Title: A Phase 1, Nonrandomized, Open-Label Trial to Evaluate the Effect of Hepatic Impairment on the Single Dose Pharmacokinetics of Intravenous TAK-954

NCT Number: NCT03277274

SAP Approve Date: 05 September 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.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-954-1006

A Phase 1, Nonrandomized, Open-Label Trial to Evaluate the Effect of Hepatic Impairment on the Single Dose Pharmacokinetics of Intravenous TAK-954

PHASE 1

Version: Final

Date: 05 September 2018

Prepared by:

PPD

Based on:

Protocol Version: Amendment 01

Protocol Date: 06 October 2017

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1.2 Approval Signatures

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

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
CCI	[redacted]
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
CI	confidence interval
CL	clearance
CCI	[redacted]
C_{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
CCI	[redacted]
HR	heart rate
LLN	lower limit of normal
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
PGx	pharmacogenomics
PK	pharmacokinetics
PT	Preferred term
PTE	Pretreatment adverse event
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System organ class
CCI	[redacted]
TEAE	treatment-emergent adverse event
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objective

The primary objective of the trial is to evaluate the effect of varying degrees of hepatic function on the single dose pharmacokinetics of IV TAK 954.

4.2 Secondary Objective

The secondary objective of the trial is to evaluate the safety and tolerability of single IV doses of TAK 954 in subjects with varying degrees of hepatic function.

4.3 Exploratory Objectives

Exploratory objectives of this trial include:

CCI

[redacted]

4.4 Study Design

This is a phase 1, nonrandomized, open-label trial in males and females (non-childbearing potential) with hepatic impairment and healthy males and females. Table 4.a displays the number of subjects who will participate in the study based on design options:

Table 4.a Number of Subjects Based on Study Design Options

Group	Number of Subjects	Total Number of Subjects
Reduced Study Design		
Group 1 (Mild)	0	~24
Group 2 (Moderate)	Minimum of 8	
Group 3 (Severe)	Maximum of 8	
Group 4 (Healthy)	Minimum of 8	
Full Study Design		
Group 1 (Mild)	Minimum of 8	~32
Group 2 (Moderate)	Minimum of 8	
Group 3 (Severe)	Maximum of 8	
Group 4 (Healthy)	Minimum of 8	

The groups will be enrolled in a staggered fashion, beginning with Group 2 (Child-Pugh Class B). After safety and PK data are available for 2 subjects in Group 2, dosed at 0.2 mg, Takeda personnel and the investigator will review this data and confirm or modify the TAK-954 dose for the remaining 6 subjects. Enrollment of healthy subjects (Group 4) may begin after the second moderately hepatically-impaired subject (Group 2) is enrolled. As much as possible, the healthy

subjects should be comparable to the hepatic impairment groups with respect to median age and weight (approximately 50% of healthy subjects on each side of the median age and weight of currently enrolled hepatically-impaired subjects grouped together), gender, and race. This will be decided by the investigator in discussion with Takeda. When Group 2 has completed, and following another assessment of PK and safety, Takeda personnel and the investigator will decide whether to enroll subjects in Group 1 (Child-Pugh Class A) or not (reduced vs full trial design). During this review the dose for subjects from Group 1 and/or Group 3 will be selected.

Table 4.b Hepatic Function Categories Based on Child-Pugh Score

Assessment Parameters	Points Scored for Observed Findings (a)		
	1 point	**2 points**	**3 points**
Encephalopathy grade (b)	none	1 or 2	3 or 4
Ascites	absence	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, seconds prolonged	<4	4 to 6	>6

Source:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.
(a) Classification of clinical severity:
Mild (Class A): total score 5-6 points.
Moderate (Class B): total score 7-9 points.
Severe (Class C): total score 10-15 points.
(b) Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

The trial will include a Screening Visit, an in-patient period, and a Follow-up Visit.

Blood for free and total plasma concentration and urine samples for assessment of TAK-954 concentrations will be collected before the start of the TAK-954 infusion and at intervals up to 96 hours after the start of the infusion. Samples may be assayed for TAK-954 metabolites. TAK-954 and its metabolites may also be assayed in urine, data permitting and if deemed possible. Plasma protein binding of TAK-954 will also be assessed.

Whole blood samples for DNA PGx analysis and RNA isolation will be collected predose on Day 1.

Safety will be assessed by monitoring for AEs, ECGs, vital signs, safety laboratory tests, and physical examinations throughout the trial.

