



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

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**TAKEDA PHARMACEUTICALS
PROTOCOL**

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

Sponsor: Takeda Development Center Americas, Inc.
Takeda Development Centre Europe Ltd.

Trial Number: TAK-954-1006

Compound: TAK-954

Date: 06 October 2017 **Version/Amendment
Number:** 01

Amendment History:

Date	Amendment Number	Amendment Type (for regional European purposes only)	Region
23 May 2017	Initial version	Not applicable	Global
06 October 2017	01	Non-substantial	Global

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1.0 TRIAL SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. Takeda Development Centre Europe Ltd.	Compound: TAK-954
Study Number: TAK-954-1006	Phase: 1
Protocol Title: A Phase 1, Nonrandomized, Open-Label Trial to Evaluate the Effect of Hepatic Impairment on the Single Dose Pharmacokinetics of Intravenous TAK-954	
Trial Design: <p>This is a phase 1, nonrandomized, open-label trial in male and female subjects (non-childbearing potential) with hepatic impairment as defined by the Child-Pugh Score. The trial is designed to investigate the effect of hepatic impairment on the pharmacokinetics (PK) of intravenous (IV) TAK-954. Healthy subjects will be enrolled which will be similar to subjects in the impaired hepatic function groups with respect to age, weight (approximately 50% of healthy subjects on each side of the median age and weight of all hepatically-impaired subjects grouped together), gender, and race. This will be decided by the investigator in discussion with Takeda.</p> <p>The trial will include a Screening Visit, an in-patient period, and a Follow-up Visit. The groups will be enrolled in a staggered fashion, beginning with Group 2 (Child-Pugh Class B). Safety and available PK data for 2 subjects in Group 2, dosed at 0.2 mg, will be reviewed by Takeda personnel and the investigator to 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 has enrolled. There will be approximately 8 healthy subjects in total. When Group 2 has completed, and following another assessment of the safety and available PK data, Takeda personnel and the investigator will decide whether to enroll subjects in Group 1 (Child-Pugh Class A) or not (reduced versus full study design). During this review, the dose for subjects from Group 1 (if enrolled) and/or Group 3 will be selected. Additional healthy subjects may be enrolled for Group 1 and/or Group 3 (mild and/or severe) if needed.</p> <p>If it is a reduced study design, there will be approximately 8 subjects with moderate hepatic impairment and approximately 8 healthy subjects, and a maximum of 8 subjects with severe hepatic impairment with additional healthy subjects if needed. If it is a full study design, there will be approximately 8 subjects with moderate hepatic impairment, approximately 8 healthy subjects, approximately 8 subjects with mild hepatic impairment, a maximum of 8 subjects with severe hepatic impairment, with additional healthy subjects if needed.</p> <p>Subjects will reside in the clinical research unit (CRU) from Day -1 until after the PK sample collection on the morning of Day 3. At the discretion of the investigator, subjects may be requested to remain in the CRU longer. Subjects will return to the clinic for PK sample collection on Days 4 and 5. After completion of the trial (or after subject withdrawal), all subjects will return for a Follow-up Visit 10 to 14 days after the dose of trial drug.</p>	
Primary Objective: <ul style="list-style-type: none">• To evaluate the effect of varying degrees of hepatic function on the single-dose PK of IV TAK-954.	
Secondary Objectives: <ul style="list-style-type: none">• To evaluate the safety and tolerability of single IV doses of TAK-954 in subjects with varying degrees of hepatic function.	
Subject Population: Group 1: Males and females (non-childbearing potential) with mild hepatic impairment (Child-Pugh Class A). Group 2: Males and females (non-childbearing potential) with moderate hepatic impairment (Child-Pugh Class B). Group 3: Males and females (non-childbearing potential) with severe hepatic impairment (Child-Pugh Class C). Group 4: Healthy males and females (non-childbearing potential).	

Number of Subjects: Up to approximately 32 subjects (with 8 planned per group) will be enrolled in this trial.	Number of Sites: Multiple sites
Dose Levels: TAK-954 0.2 mg.	Route of Administration: TAK-954 IV.
Duration of Treatment: One single dose.	Period of Evaluation: Approximately 6 to 7 weeks.
Main Criteria for Inclusion:	
All subjects: Male and female subjects (non-childbearing potential) who are aged 18 to 75 years, inclusive, with a body mass index (BMI) between 18 to 35 kg/m ² .	
Groups 1 to 3: Subjects with hepatic impairment who are medically stable as determined by the investigator, based on medical history and clinical evaluations including physical examinations, clinical laboratory tests, vital sign measurements, and 12-lead electrocardiograms (ECGs) performed at the Screening Visit and at check-in on Day -1.	
Group 4: Healthy subjects.	
Main Criteria for Exclusion:	
Groups 1 to 3: Subjects who have:	
<ul style="list-style-type: none">• A history of hepatic carcinoma, hepatorenal syndrome, or presence of a liver mass by ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI), or acute liver disease caused by an infection or drug toxicity.• Have severe hepatic encephalopathy (> Grade II Portal Systemic Encephalopathy Score).• Surgical porto-systemic shunts, including transjugular intrahepatic portosystemic shunt.• A history of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than 1 month prior to trial entry.• Bilirubin levels above 5 times the upper limit of normal (ULN) at Screening or Day -1 for Groups 1 and 2; there is no limit for Group 3.• Severe/advanced ascites and/or pleural effusion which requires emptying and albumin supplementation, as judged by the investigator.• Renal creatinine clearance (CLcr) ≤50 mL/min, calculated using the Cockcroft-Gault equation (https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc) from the serum creatinine measurement taken at Screening.	
Group 4: Subjects who have a history of clinically significant endocrine, gastrointestinal (GI) [including motility disorder and intestinal obstruction], cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases will be excluded from the trial.	

