Title: A Phase 1, Open-Label, Parallel Group Trial to Evaluate the Effect of Renal Impairment and Dialysis Treatment on the Pharmacokinetics of a Single Intravenous Dose of TAK-954

NCT Number: NCT03296787

SAP Approve Date: 12 December 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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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-954-1007

A Phase 1, Open-Label, Parallel Group Trial to Evaluate the Effect of Renal Impairment and Dialysis Treatment on the Pharmacokinetics of a Single Intravenous Dose of TAK-954

PHASE 1

Version: Final

Date: 12 December 2018

Prepared by:

PPD

Based on:

Protocol Version: Amendment 1

Protocol Date: 09 October 2017

1.1 Approval Signatures

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

Study Title: A Phase 1, Open-Label, Parallel Group Trial to Evaluate the Effect of Renal Impairment and Dialysis Treatment on the Pharmacokinetics of a Single Intravenous Dose of TAK-954

Approvals:

PPD

Date

Date

Date

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT APPENDICES

3.0 LIST OF ABBREVIATIONS

5-HT4	serotonin type 4
β-hCG	β–human chorionic gonadotropin
AE	adverse event
Ae	amount of drug excreted in urine
Ae_t	amount of drug excreted in urine from time 0 to time t
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{72}	area under the plasma concentration-time curve from time 0 to 72 hours
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measurable time point.
AUC_t	area under the plasma concentration-time curve from time 0 to time t.
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity.
BMI	body mass index
CFR	Code of Federal Regulations
CG	Cockcroft and Gault
CL	Total clearance after IV administration, calculated using the observed value of the last quantifiable concentration
CLcr	creatinine clearance
CL_D	dialysis clearance
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
CRU	clinical research unit
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P-450
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
EFI	enteral feeding intolerance
EMA	European Medicines Agency
ESRD	end stage renal disease
f_e	fraction of drug excreted in urine
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal

HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
RI	renal impairment
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
V_z	volume of distribution during the terminal disposition phase after intravenous administration, calculated using the observed value of the last quantifiable concentration
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives of the trial are to evaluate the effect of varying degrees of renal function on the PK of TAK-954 following single-dose IV administration and to investigate the impact of hemodialysis on the PK of single IV doses of TAK-954.

4.2 Secondary Objectives

To evaluate the safety and tolerability of TAK-954 following single-dose IV administration in subjects with varying degrees of renal function.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This is a phase 1, open-label, parallel group trial in subjects with normal renal function as well as subjects with mild, moderate, and severe renal impairment (RI) and end stage renal disease (ESRD) as defined in the table below.

Group	Description of Subjects	Estimated Creatinine Clearance (CLcr) Range (mL/min)	Treatment Regimen
A	Normal renal function (healthy)	≥90	Treatment 1: 0.2 mg TAK-954 Treatment 2: CCI [redacted]
B	Mild RI	60-<90	Treatment 1: 0.2 mg TAK-954
C	Moderate RI	30-<60	Treatment 1: 0.2 mg TAK-954 Treatment 2: CCI [redacted]
D	Severe or ESRD not requiring dialysis	<30	Treatment 1: 0.2mg TAK-954
E	ESRD requiring dialysis	<15	Period 1: 0.2 mg TAK-954 (1 hour after dialysis) Period 2: 0.2 mg TAK-954 (2 hours before dialysis)

At the Screening Visit, for baseline categorization purposes, subjects will be stratified into groups by the degree of RI calculated using the Cockcroft and Gault (CG) equation below:

$$\text{CLcr (mL /min)} = \frac{[140 - \text{age (years)}] \bullet \text{total body weight (kg)} \bullet (0.85 \text{ for females})}{72 \bullet \text{serum creatinine (mg/dL)}}$$

Subjects will receive a single dose of 0.2 mg TAK-954 administered as a 60-minute intravenous (IV) infusion. For standardization purpose, trial drugs will be administered following an 8-hour fast. For Groups A (healthy), C (moderate RI), and E (ESRD with dialysis), the trial will include a Screening Visit, 2 treatment periods, and a Follow-up Visit. For Groups B (mild RI) and D (severe RI or ESRD not requiring dialysis), the trial will include a Screening Visit, 1 treatment period, and a Follow-up Visit.