After completion of the trial (or after subject withdrawal), all subjects will return for a Follow-up Visit, approximately 10 to 14 days after the dose of trial drug.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints of the trial are the following PK parameters (expressed as total and free):

- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time 0 to the last measurable time point, (AUC_{last}).
- Area under the concentration-time curve from time 0 to and extrapolated to infinity (AUC_{∞}).

5.2 Safety Endpoints

Safety endpoints include the following:

Safety and tolerability will be assessed through physical examinations, ECGs, vital signs, and clinical laboratory assessments, and collection of spontaneous AEs.

5.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

PK parameters:

CCI

6.0 DETERMINATION OF SAMPLE SIZE

The planned sample size of 8 subjects in each hepatic function group is in line with regulatory guidance for these types of studies ("FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" and "EMEA Guideline on The Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function"). The sample size of 8 healthy subjects allows for healthy subjects to be represented for a comparator or reference.

Subjects who drop out may be replaced at the discretion of the sponsor in consultation with the investigator. Subjects who replace dropouts will begin the trial as a new subject.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Continuous data will be summarized using the following: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, 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 percentage of subjects for each category where appropriate.

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

All statistical tests will be two-tailed at α=0.05 level for significance unless otherwise stated. P-values (when rounded to three digits) less than or equal to α are reported as "significant". "No statistically significant difference" means that all p-values for the tests are greater than α. All computations will be performed prior to rounding.

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. The confidence interval (CI) for a parameter estimate will be presented using the same number of decimal places as the parameter estimate. Percentage will be presented to 1 decimal place (e.g., 80.1%). All p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

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}.

7.1.2 Definition of Study Visit Windows

There will be no visit windowing.

7.1.3 Conventions for Missing Adverse Event Dates

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

7.1.4 Conventions for Missing Concomitant Medication Dates

There will be no imputation of incomplete or missing concomitant medication 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

The following analysis sets will be used for analysis and presentation of the study data:

- Safety Set: The safety set will consist of all subjects who are enrolled and receive the study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.
- Pharmacokinetic (PK) Set: The PK set will consist of all subjects who are enrolled and receive the appropriate dose of trial drug and have at least 1 measurable plasma concentration or amount of drug in the urine for TAK-954. All subjects with valid PK parameter estimates will be included in the summaries and analyses for that parameter. The subjects receive inappropriate dose will not be included in PK set, but the data from those subjects will be listed and flagged.

7.3 Disposition of Subjects

The number and percentage of subjects who are enrolled, complete study drug and study visits, and who prematurely discontinue study drug and/or study visits will be summarized by hepatic function group (healthy subjects, mild, moderate and severe hepatic impairment) and overall. Subjects' study completion data, including reasons for premature termination, will be listed. Additionally, disposition information for screen failures will be listed. A listing of inclusion/ exclusion criteria not met will be provided for subjects who did not meet at least one inclusion criterion.

Significant protocol deviations will be listed and summarized.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for subjects in the safety set. Summaries will be presented by all subjects and each hepatic function group. Summary statistics (number of subjects (N), mean, SD, median, minimum, and maximum) will be presented for continuous variables (e.g., age, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (e.g., sex, ethnicity, and race). Individual subject demographic and baseline characteristic data will be provided in the data

listings. In addition, baseline hepatic function parameters and Child-Pugh scores will be summarized by group.

Demographic variables for screen failure subjects and reasons for screen failures will be summarized for subjects who are screened but not enrolled in the study.

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 20.0 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 site and subject number. The listing will contain subject identifier, hepatic function group, 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 30 days prior to signing of informed consent. 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, hepatic function group, 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 2018 March DDE B2 or higher.

7.7 Study Drug Exposure and Compliance

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

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic Analysis

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

PK blood for plasma concentration and urine samples for TAK-954 (and metabolites, if possible), and plasma protein binding will be collected as specified in the Schedule of Trial Procedures (See Appendix C).

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 from dosing will not be captured as a protocol deviation, as long as the exact time of dosing and the sample collection is noted on eCRF.

7.9.1 Summary of Concentrations in Plasma

Descriptive statistics (e.g. mean, standard deviation, standard error, %CV, minimum, median and maximum) will be used to summarize concentrations of TAK-954 (and metabolites, if possible) according to the hepatic function group (healthy subjects and mild, moderate, severe hepatic impairment). If applicable, the amount of TAK-954 excreted in urine will also be summarized by hepatic function group using descriptive statistics. For protein binding data, concentration, unbound percentage, bound percentage and recovery percentage will be summarized according to hepatic function group using descriptive statistics.

Linear and semi-logarithmic plots of the mean and individual concentration-time curves will be provided.

Individual concentration data will be presented in the data listing.