Endpoints and Criteria for Evaluation:

Primary endpoints:

Plasma PK parameters (expressed as total and free; maximum plasma concentration at the end of the infusion [C_{max}], area under the plasma concentration time curve from time zero to the last measurable time point [AUC_{last}], and area under the plasma concentration time curve from time zero and extrapolated to infinity [AUC_{∞}])).

Safety endpoints:

Safety and tolerability will be assessed through physical examinations, ECGs, vital signs, and clinical laboratory results as well as collection of spontaneous adverse events.

Statistical Considerations:

PK:

At this stage of the development of TAK-954, the exposure-response relationship for efficacy and safety has not been characterized. An increase of 2.5-fold or less in TAK-954 exposures will not warrant dose adjustments. PK parameters will be compared between normal and hepatically-impaired groups, classified by Child-Pugh Score and summarized descriptively.

Descriptive statistics (eg, mean, SD, standard error, percent coefficient of variation [%CV], minimum, median, and maximum) will be used to summarize concentrations of TAK-954 (CCl [REDACTED]) and PK parameters according to the hepatic function group (mild, moderate, and severe hepatic impairment, and healthy subjects).

Linear and semi-logarithmic plots of the mean and individual concentration-time curves will be provided. Individual plasma concentration and PK parameter data will be presented in the data listing.

An analysis of variance will be performed on log transformed C_{max} and area under the plasma concentration-time curve (AUC) to compare each hepatically-impaired group with the healthy subject group and 90% confidence interval (CI) for the ratio of geometric means from subjects with hepatic impairment versus healthy subjects will be provided. In addition, the effect of other factors and covariates (such as gender and body weight) on the relationship between TAK-954 PK parameters and level of hepatic impairment will also be investigated.

Safety:

Safety data will be presented by hepatic function group. Treatment-emergent adverse events (TEAEs) will be summarized by causal relationship to the trial drug and by intensity for each hepatic function group. Clinical laboratory variables, ECGs, and vital signs parameters (uncorrected and corrected QT intervals, PR, and QRS and heart rate) will be summarized with descriptive statistics for baseline, postdose, and change from baseline to postdose values by hepatic function group.

Sample Size Justification:

The planned sample size of 8 subjects in each hepatic function group is in line with regulatory guidance for these types of studies (“Food and Drug Administration Guidance for Industry PK in Patients with Impaired Hepatic 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 Hepatic Function”).

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

1.1 Protocol Amendment 01 Summary of Changes

Rationale for Amendment 01

The primary reason for this amendment is in response to comments from the Czech Competent Authority State Institute for Drug Control, namely to amend the postmenopausal criteria to be consistent with the Clinical Trial Facilitation Group “Recommendations related to contraception and pregnancy testing in clinical trials”, as well as to add further clarity that it is not possible for the Informed Consent to be signed by a legal guardian.

The amendment opportunity was taken to make additional nonsubstantial changes, including clarifications, additional routine safety precautions, and the removal of redundant exploratory endpoints.

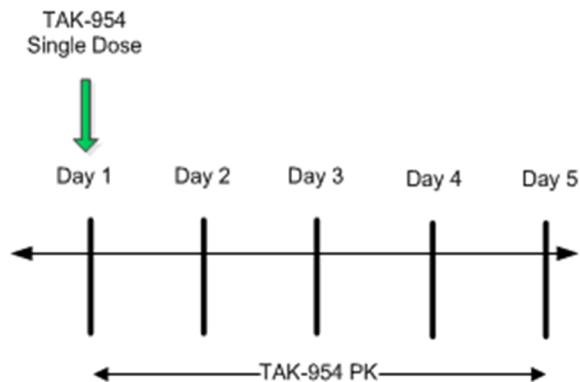
Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see [Appendix E](#).

Changes in Amendment 01

1. Clarification of number of subjects.
2. Revision of postmenopausal criteria.
3. The addition of an exclusion criteria for subjects with QTcF >450 msec.
4. The addition of an exclusion criteria for a positive human immunodeficiency virus (HIV) and hepatitis test for healthy subjects.
5. **CCI** [REDACTED]
6. Removal of “legal representative” language.
7. Addition of an exclusion criteria for subjects with legal incapacity or limited legal capacity.
8. Added information regarding pregnancy.
9. Added pregnancy test at check-in on Day -1.
10. Revised exclusion criteria based on bilirubin levels.
11. Pregnancy and contraception wording changed.
12. Clarification to altering the trial design.
13. Additional vital sign measurements added.
14. Added exclusion criteria for restricted concomitant medications.

