g., age, height, weight, and BMI), and the number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (e.g., gender, ethnicity and race of the subject) will be tabulated. Individual subject demographic and baseline characteristics data will be listed.

There will be no inferential analysis of demographic and baseline characteristics.

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that resolved at or prior to the time of informed consent. Concurrent medical conditions are defined as significant conditions or diseases that are present or ongoing at signing of informed consent.

Medical history and concurrent medical conditions will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0 or higher). No summary statistics for medical history and concurrent medical conditions will be provided.

Medical history and concurrent medical conditions will be listed by subject number. The listing will contain subject identifier, system organ class (SOC), preferred term (PT), whether there was any medical history or concurrent condition, and, if yes, a detail of the medical history or concurrent condition.

There will be no inferential analysis of medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped at or within 7 days prior to administration of the initial dose. Concomitant medications are recorded on the eCRF and include any medications, other than study drug, taken at any time from signing of informed consent through the end of the study. No summary statistics for medication history and concomitant medications will be provided.

All medication history and concomitant medications will be listed by site and subject number. The listings will contain subject identifier, World Health Organization Drug Dictionary (WHODrug) preferred medication name, dose, unit, frequency, route, start date, stop date, whether the medication was ongoing, and reason for use. No inferential statistics will be presented.

Medication history and concomitant medications will be coded using the WHODrug Global B2 or higher.

7.7 Study Drug Exposure and Compliance

The date, start and end of infusion time of study drug for each subject will be reported in the data listings. Summaries of TAK-954 PK data will be provided; details can be found in section 7.9. No other summaries of the extent of exposure to study drug or compliance calculations are planned.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

All PK summaries and analyses will be based on the PK set.

Samples for total radioactivity concentration determination in whole blood, plasma, urine, and feces, the determination of concentration of TAK-954 in plasma and urine, and metabolite profiling in plasma, urine and feces will be collected as specified in the Schedule of Study Procedure (see Appendix A).

7.9.1 Pharmacokinetic Analysis

7.9.1.1 TAK-954 Concentration and Total Radioactivity Data

Descriptive statistics (n, mean, SD, geometric mean, coefficient of variation (%CV), median, minimum, and maximum) will be used to summarize plasma concentration of TAK-954 and its metabolites and total radioactivity in whole blood and plasma at each scheduled time point, respectively. Linear and semi-logarithmic mean and individual plots of plasma concentration of TAK-954 and total radioactivity will be displayed by time, respectively. Nominal sampling times, rather than actual times, will be used in generating mean concentration-by-time curves; while actual sampling times will be used in individual plots.

The ratio of total radioactivity in whole blood to plasma, and the ratio of plasma TAK-954 to total radioactivity in plasma will be derived and summarized at each time point.

Individual plasma concentration data will be listed.

7.9.1.2 PK Parameters

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, using Phoenix WinNonlin:

- 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}.
- CL_R(TAK-954 only)

The following fecal parameter will be calculated for total radioactivity:

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

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.

Descriptive statistics (N, mean, SD, %CV, median, minimum and maximum) will be used to summarize the PK parameters. In addition, geometric means will be calculated.

Additional analyses may be performed as deemed appropriate.

All PK parameter data will be listed.

7.9.1.3 Radioactivity Parameters/ Profiles

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.

Mass balance will be assessed by percent and cumulative percent of administered radioactivity dose recovered in urine, feces and their combined total at appropriate time points.

Descriptive statistics (N, mean, SD, %CV, median, minimum and maximum) will be summarized by each scheduled timepoint.

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

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

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

The results of metabolite profiling will be included in a separate report.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety analyses include AEs, clinical laboratory evaluations, vital sign results, 12-lead ECG results, and other safety parameters. The safety set will be used for all summaries of safety parameters.

7.11.1 Adverse Events

An adverse event (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 study participation. A treatment-emergent adverse event (TEAE) is defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, which occurs on or after the administration of the study drug and no more than 30 days after receiving the study drug (onset date minus date of last dose +1 ≤ 30). A TEAE may also be a pretreatment AE or a concurrent medical condition diagnosed prior to the date of study drug that increases in severity after the start of dosing. Any event with partially or completely missing onset date information will be considered treatment emergent unless the available information indicates that the onset occurred outside the window (onset date - date of last dose +1 > 30) or onset date prior to the first dose.

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0 or higher).

AEs are recorded in the eCRF as being related or not related to study drug and study procedure. AEs that are recorded as related to study drug and/or study procedure will be summarized separately. AEs will also be presented by intensity/severity (mild, moderate, and severe).

When calculating the frequency and percentage of subjects who reported AEs, a subject will be counted only once for each SOC or PT when multiple AEs are coded to the same SOC or PT.

AEs with missing intensity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. If the relationship of an event is missing, the relationship for the event will be considered to have been related.

The TEAE summary tables will include numbers and percentages of subjects experiencing at least one TEAE by SOC and PT and will be tabulated. The following is a list of TEAE summary tables to be generated:

- Overview of TEAEs.
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Drug-Related TEAEs by SOC and PT.

Also, non-treatment-emergent AEs will be summarized by SOC and PT. Data listings will be provided for all AEs including TEAEs, AEs leading to trial drug discontinuation, and SAEs.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be assessed using the Safety Set and will be evaluated and presented using International System of Units (SI) units unless otherwise stated. Refer to Appendix A for scheduled clinical laboratory test measurements.

For hematology and chemistry tests, descriptive statistics (N, mean, median, SD, minimum and maximum) will be summarized for baseline, post-baseline, and change from baseline values by study visit. Only the scheduled measurements will be included in the summary. No inferential statistics will be presented.

Listings of all clinical safety laboratory data will be provided and will be presented in both SI and conventional units. Laboratory data outside of the normal reference range will be indicated in the listings and flagged. The listing will include site number, subject identifier, age (at informed consent), gender, study visit, and sample collection date.

7.11.3 Vital Signs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize vital sign parameters at baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Only the scheduled visits will be included in the summary. No inferential statistics will be presented.

All vital sign results for all subjects in the Safety Set will be listed by subject in the data listings and abnormal values will be flagged.

7.11.4 12-Lead ECGs

The scheduled 12-lead ECG data will be collected according to Appendix A. The ECG parameters include heart rate, PR interval, QRS interval, QT interval, and QTcF interval, and the interpretation of the ECG profile by the principal investigator.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters will be presented for baseline, each post-baseline visit, and changes from baseline in quantitative ECG parameters to each post-baseline visit. Only the scheduled measurements will be included in the summary. No inferential statistics will be presented.

All ECG data will be presented in the listings. Abnormal values will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Based on consultation with pharmacovigilance, the last pre-dose value will be used as the Baseline for ECG summaries, rather than Screening as stated in the protocol. Based on discussion with the team, instead of the individual excretory metabolite profiles, pooled excretory metabolite profiles will be established.

8.0 REFERENCES

1. 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, Millennium Pharmaceuticals, Inc., Initial. Trial No. TAK-954-1005, dated 26 March, 2018.

Appendix A 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											
Hepatitis panel	X											
Pharmacokinetics (PK) Evaluations												
Blood collection for total radioactivity in			X----------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**	
whole blood and plasma, TAK-954 in plasma, and metabolite profiling [c]												
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.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	24-Oct-2018 14:11 UTC
	Clinical VP Approval	24-Oct-2018 14:21 UTC
	Biostatistics Approval	24-Oct-2018 15:10 UTC
	Clinical Pharmacology Approval	24-Oct-2018 15:44 UTC