Enrollment will be staggered, beginning with moderate RI (Group C) and severe RI or ESRD not requiring dialysis (Group D) subjects. The enrollment of healthy subjects (Group A) will begin after approximately 25% of the subjects from moderate and/or subjects with severe RI or ESRD not requiring dialysis have been enrolled. The enrollment of mild RI subjects (Group B) and subjects with ESRD requiring dialysis (Group E) will depend on available safety and pharmacokinetic (PK) data from subjects with moderate RI (Group C) and severe RI or ESRD not requiring dialysis (Group D). Takeda personnel and the investigators will review safety and PK data from the subjects with moderate RI and severe RI or ESRD not requiring dialysis and confirm or modify the TAK-954 dose and decide whether or not to enroll subjects with mild RI and/or subjects requiring dialysis. Additional healthy subjects may be enrolled if necessary.

Healthy (Group A) and moderate RI (Group C) subjects:

Healthy and moderate RI subjects will receive a single dose of TAK-954 0.2 mg (Treatment 1). Blood samples for the assessment of TAK 954 and its metabolites will be collected before the start of the TAK 954 infusion and through 120 hours after the start of the infusion. TAK-954 and its metabolites will be assayed in urine. Plasma protein binding of TAK 954 will also be assessed. CCI [redacted]

For Treatment 1, subjects will be confined from Day -1 until the completion of the last PK sample collection on the morning of Day 3, or at the discretion of the investigator. For Treatment 2, subjects will be confined from Day -1 until completion of the last PK sample collection on the morning of Day 2. After completion of the trial (or following subject withdrawal), all subjects will return for a follow-up visit, 10 to 14 days after their last dose of trial drug.

Mild RI (Group B) and severe RI or ESRD not requiring dialysis (Group D):

Subjects with mild RI (if enrolled) and severe RI or ESRD not requiring dialysis will receive a single dose of TAK-954 0.2 mg (Treatment 1). Blood samples for the assessment of TAK 954 and its metabolites will be collected before the start of the TAK 954 infusion and through 120 hours after the start of the infusion. TAK-954 and its metabolites will be assayed in urine. Plasma protein binding of TAK 954 will also be assessed.

For Treatment 1, subjects will be confined from Day -1 until the completion of the last PK sample collection on the morning of Day 3, or at the discretion of the investigator. After

completion of the trial (or following subject withdrawal), all subjects will return for a follow-up visit, 10 to 14 days after their last dose of trial drug.

Subjects with ESRD requiring dialysis (Group E):

For subjects requiring dialysis, the trial will consist of 2 treatment periods. In Period 1, subjects will receive TAK-954 1 hour after the end of hemodialysis. In Period 2, subjects will receive TAK-954 2 hours before the start of a standard 4-hour of hemodialysis. In both periods, blood samples for the assessment of TAK 954 and its metabolites will be collected before the start of the infusion and through 72 hours after the start of the infusion. Urine will be collected for 24 hours for the determination of TAK-954 and its metabolites, provided the subject is not anuric. Plasma protein binding of TAK 954 will also be assessed. All PK blood samples must be collected before the start of subjects' next hemodialysis session.

For Period 2, samples from the dialysis fluid (dialysate) and blood will be obtained simultaneously immediately after start of dialysis, during dialysis, and end of dialysis from arterial and venous lines to the dialyzer. The 2 treatment periods will be separated by a minimum of 13 days from Day 1 in Period 1 and Day 1 of Period 2.

The total volume of dialysate used in the dialysis should be recorded. Blood flow, dialysate flow during the dialysis, the make and model of the dialyzer, and type of dialysis membrane (high-flux, low-flux) should be recorded.

Subjects will be confined from Day -1 until after the last PK sample collection on the morning of Day 3 for both Periods 1 and 2, or at the discretion of the investigator. After completion of the trial (or following subject withdrawal), all subjects will return for a follow-up visit, 10 to 14 days after their last dose of trial drug.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

The primary endpoints of the trial will include the following:

Plasma PK parameters will be collected predose and up to 120 hours postdose:

- C_{max}.
- Area under the plasma concentration-time curve from time 0 to 72 hours (AUC_{72}).
- Area under the plasma concentration-time curve from time 0 to the last measurable time point, (AUC_{last}).
- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}).