2.0 TRIAL SCHEMATIC



PK=pharmacokinetic.

3.0 SCHEDULE OF TRIAL PROCEDURES

Assessment	Screening	Trial Days							Follow-up/Early Termination
		Day	-28 to -2	-1	1	2	3	4	
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							
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						

Footnotes are on last table page.

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Assessment	Screening	Trial Days							Follow-up/Early Termination
		Day -28 to -2	-1	1	2	3	4	5	
Hours Postdose			0	24	48	72	96		
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.

4.0 INTRODUCTION

4.1 Background

Critically ill patients who require enteral feeding frequently have reduced gastrointestinal (GI) motility, develop enteral feeding intolerance (EFI), which can lead to several complications including not meeting daily calorie and protein requirements [1]. The addition of malnutrition in these patients is associated with impairment of immunological function, increased risk of infection, prolongation of mechanical ventilation, increased length of intensive care unit (ICU) and hospital stay, and ultimately higher mortality [2,3].

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Please refer to the TAK-954 Investigator's Brochure for complete information on the investigational product.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

4.2 Rationale for the Proposed Trial

This is a phase 1, nonrandomized, open-label trial in male and female subjects (non-childbearing potential) with hepatic impairment and healthy subjects designed to investigate the effect of hepatic impairment on the PK of IV TAK-954.

4.3 Benefit/Risk Profile

There is no expected clinical benefit to the trial participants. Potential risks are based on clinical findings, the mechanism of action, and nonclinical findings.

Also, there is minimal risk associated with trial procedures including scheduled, periodic phlebotomy (limited to <500 mL) and noninvasive procedures including vital sign assessments and ECGs. The principal mitigation for these risks includes appropriate selection of the trial populations, the CRU setting, which permits close monitoring and rapid institution of appropriate care as needed, appropriate specified monitoring procedures, and utilization of experienced staff trained in trial procedures. Overall, the risk:benefit profile is considered appropriate for this trial.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 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.

5.1.2 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.

5.1.3 Exploratory Objectives

Exploratory objectives of this trial include:

CCI



5.2 Endpoints

5.2.1 Primary Endpoint

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_{∞}).

5.2.2 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.

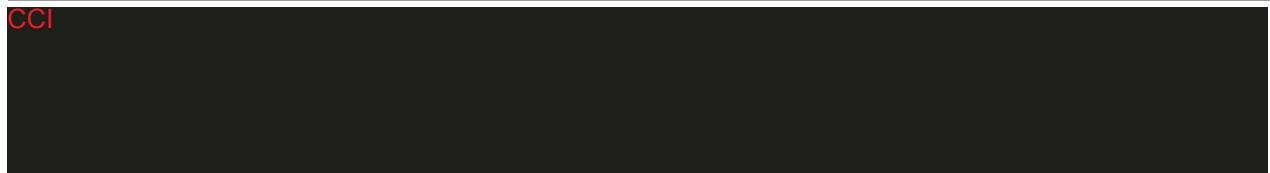
5.2.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

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6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial 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 6.a** displays the number of subjects who will participate in the study based on design options:

Table 6.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 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 6.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.

CCI



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.

6.2 Rationale for Trial Design, Dose, and Endpoints

6.2.1 Rationale of Trial Design and Dose

Although TAK-954 did not appear to be extensively metabolized in clinical studies following oral administration, it is possible that changes in hepatic function may impact TAK-954 exposure, and impaired organ function is a potential complication associated with critical illness. The impact of hepatic impairment on TAK-954 is not yet known.

The purpose of this trial is to investigate the effect of hepatic impairment on the PK of IV TAK-954. **CCI**



6.2.2 Rationale for Endpoints

6.2.2.1 PK

To determine the PK of TAK-954 in hepatically-impaired subjects with similar healthy subjects, the primary endpoint for this trial will consist of standard PK variables (C_{max} , AUC_{last} , and AUC_{∞}).

6.2.2.2 Safety Endpoints

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

6.2.2.3 Exploratory Endpoints

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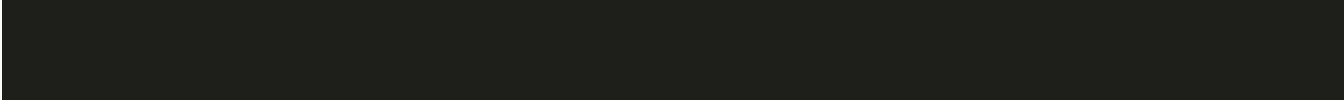


6.3 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a phase 1 assessment of TAK-954 in humans, and the PK and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 clinical trials. Modifications outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

- Decrease the dose of the trial drug administered.
- A planned PK data review may be eliminated if agreed to by Sponsor and investigator.
- Addition of a PK data review.
- The number of subjects in the severe hepatically-impaired cohort may be less than 8 subjects.