7.9.2 Analysis of Pharmacokinetic Parameters

PK parameters will be compared between normal and hepatically-impaired groups, classified by Child-Pugh Score and summarized descriptively. PK parameters of TAK-954 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.

The following plasma PK parameters (free and total) for TAK 954 will be calculated:

- C_{max}
- AUC_{∞}
- $AUC_{last.}$

Specific or additional PK parameters may be added as appropriate per the Clinical Pharmacology Analysis Plan (CPAP).

Descriptive statistics (e.g. mean, standard deviation, standard error, %CV, minimum, median and maximum) will be used to summarize PK parameters (expressed as free and total) according to the hepatic function group (healthy subjects and mild, moderate, severe hepatic impairment). In addition, geometric means will be calculated for C_{max} and AUCs.

All pharmacokinetic parameters will be provided in a data listing.

An analysis of variance (ANOVA) will be performed on log transformed C_{max}, AUCs (total and free) and CL to compare each hepatically-impaired group with the normal hepatic function group and 90% confidence intervals for the ratio of central values from each hepatic impairment group versus normal function group will be provided. In addition, an analysis of covariance (ANCOVA) with hepatic function group as a fixed effect, age, gender and body weight as covariates will be performed on log transformed Cmax, AUCs (total and free) and CL to investigate effect of covariates on the relationship between TAK-954 PK parameters and level of hepatic impairment. Tests will be performed on all covariates, 0.05 significance level will be used.

In addition, the relationship between Child-Pugh scores, baseline serum bilirubin, serum albumin, prothrombin time and TAK-954 C_{max}, C_{maxu}, AUC_{last}, AUC_{lastu}, AUC_{∞} and $AUC_{\infty u}$ will be evaluated graphically. Regression approaches will be used to evaluate these relationships if appropriate.

Additional analyses will be included, if appropriate. Any deviation from the analysis plan will be reported in the Clinical Study Report.

Individual pharmacokinetic parameter data will be presented in the data listing.

7.10 Other Outcomes

Subject must sign a PGx informed consent/be consented for sampling of whole blood for PGx analysis to occur. PGx sampling is optional.

Whole blood samples for DNA and RNA isolation will be collected from each consented subject in the trial. If necessary and feasible, a second aliquot of blood may be taken at a later time point if isolation of DNA from the first sample was not successful or possible.

The sample collection information for PGx will be listed.

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

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study, but prior to administration of any study drug; 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 the 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 data minus date of 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 data - date of dose +1 ≤ 30).

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0 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. For the intensity or relatedness summaries, if a subject reports multiple AEs coded to the same SOC or PT, the AE with maximum intensity or strongest relationship will be included in the summary.

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 by hepatic function groups and overall. The following is a list of TEAE summary tables to be generated:

- Overview of TEAEs.
- TEAEs by SOC and PT
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Serious TEAEs by SOC and PT
- Most Frequent Non-Serious TEAEs by PT (>=5% subjects in any group)
- Drug-Related TEAEs by SOC and PT.
- Relationship of TEAEs to Study Drug by SOC and PT (related vs not related).
- Intensity of TEAEs by SOC and PT.
- Intensity of Drug-Related TEAEs by SOC and PT.
- PTE 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 consist of chemistry, hematology, urinalysis, and other tests. 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 C for scheduled clinical laboratory test measurements.

Clinical laboratory variables will be summarized by hepatic function group with descriptive statistics (N, mean, median, SD, minimum and maximum) for Baseline, postdose, and change from Baseline to postdose values. Instead of Calcium, corrected Calcium will be summarized. Corrected Calcium can be calculated via the following formulas.

- In conventional units: Corrected Calcium [mg/dL] = (0.8 * (4[mg/dL] – Albumin[mg/dL])) + Calcium[mg/dL].
- In SI units: Corrected Calcium [mmol/L] = (0.02 * (40[g/L] – Albumin[g/L])) + Calcium[mmol/L].

Here 4mg/L and 40g/L represent normal Albumin levels.

Only the scheduled measurements will be included in the summary. The baseline value will be defined as the pretreatment assessment immediately prior to administration of study drug. No inferential statistics will be presented.

All clinical laboratory data in SI and conventional Units will be presented in the data listings.

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. No inferential statistics will be presented.

For each vital sign parameter, boxplots for predose/ postdose values and the change from the predose by hepatic function group will be prepared.