Urine PK parameters will be collected predose and up to 24 hours postdose:

- Amount of drug excreted in urine (Ae).
- Fraction of drug excreted in urine (f_e).
- Renal clearance (CL_R).

Dialysate PK concentrations will be collected predose and up to 4 hours postdose:

- Dialysate clearance (CL_D).

5.1.2 Safety Endpoints

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

5.1.3 Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The planned sample size of 8 subjects in each renal function group is in line with regulatory guidance for these types of studies ("Food and Drug Administration Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" and "European Medicines Agency Guideline on the Evaluation of the PK of Medicinal Products in Patients with Impaired Renal Function").

Subjects who drop out may be replaced at the discretion of the investigators in consultation with the sponsor.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

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

Unless otherwise stated, baseline value is defined as the last observed value before the first dose of study medication.

All data analyses and figures will be generated using 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 will be calculated relative to the date of the first dose of the study drug. 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 of the subject}. 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 of the subject + 1}.

7.1.3 Definition of Study Visit Windows

There will be no visit windows.

7.1.4 Conventions for Missing Adverse Event Dates

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

7.1.5 Conventions for Missing Concomitant Medication Dates

There will be no imputation of incomplete or missing concomitant medication dates.

7.1.6 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

7.2 Analysis Sets

Safety set

The safety set will consist of all subjects who are enrolled and receive at least 1 dose of trial drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Set

The PK set will consist of all subjects who are enrolled and receive at least 1 dose of trial drug and have at least 1 measurable TAK-954 plasma concentration. All subjects with valid PK parameter estimates will be included in the summaries and analyses for that parameter.

If any subject is found to be noncompliant with the dosing schedule or has incomplete data, a decision will be made on a case-by-case basis as to whether that subject should be included in the PK analyses; however, data for all subjects will be presented in the data listings.

7.3 Disposition of Subjects

Disposition of all screened subjects (denominator) will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

Summaries will be presented by renal impairment group and overall.

Disposition of all enrolled subjects will be tabulated by renal impairment group and overall:

- All subjects received at least one dose of study drug (denominator).
- Subjects who completed the study drug.
- Subjects who prematurely discontinued study drug.
- Subjects who completed all study visits.
- Subjects who prematurely discontinued study visits.

Primary reasons for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. Reasons for premature discontinuation of study drug/study visit will be presented for each subject in listings.

Disposition of screen failure subjects will be summarized descriptively. Primary reasons for failure will be summarized and will be presented in a data listing.

Significant protocol deviations will be listed and summarized.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using the safety set by renal impairment group.

Summary statistics will be presented for continuous variables (age, height, weight, and body mass index [BMI]). The number and percentage subjects within each category will be presented for categorical variables (for example, gender, race, etc.). Creatinine clearance and eGFR values will also be summarized.

Individual subject demographic and baseline characteristic data will be listed.

Demographic variables of screen failure subjects will be summarized overall for subjects who are screened but not enrolled in the study.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 18 or higher) coding system.

Medical history includes any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases present at signing of informed consent.

All medical history and concurrent medical condition data will be listed by site (study center) and subject number. The listing will contain subject identifier, renal impairment 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. No inferential statistics will be presented.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped at or within 28 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 between informed consent and the end of the study.

All medication history and concomitant medications will be listed by site (study center) and subject number. The listings will contain subject identifier, renal impairment 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 Version 01March 2015 or higher.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in a data listing. Summaries of TAK-954 PK concentration data will be provided (See Section 7.9.1). No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Plasma 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. These values will be flagged in the data listings and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

7.9.1 Pharmacokinetic Analysis

The PK set will be used for all summaries of PK data. Summaries will be provided by renal function group using Cockcroft-Gault formula (CL_{cr}) and Modification of Diet in Renal Disease formula (eGFR).

Cockcroft and Gault (CG) equation:

$$\text{CLcr (mL /min)} = \frac{[140 - \text{age (years)}] \bullet \text{total body weight (kg)} \bullet (0.85 \text{ for females})}{72 \bullet \text{serum creatinine (mg/dL)}}$$

Modification of Diet in Renal Disease equation:

eGFR (mL/min/1.73 m^2) = 175 x $(S_{cr,std})^{-1.154}$ x $(age)^{-0.203}$ x (0.742 if female) x (1.212 if African American),

where $S_{cr,std}$ is serum creatinine measured with a standardized assay.