CCI



Up to an additional 50 mL of blood may be drawn for PK analyses. This may include repeat samples or modified PK time points based on emerging data from previous subjects/cohorts in the

study as per protocol. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume.

The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) currently outlined in the protocol may be modified during the trial based on data as it is analysed per protocol from previous subjects/cohorts in the study. These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatinine kinase to serum chemistry panel that was already drawn).

It is understood that the current trial may employ some or none of the alterations described above. Any of these per protocol alterations (part of trial design to meet its objectives) must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at the discretion of the investigator. Any other changes, if considered substantial, will be documented in a protocol amendment which will require approval before they are implemented.

6.3.1 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, the collections of the blood samples for TAK-954 (PK) are the critical procedures.

- At any postdose time point, the blood samples for TAK-954 (PK) needs to be collected as close to the exact nominal time point as possible.
- All other procedures should be completed as close as possible, either before or after the prescribed/scheduled time.
 - ECG and vital signs measurements should be performed before the nominal time of the TAK-954 (PK) if scheduled together.
- The order of priority can be changed during the trial with joint agreement of the investigator and the sponsor.
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

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

6.4.2 Definition of End of the Trial

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

6.4.3 Definition of Trial Discontinuation

Trial discontinuation because of nonsafety reasons, such as:

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

Trial discontinuation because of safety reasons:

- Early trial termination because of unanticipated concerns of safety to the trial subjects arising from clinical or preclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial.

6.4.4 Criteria for Premature Termination or Suspension of the Trial

6.4.4.1 Criteria for Premature Termination or Suspension of Trial Sites

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

6.4.4.2 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must meet the requirements as indicated in [Table 7.a](#):

Table 7.a Inclusion Criteria

	Subjects:	All Subjects	Groups 1-3 (Hepatic Impaired ONLY)	Group 4 (Healthy Subjects ONLY)
1.	Must understand the trial procedures and agree to participate by providing written informed consent.	X		
2.	Must be willing and able to comply with all trial procedures and restrictions.	X		
3.	Must be a man or woman (with no childbearing potential) aged 18 to 75 years, inclusive, at the Screening Visit.	X		
4.	Must have a BMI ≥ 18 and ≤ 35 kg/m ² at the Screening Visit.	X		
5.	Must meet birth control requirements (a).	X		
6.	Must have a Child-Pugh Score of Class A, B, or C (b).		X	
7.	Diagnosis of cirrhosis due to parenchymal liver disease, which is confirmed and documented by at least 1 of the following: medical history, physical examination, hepatic ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI), or liver biopsy.		X	
8.	Should be on a stable drug regimen. If subjects are in a fluctuating treatment regimen, they may be considered for inclusion if the underlying disease is under control. However, these subjects must have sponsor approval prior to the dose of trial medication.		X	
9.	Must be similar to subjects in the impaired hepatic function groups with respect to age, weight (approximately 50% of healthy subjects on each side of the median age and weight of all hepatically-impaired subjects grouped together), gender, and race. This will be decided by the investigator in discussion with Takeda.			X
10.	Is considered to be healthy (for healthy subjects) or medically stable (for subjects with hepatic impairment) as determined by the investigator, based on medical history and clinical evaluations including physical examination, clinical laboratory tests, vital sign measurements, and 12-lead ECG performed at the Screening Visit and at check-in on Day -1. Subjects with hepatic impairment should have no clinically significant changes in medical history or clinical laboratory values within 30 days prior to trial drug administration on Day 1. If clinical laboratory tests within 30 days prior to trial drug administration on Day 1 are unavailable, clinical laboratory tests on Day -1 may be compared with those from the Screening Visit and used by the investigator to determine the subject's medical status.	X		
11.	Must be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before administration of the initial dose of the trial drug/invasive procedure.			X
12.	Must abstain from the use of tobacco- or nicotine-containing products 48 hours prior to dosing and during confinement in the clinic.		X	

Footnotes are on last table page.

(a) The following birth control requirements will be met if the subject:

- Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from consent until 30 days after administration of the trial drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1 year post-bilateral vasectomy procedure from consent. A male subject whose vasectomy procedure was performed less than 1 year before consent must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
- Is a male subject who agrees to not donate sperm from consent until 30 days after administration of trial drug.
- Is a female subject with no childbearing potential, defined by at least 1 of the following criteria:
 - Postmenopausal (defined as 12 months of amenorrhea without an alternative medical cause with serum FSH levels >40 mIU/mL). Appropriate documentation of FSH levels is required.
 - Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
 - Had a tubal ligation with appropriate documentation of surgical procedure.
 - Has a congenital condition resulting in no uterus

(b) Child-Pugh Class:

- Group 1: Subjects with mild hepatic impairment (Child-Pugh Class A).
- Group 2: Subjects with moderate hepatic impairment (Child-Pugh Class B).
- Group 3: Subjects with severe hepatic impairment (Child-Pugh Class C).