Individual results of vital signs that meet Takeda's markedly abnormal criteria (see Appendix A) will be summarized and provided in the data listings. If a subject has a MAV for a particular vital sign parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 postdose MAV signs measurement will be summarized by hepatic function group. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

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

7.11.4 12-Lead ECGs

The scheduled 12-lead ECG data will be collected according to Appendix C. The ECG parameters include heart rate, PR-interval, QRS-duration, QT-interval, 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. If more than 1 ECG parameter is measured at the same scheduled time point, the latest value will be used. No inferential statistics will be presented.

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet Takeda's markedly abnormal criteria (see Appendix B) will be provided in the data listings. Shift tables will be generated to show the investigator's ECG interpretations at each postdose collection by the interpretation at Baseline.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Physical examination findings will be presented in the data listings.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

8.0 BASED ON CONSULTATION WITH PHARMACOVIGILANCE, THE CORRECTED CALCIUM WILL BE SUMMARIZED, RATHER THAN CALCIUM AS STATED IN THE PROTOCOL. REFERENCES

1. A Phase 1, Nonrandomized, Open-Label Trial to Evaluate the Effect of Hepatic Impairment on the Single Dose Pharmacokinetics of Intravenous TAK-954, Takeda Development Center Americas, Inc. and Takeda Development Centre Europe Ltd., Amendment 01, Trial No. TAK-954-1006, dated 06 October, 2017.

Appendix A Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	<35.6	>37.7

Appendix B Criteria for Identification of Markedly Abnormal 12-Lead ECG Parameters

Parameter	Unit	Lower Criteria	Upper Criteria
HR	bpm	<50	>120
QTcF-interval	msec	≤50	≥500 OR ≥30 change from baseline and ≥450

Appendix C Schedule of Trial Procedures

Assessment	Screening	Trial Days						Follow-up/Early Termination
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**10-14 days after the dose**
Hours Postdose			**0**	**24**	**48**	**72**	**96**	
Administrative Procedures								
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Medical history/demographics	X							
Prior and concomitant medication review	X----------							----------X
Clinic Procedures/Assessments								
Full physical examination	X	X			X			X
Semirecumbent vital signs (heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]	X	X	X (a)	X	X	X	X	X
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature)	X		X					
Height	X							
Weight	X							
Body mass index (BMI)	X							
Standard 12-lead electrocardiogram (ECG)	X	X	X (a)	X	X	X		X
Adverse event (AE) monitoring	X----------							----------X
Laboratory Procedures/Assessments								
Serum chemistry	X	X			X			X
Hematology (b)	X	X			X			X
Urinalysis	X	X			X			X
Serum follicle-stimulating hormone (FSH)	X							
Urine drug screen	X	X						
Alcohol breath or urine alcohol test (c)	X	X						
HIV test	X							
Hepatitis panel	X							
Urine pregnancy test (hCG)		X						

Footnotes are on last table page.

Assessment	Screening	Trial Days						Follow-up/Early Termination
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**10-14 days after the dose**
Hours Postdose			**0**	**24**	**48**	**72**	**96**	
Pharmacokinetics (PK) Evaluations								
Plasma samples for TAK-954 (d)			X	X	X	X	X	
Urine sample for TAK-954 PK (e)			X	X	X			
Plasma sample for protein binding (f)			X					
Pharmacogenomic (PGx) Evaluations								
Blood sample for DNA PGx (optional)			X					
Blood sample for RNA PGx (optional)			X					
Drug Administration								
TAK-954 dosing			X					
Other								
Confinement (g)		X	X	X	X			
Meals			X					

(a) Assessments at predose (within 30 minutes), 1 (just after the end of infusion), 2, and 4 hours postdose (relative to TAK-954 start infusion start). Additional blood pressure and HR assessments will be taken at 0.5 and 12 hours after the start of infusion.
(b) Complete blood count and for Screening Visit only, coagulation screen (prothrombin time, international normalized ratio [INR], and activated partial thromboplastin time).
(c) Additional alcohol breath or urine alcohol tests may be done at the discretion of the investigator.
(d) Time points for PK blood samples for TAK-954: predose (within 30 minutes), and 0.33, 0.5, 0.67, 1 (just after the end of infusion), 1.5, 2, 3, 4, 6, 12, 24, 36, 48, 72 and 96 hours after start of infusion.
(e) Urine collected at predose, 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours postdose (relative to TAK-954 infusion start).
(f) Plasma for protein binding: 1 and 12 hours postdose (relative to TAK-954 infusion start).
(g) Length of confinement may be extended at the investigator's discretion.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	07-Sep-2018 14:56 UTC
	Statistical Approval	07-Sep-2018 16:23 UTC
	Biostatistics Approval	09-Sep-2018 17:49 UTC
	Clinical Pharmacology Approval	10-Sep-2018 17:46 UTC