7.9.1.1 Pharmacokinetic Concentrations

Samples for PK analysis will be collected as specified in the Schedule of Trial Procedures (see Section 3.0 in Protocol).

7.9.1.2 Summary of Concentrations in Plasma, Urine and Dialysate

For each renal impairment group (Group A-D), descriptive statistics (number of subjects (N), mean, standard deviation (SD), standard error (SE), coefficient of variation (%CV), minimum, median, and maximum) will be used to summarize the plasma (total and free for TAK-954 only), urine concentrations of TAK-954 and any measured metabolites by collection timepoint.

For Group E (ESRD requiring dialysis), descriptive statistics (number of subjects (N), mean, standard deviation (SD), standard error (SE), coefficient of variation (%CV), minimum, median, and maximum) will be summarized for the plasma (total and free, arterial and venous for TAK-954), urine and dialysis fluid sample concentrations of TAK-954 and volume of urine collected and any measured metabolites at each collection timepoint by treatment period. Individual plasma concentrations of TAK-954 (total and free, arterial and venous), dialysate concentrations of TAK-954 and any measured metabolites at each scheduled sampling time and volume of urine collected and amounts of TAK-954 and any measured metabolites (if available) excreted in urine at each scheduled sampling interval will be presented in listings.

For Group A (healthy) and Group C (moderate RI), subjects CCI [redacted]

CCI

[redacted]

7.9.1.3 Pharmacokinetics Parameters

The PK parameters of TAK-954 CCI [redacted] 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 CPAP.

The following PK parameters for TAK-954 will be calculated:

Plasma PK parameters (free and total):

- $C_{max.}$
- $AUC_{72.}$
- $AUC_{last.}$
- $AUC_{\infty.}$
- $t_{1/2z.}$
- CL.
- $V_{z.}$

Urine PK parameters:

- $Ae_{last.}$
- $f_{e.}$
- $CL_{R.}$

Dialysate PK parameters:

- $CL_{D.}$

CCI

[redacted]

CCI

[redacted]

Descriptive statistics (N, mean, SD, SE, %CV, median, minimum, and maximum) will be used to summarize the plasma (for both free and total), urine, and dialysate (for Group E) PK parameters for TAK-954 and its measured metabolites by renal impairment group. In addition, geometric means will be computed for AUC_{72}, AUC_{last}, AUC_{∞}, and C_{max}. Individual plasma (both free and total for TAK-954), urine and dialysate PK parameters will be presented in a data listing.

For Group A (healthy) and Group C (moderate RI), descriptive statistics (N, mean, SD, SE, %CV, median, minimum, and maximum) will also be used to summarize the plasma and urine PK parameters CCI [redacted] In addition, geometric means will be computed for AUC_{last}, AUC_{∞}, and C_{max}. Individual plasma and urine PK parameters will also be presented in a data listing.

Additionally, for each renal impairment group (Group A-E), descriptive statistics (number of subjects (N), mean, SD, SE, %CV, minimum, median, and maximum) will be used to summarize the plasma protein binding (concentration data from donor (plasma) side and receiver (dialysate) side, % unbound, % bound, and % recovery) of TAK-954. Individual plasma protein binding of TAK-954 will be presented in listings.

CCI

[redacted]

All pharmacokinetic parameters estimated will be provided in a listing.

7.9.1.4 Evaluating the Effect of Varying Renal Function on TAK-954 Pharmacokinetics

Regression models will be used to evaluate the relationship between renal function and the following PK parameters of TAK-954 and its metabolites: C_{max}, AUC_{72}, AUC_{last}, AUC_{∞}, CL (total and free) and CL_R, t_{max} and λ_z. Two separate models will be performed: one with CLcr as the renal function included in the model as the independent continuous variable, and one with eGFR as the renal function included in the model as the independent continuous variable. Analysis will be performed using the first period data with and without Group E (ESRD requiring dialysis) subjects. Linear and quadratic regressions will be performed. If the quadratic term is not statistically significant, then linear regression will be the final model.