7.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject meets any of the criteria in [Table 7.b](#):

Table 7.b Exclusion Criteria

	Subjects who:	All Subjects	Groups 1-3 (Hepatic Impaired ONLY)	Group 4 (Healthy Subjects ONLY)
1.	Have participated in another investigational trial within 4 weeks before the pretrial (Screening) visit. The 4-week window will be derived from the date of the last trial procedure and/or AE related to the trial procedure in the previous trial to the pretrial/Screening Visit of the current trial.	X		
2.	Have legal incapacity or limited legal capacity.	X		
3.	Are an employee or immediate family member (eg, spouse, parent, child, sibling) of the sponsor.	X		
4.	Are a breastfeeding woman.	X		
5.	Have a QTcF > 450 msec at Baseline.	X		
6.	Have a positive urine drug screening test result at the Screening Visit or at check-in on Day -1.			X
7.	Have a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV), or HIV antibody/antigen, at Screening. Note: Subjects with positive HBV or HCV serology may be enrolled if quantitative PCR for HBV or HCV viral RNA is negative.			X
8.	Have a positive urine drug screening test result at the Screening Visit or at check-in on Day -1, unless the positive drug screen is due to prescription drug use and is approved by the investigator and the sponsor's medical monitor.		X	
9.	Ingest alcohol within 72 hours prior to trial drug administration and during the confinement period.		X	
10.	Ingest alcohol within 7 days prior to trial drug administration and during the confinement period.			X
11.	Have a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).			X
12.	Have a substance abuse disorder.	X		
13.	Have a history of cancer (malignancy).			X
14.	Have a history of cancer (malignancy) with the following exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥ 10 years prior to the Screening Visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the Screening Visit; or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.		X	

	Subjects who:	All Subjects	Groups 1-3 (Hepatic Impaired ONLY)	Group 4 (Healthy Subjects ONLY)
15.	Have a known hypersensitivity to any component of the formulation of TAK-954 or related compounds.	X		
16.	Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 8 weeks of the first dose.	X		
17.	Have a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases.			X
18.	Have a history of hepatic carcinoma, hepatorenal syndrome, or presence of a liver mass by ultrasound, CT or MRI, or acute liver disease caused by an infection or drug toxicity.		X	
19.	Have surgical porto-systemic shunts, including transjugular intrahepatic portosystemic shunt.		X	
20.	Have a history of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than one month prior to Screening.		X	
21.	Have bilirubin levels above 5 times the upper limit of normal (ULN) at Screening or Day -1 for Groups 1 and 2 (no limit for Group 3).		X	
22.	Have bilirubin levels above 1.5 times the ULN at Screening or Day -1.			X
23.	Have severe hepatic encephalopathy (> Grade II Portal Systemic Encephalopathy Score).		X	
24.	Have severe/advanced ascites and/or pleural effusion which requires emptying and albumin supplementation, as judged by the investigator.		X	
25.	Have renal creatinine clearance (CLcr) \leq 50 mL/min, calculated using the Cockcroft-Gault equation (https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc) from the serum creatinine measurement taken at Screening.		X	
26.	Are unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial, and until the Follow-up Visit. See Section 7.3.			X
27.	Are unable to refrain from or anticipates the use of: <ul style="list-style-type: none"> • strong CYP3A4 inhibitors or inducers • serotonin agonists or antagonists • monoamine oxidase inhibitors • noradrenergic agonists • selective serotonin reuptake inhibitors • gamma—aminobutyric acid antagonists • N-methyl-D-aspartate receptor antagonists beginning approximately 7 days before administration of the trial drug, throughout the trial, until the Follow-up Visit.		X	

	Subjects who:	All Subjects	Groups 1-3 (Hepatic Impaired ONLY)	Group 4 (Healthy Subjects ONLY)
28.	Consume excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.	X		

7.3 Excluded Medications, Supplements, and Dietary Products

Use of excluded agents (prescription or nonprescription) or dietary products is outline in [Table 7.c.](#)

Table 7.c Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and Enrollment (Days -28 to Predose [Day 1])	Post-Enrollment (Day 1) to Follow-up Visit
Tobacco- and nicotine-containing products (a)	Completely restricted 48 hours prior to dosing (start of infusion).	Restricted during confinement.
Cannabis products	Completely restricted.	Completely restricted.
Alcohol (b)	Completely restricted for a minimum of 3 and 7 days before dosing, respectively, for hepatically-impaired subjects and healthy subjects.	Completely restricted during the confinement period.
Xanthine and/or caffeine	Completely restricted 48 hours before dosing (start of infusion).	Completely restricted 48 hours after dosing (start of infusion). At all other times no more than 6 units/day.
Medications for healthy subjects	Completely restricted 7 days before dosing.	Completely restricted (c).
Medications for hepatically-impaired subjects	Concomitant medications allowed.	Concomitant medications allowed.
Food substance		
Grapefruit /grapefruit juice	Completely restricted 7 days before dosing (starting of infusion).	Completely restricted.
Fruit	No restriction.	No restriction.
Fruit juice	No restriction.	Dosing will occur without consumption of fruit juice. Fruit juice is restricted until 4 hours after dosing (start of infusion).
Mustard green (d)	Completely restricted 7 days before dosing (start of infusion).	Completely restricted.
Charbroiled meat	Completely restricted 7 days before dosing (start of infusion).	Completely restricted.

(a) Subjects in Groups 1-3 will abstain from the use of tobacco- or nicotine-containing products 48 hours prior to dosing and during confinement in the clinic.

(b) Outside the confinement period, regular alcohol consumption below 24 units for males and 17 units for females per week (1 unit equals 354 mL/12 ounces of beer, 118 mL/4.0 ounces of wine, or 29.5 mL/1.0 ounces of spirits) is allowed. In addition to Screening and Day -1, subjects may undergo an alcohol breath or urine test at other times at the discretion of the investigator.

(c) If medications are required to treat an AE, certain medications may be allowed after discussion and agreement between the sponsor and principal investigator.

(d) Mustard green family includes kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, and mustard.

For subjects in Groups 1, 2, and 3, concomitant medications may be given if they are necessary for the welfare of the subjects (eg, standard therapy for underlying disease), are not contraindicated with TAK-954, and are unlikely to interfere with the PK of TAK-954. Concomitant medications to treat concurrent diseases or co-morbidities should be maintained at a stable dose and regimen from the Screening Visit throughout the trial; however, medication adjustments may be made by the investigator with Sponsor approval based on the subject's condition and standard of care.

Occasional use of acetaminophen/paracetamol (≤ 1 g/day) or other medication is allowed as approved by Takeda on a case-by-case basis.

Subjects must be instructed not to take any medications, including OTC products, without first consulting with the investigator. However, if a medication is taken, it is the responsibility of the investigator to ensure that the details regarding the medication are recorded in full in the electronic case report form (eCRF).

7.4 Diet, Fluid, and Activity

7.4.1 Diet and Fluid

All subjects must abstain from all food and drink (except water) at least 8 hours before any safety laboratory evaluations. Subjects should also abstain from all food and drink (except water) overnight before the dosing day.

Water may be consumed without restrictions. Non-caffeinated drinks may be consumed with meals and evening snack.

Lunch and dinner will be provided approximately 4 and 9 hours, respectively, after dosing (starting of infusion). An evening snack will also be permitted.

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (eg, weight lifting, running, bicycling) from the Screening Visit until the Follow-up Visit.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

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

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the trial. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

7.7 Subject Replacement

If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The trial site should contact the sponsor for the replacement subject's treatment assignment and allocation number.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

8.1 Clinical Trial Drug

Details regarding the composition and extemporaneous preparation of the active ingredient are found in the Pharmacy Manual and/or similar documents. Clinical trial drug will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the sponsor needs to be contacted before dosing.

8.1.1 Clinical Trial Drug Labeling

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

8.1.2 Clinical Trial Drug Inventory and Storage

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

8.1.3 Clinical Trial Drug Blinding

This is an open-label trial; therefore, the sponsor, investigator, and subject will know the treatment administered.

8.1.4 Accountability and Destruction of Sponsor-Supplied Drugs

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

8.1.5 Ancillary Supplies

All ancillary supplies will be provided by either the site or Takeda, based upon availability. If provided by Takeda, unused ancillary supplies will be accounted for and disposed of as directed by Takeda or a Takeda designee.

9.0 TRIAL PROCEDURES

The following sections describe the trial procedures and data to be collected as indicated in the Schedule of Trial Procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator. For information regarding procedures that are scheduled concurrently, see Section 6.3.1.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters into the trial and before any protocol-directed procedures are performed. The requirements of informed consent are described in Section 13.2.

In the case where subjects have screening assessments performed prior to the trial, the data from the general/site screening could be included/used in the trial for those who were enrolled, as long as the procedure was performed within the protocol screening/enrollment window. A generic site screening form may be used.

9.1.2 Assignment of Screening Numbers

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

9.1.3 Inclusion and Exclusion Criteria

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

9.1.4 Medical History/Demographics

Qualified site personnel are to collect subject significant medical history (past and ongoing) per the site's standard of care and appropriate clinical judgment as well as subject demographics.

9.1.5 Prior and Concomitant Medication Review

Medications are defined as prescription and over-the-counter drugs, vitamin supplements, nutraceuticals, and oral herbal preparations. Qualified site personnel are to review subject medication use.

9.1.6 Physical Examinations

Qualified site personnel will conduct physical examinations.