The results from regression model will be presented in table (parameter estimates, standard error, overall p-value, and R-squares). Predicted value of the PK parameters of TAK-954 and its associated 95% CI in each renal impairment group will be presented in the table. Scatter plots of TAK-954 PK parameters, C_{max}, AUC_{72}, AUC_{last}, AUC_{∞}, CL (total and free) and CL_R and its metabolites will be plotted against CL_{cr}, and eGFR. Regression line and 95% CI will be presented on the graphs.

To evaluate the effect of renal impairment on the PK of TAK-954 and any measured metabolites, an analysis of variance (ANOVA) with renal function group as a fixed effect will be performed on $t_{1/2}$ and the natural logarithms of AUC_t, AUC_{72}, AUC_{∞}, C_{max}, CL and CL_R for TAK-954 and any measured metabolites. Within the ANOVA framework, comparisons of each renal impairment group versus the normal renal function group will be made using appropriate contrast statements.

CCI

Additional pharmacokinetic analysis will be performed if appropriate.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 PGx Measurement

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

PGx is the study of variations of DNA and RNA characteristics as related to drug response. There is increasing evidence that an individual's genetic background may impact the PK (absorption, distribution, metabolism, and excretion), PD (pharmacologic effects), and/or the clinical outcome (efficacy and/or safety).

Whole blood samples for DNA and RNA isolation will be collected from each consented subject in the trial, and will be listed in the data listings, if collected.

7.11 Safety Analysis

Safety analyses include AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters. The safety set will be used for all summaries of safety parameters. The safety endpoints will be presented by regimen related to TAK-954 only in each renal impairment group.

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 medication; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. PTE and AE verbatim terms will be coded by SOC and PT using MedDRA (version 19 or later).

TEAEs will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occur after the first dose of study drug and up to 30 days (onset date – last date of dose + 1 ≤30) after the last dose of study drug or early termination.

TEAEs are recorded in the eCRF as being related or not related to study drug and study procedure. TEAEs that are recorded as related to study drug and/or study procedure will be summarized separately. TEAEs will also be presented by intensity/severity (mild, moderate, and severe). Serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death will also be summarized using SOC and PT.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE 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.

In general, AEs will be tabulated at the following levels: overall summary (subjects with at least 1 AE in any dose or regimen), the MedDRA SOC, and the MedDRA PT. The tables will include the number and percentage (N[%]) of subjects. The following summary tables will be generated:

- Overview of Treatment-Emergent Adverse Events.
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Treatment-Emergent Adverse Events by Preferred Term.
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Most Frequent (>5% or >=2 subjects) Non-Serious Adverse Events by Preferred Term.
- Most Frequent (>5% or >=2 subjects) Non-Serious Adverse Events by System Organ Class and Preferred Term.
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term.

- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by Preferred Term.
- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Pretreatment Adverse Events by System Organ Class and Preferred Term.

In addition, subject mappings for the TEAEs by SOC and PT will be generated.

Data listings will be provided for PTEs, TEAEs, TEAEs leading to study drug discontinuation, SAEs, and AEs that resulted in death.

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.

All laboratory test parameters will be displayed in individual subject data listings in SI units (and conventional (CV) units, if available). For test results not in SI units, the conversion to SI units will be done in derived analysis data sets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived dataset. All summaries and analyses will be based on the values using these preferred SI units.

Only observations within 14 days of the last dose of study drug will be included in the tables. No inferential statistics will be presented unless otherwise stated. List of all the clinical laboratory evaluations can be found in Protocol Section 9.2.1.1.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed and change from baseline values will be presented by renal function groups. Study baseline will be used for change from baseline. Note that "character" urinalysis tests will only be listed.

Listings of all clinical safety laboratory data will be provided in the listings and will be presented in SI units (and CV units, if available). Laboratory data outside of the normal reference range will be indicated in the listings. In addition, MAVs, identified by the criteria defined in Appendix A, will be flagged.

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 observations within 7 days of the study drug will be included in the tables. For each vital sign variable, boxplots for predose/postdose values and the change from the predose by renal impairment group will be prepared.