9.1.7 Vital Sign Measurements

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

Subjects should rest in a semirecumbent position for at least 5 minutes before having vital sign measurements obtained. Vital signs will include HR, systolic blood pressure, and diastolic blood pressure, body temperature, and respiratory rate. The same method (eg, same and appropriately sized cuff, manual, or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

9.1.8 Height and Weight

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

9.1.9 BMI

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI = \text{kg}/\text{m}^2$).

BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

9.1.10 12-Lead ECG

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

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

QT intervals with Fridericia correction method (QTcF) will be used to calculate QT intervals in this trial.

A predose ECG will be obtained within approximately 30 minutes before dosing. This measurement will be used as the baseline. The principal investigator should arrange to have a trial cardiologist available as needed to review ECG tracings with abnormalities.

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

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

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

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

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

9.1.11 AE Monitoring

AE monitoring begins after signing of informed consent. A complete description of AE collections and procedures is provided in Section 10.0.

9.1.12 Pregnancy

Women of childbearing potential will not be included in this trial.

Male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in [Appendix D](#) containing highly effective contraception.

If any subject is found to be pregnant during the trial, she should be withdrawn from the trial and any Takeda-supplied drug and should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the trial 30 days after the last dose should also be recorded following authorization from the subject's partner. All pregnancies, including female partners of male subjects, in subjects on active trial drug will be followed up to final outcome. The outcome of the pregnancy, including any premature termination, must be reported to the sponsor.

9.2 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be taken after a minimum 8-hour overnight fast on the days stipulated in the Schedule of Trial Procedures (Section 3.0).

9.2.1.1 Clinical Laboratory Tests

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Bicarbonate	Chloride
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total), if above ULN, will be fractionated
Protein (total)	

Hematology

Hematology will consist of the following tests:

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

Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrite

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of RBC/high-power field, WBC/high-power field, and casts.

Urine Drug Screen

A urine drug screen will include the following tests:

Amphetamines	Cotinine
Barbiturates	3,4-methylenedioxy-methamphetamine (MDMA)
Benzodiazepines	Methadone/metabolite
Cannabinoids	Opiates
Cocaine/metabolites	Phencyclidine

Alcohol Screen

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

Urine

Urine evaluations will include the following test:

hCG for pregnancy (all females)

9.2.1.2 Screening

Serum

Serum evaluations will include the following tests:

HIV test	Hepatitis panel, including HBsAg and anti-HCV
FSH (females only)	International normalized ratio (INR)
Prothrombin time	Activated partial thromboplastin time

9.3 PK and PGx Samples

A portion of the DNA sample will be analyzed for the presence of allelic variants in drug metabolizing enzymes, drug transporters, or putative drug targets that may contribute to the variability in the PK of TAK-954 (Drug Metabolism Enzymes and Transporters).

As PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Samples for PK analysis will be collected as specified in the Schedule of Trial Procedures (Section 3.0). Please refer to the Laboratory Manual for information on the collection, processing, and shipment of samples to the central laboratory.

It is anticipated that the total blood volume drawn for the trial will be approximately 170 mL.

Primary specimen collection parameters are provided in [Table 9.a](#).

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-954 PK	Plasma		PK measurements	Mandatory
Urine sample for TAK-954 PK	Urine		PK measurements	Mandatory
Blood sample for DNA PGx	Blood	DNA	PGx measurements	Optional
Blood sample for RNA PGx	Blood	RNA	PGx measurements	Optional
Plasma for protein binding	Plasma		PK measurement	Mandatory

9.3.1 PK Evaluations

The 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. A more detailed description will be given in the clinical pharmacology analysis plan (CPAP).

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

- C_{\max}
- AUC_{∞}
- AUC_{last}

Other PK parameters may be calculated if deemed necessary for the interpretation of the data. 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.

CCI

9.3.2 PGx Measurements

9.3.2.1 Blood Sample for DNA and RNA PGx Measurements

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).

PGx research in this trial may be conducted to understand how individual genetic variation in subjects impacts their trial drug treatment response. This information may be also be used, for example, to develop a better understanding of the safety and efficacy of TAK-954 and other trial drugs, to increase understanding of the disease/condition being studied and other related conditions, gain a better understanding of the drug pharmacology and for generating information needed for research, development, and regulatory approval of tests to predict response to TAK-954.

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.

Since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

9.3.2.2 Biological Sample Retention and Destruction

In this trial, specimens for genome/gene analysis will be collected as described in the Laboratory Manual. The genetic material will be initially stored at the site, vendor, or a comparable laboratory, under contract to Takeda, with validated procedures in place, and then preserved and retained at the vendor, or a comparable laboratory with validated procedures in place, for up to but not longer than 15 years from the end of the trial when the trial report is signed, or if less, the maximum period permitted under applicable law or until consent is withdrawn.

The sponsor and vendors working with the sponsor will have access to the samples collected and any test results. All samples collected during the trial will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier as in the main trial but using a code that is different from the code attached to the health information and other clinical test results collected in the trial. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The sample identifier will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent at any time and request disposal of a stored sample. Any remaining sample that can be identified as coming from the subject will be destroyed. The trial doctor and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

9.4 Trial Drug Administration

Eligible subjects will be allocated to trial treatment by nonrandom assignment on Day 1 and will receive a single IV dose of 0.2 mg TAK-954 administered as a 60-minute infusion.