Vital sign MAVs, identified by the criteria defined in Appendix B, will be listed. If a subject has a MAV for a particular vital signs parameter, all visits for that subject for that parameter will be listed. All observations, including ones at unscheduled visits, will be included in the MAV evaluation.

Listings of all vital signs data will be provided in the listings, and vital sign MAVs will be flagged.

7.11.4 12-Lead ECGs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters, including heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (Fredericia's correction, will be presented for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Only the scheduled measurements will be included in the summary. Only observations within 7 days of the study drug will be included in the tables. No inferential statistics will be presented.

ECG MAVs, identified by the criteria defined in Appendix C, will be listed. If a subject has a MAV for a particular 12-lead ECG parameter, all visits for that subject for that parameter will be listed. All observations, including ones at unscheduled visits, will be included in the MAV evaluation.

Overall ECG interpretation category (normal, abnormal not clinically significant, abnormal clinically significant) is collected by eCRF at baseline and at each scheduled post-baseline visit. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations with missing, if applicable, and total categories by regimen.

Listings of all 12-lead ECG data will be provided in listings, and MAVs will be flagged.

7.11.5 Physical Examinations

Physical examination findings will be presented in the data listings. No summary tables will be provided.

7.12 Interim Analysis

No interim analysis is planned.

7.13 Changes in the Statistical Analysis Plan

No changes.

8.0 REFERENCES

1. A Phase 1, Open-Label, Parallel Group Trial to Evaluate the Effect of Renal Impairment and Dialysis Treatment on the Pharmacokinetics of a Single Intravenous Dose of TAK-954, Takeda Development Center Europe, Ltd., Protocol Amendment 1, No. TAK-954-1007, dated 9 October, 2017.
2. Guidance for Industry "Pharmacokinetics in Patients with Impaired Renal Function", FDA, March 2010, Rev. (Draft).
3. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Decreased Renal Function, EMA, August 2014.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology – Criteria for Markedly Abnormal Values (SI units)

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 × LLN	>1.5 × ULN
Platelet count	Conventional	$<100 \times 10^3/\mu L$	$>450 \times 10^3/\mu L$
	SI	$<100 \times 10^9/L$	$>450 \times 10^9/L$

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry – Criteria for Markedly Abnormal Values (SI units)

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3 × ULN
AST	Both	--	>3 × ULN
GGT	Both	--	>2.5 x ULN if baseline was normal; > 2.5 x baseline if baseline was abnormal
Alkaline phosphatase	Both	--	>2.5 x ULN if baseline was normal; >2.5 x baseline if baseline was abnormal
Calcium (corrected)	Conventional	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L
	SI	<1.75 mmol/L	>2.88 mmol/L
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
	SI	--	>34.2 µmol/L
Albumin	Conventional	<LLN - 3 g/dL; <LLN - 30 g/L	--
	SI	<25 g/L	--
Total protein	Both	<0.8 × LLN	>1.2 × ULN
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>5.5 mEq/L

	SI	<3.0 mmol/L	>6.0 mmol/L
Glucose	Conventional	<LLN - 55 mg/dL	>180 mg/dL
	SI	<LLN - 3.0 mmol/L	>10 mmol/L
Bicarbonate	Conventional	<8.0 mEq/L	--
	SI	<8.0 mmol/L	--
Creatine kinase	Conventional	--	>ULN - 2.5 x ULN
	SI	--	>ULN - 2.5 x ULN
Total Cholesterol	Conventional	--	>300 mg/dL
	SI	--	>7.72 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Identification of Markedly Abnormal Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<60	>120
Systolic blood pressure	mm Hg	<90	>140
Diastolic blood pressure	mm Hg	<60	>90
Body temperature	^{o}C	<35.6	>37.7

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

Parameter	Unit	Lower Criteria	Upper Criteria
HR	bpm	<60	>120
PR-interval	msec	≤80	≥200
QRS-interval	msec	≤80	≥120
QTcF-interval	msec		≥500 OR ≥30 change from baseline and ≥450

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	14-Dec-2018 17:12 UTC
	Clinical Pharmacology Approval	14-Dec-2018 17:16 UTC
	Biostatistics Approval	14-Dec-2018 17:36 UTC
	Clinical Approval	14-Dec-2018 18:42 UTC