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

9.5 Confinement

Subjects will reside in the CRU from Day -1 until after the PK sample collection on the morning of Day 3. At the discretion of the investigator, subjects may be requested to remain in the CRU longer. Subjects discharged on Day 3 will return to the clinic for PK sample collection on Days 4 and 5.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

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

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

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

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

database. AEs associated with an overdose will be documented on the AE CRF(s) according to Section 10.2.

- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.9.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

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

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: The event is transient and easily tolerated by the subject.
Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.
Severe: The event causes considerable interference with the subject's usual activities.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.2.3 Assigning Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as "Related" if the investigator considers that there is reasonable possibility that an event is because of a trial procedure. Otherwise, the relationship should be assessed as "Not Related".

10.2.4 Start Date

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

10.2.5 Stop Date

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

10.2.6 Frequency

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

10.2.7 Action Concerning Trial Drug

- Drug withdrawn: a trial medication is stopped because of the particular AE.
- Dose not changed: the particular AE did not require stopping a trial medication.
- Unknown: only to be used if it has not been possible to determine what action has been taken.
- Not applicable: a trial medication was stopped for a reason other than the particular AE, for example, the trial has been terminated, the subject died, dosing with trial medication was already stopped before the onset of the AE.

10.2.8 Outcome

- Recovered/resolved: subject returned to first assessment status with respect to the AE.
- Recovering/resolving: the intensity is lowered by one or more stages; the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving.”
- Not recovered/not resolved: there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed trial period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining “Not recovered/not resolved.”
- Resolved with sequelae: the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: an AE that is considered as the cause of death.
- Unknown: the course of the AE cannot be followed up because of hospital change or residence change at the end of the subject’s participation in the trial.

10.2.9 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, special interest AEs, and abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the Follow-up Visit 10-14 days after the dose of TAK-954. For subjects who discontinue before the administration of trial medication, AEs will be followed until the subject discontinues trial participation.

10.2.9.2 Reporting AEs

At each trial visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may

report AEs occurring at any other time during the trial. Subjects experiencing an SAE before the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin before the first exposure to investigational product, related or unrelated to the trial procedure, need not be followed-up for the purposes of the protocol.

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

- Event term.
- Start and stop date and time.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of trial medication(s) (related or not related).
- Investigator's opinion of the causal relationship to trial procedure(s), including the details of the suspected procedure.
- Action concerning trial medication.
- Outcome of event.
- Seriousness.

10.2.9.3 Reporting SAEs

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

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

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

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

Any SAE spontaneously reported to the investigator after the AE collection period should be reported to the sponsor if considered related to trial participation.

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

SAE Follow-up

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

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

10.2.9.4 Reporting of Abnormal LFTs (Group 4 only)

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

If a subject is noted to have ALT or AST $>3\times\text{ULN}$ and total bilirubin $>2\times\text{ULN}$ for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9.3).

10.2.10 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

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

forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

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

A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the trial database, subject evaluability, or appropriateness of the planned statistical methods.

11.1.1 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 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.

11.1.2 Analysis of Demographics and Other Baseline Characteristics

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

11.1.3 PK Analysis

At this stage of the development of TAK-954, the exposure-response relationship for efficacy and safety has not been characterized. An increase of 2.5-fold or less in TAK-954 exposures will not warrant dose adjustments. PK parameters will be compared between normal and hepatically-impaired groups, classified by Child-Pugh Score and summarized descriptively.

Descriptive statistics (e.g. mean, standard deviation, standard error, % coefficient of variation [CV], minimum, median and maximum) will be used to summarize concentrations of TAK-954

CC1 [REDACTED] and PK parameters (expressed as free and total) according to the hepatic function group [healthy subjects and mild, moderate, severe hepatic impairment].

Linear and semi-logarithmic plots of the mean and individual concentration-time curves will be provided. Individual plasma concentration and pharmacokinetic parameter data will be presented in the data listing.

An analysis of variance will be performed on log transformed C_{max} and AUC to compare each hepatically-impaired group with the normal hepatic function group and 90% confidence intervals for the ratio of geometric means from each hepatic impairment group versus normal function group will be provided. In addition, the effect of other factors and covariates (such as gender and body weight) on the relationship between TAK-954 PK parameters and level of hepatic impairment will also be investigated.

A more detailed analysis will be presented in the SAP. CC1 [REDACTED]

11.1.4 Safety Analysis

The safety set will be used for all summaries of safety parameters.

11.1.4.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs with onset occurring within 30 days (onset date minus last date of dose $+1 \leq 30$) after the dose of trial drug will be included in the summary tables. All AEs will be in the listings. TEAEs will be summarized by SOC and PT with a breakdown for each hepatic function group and overall. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to trial drug (related vs not related), severity of AEs, and related SAEs. Data listings will be provided for all AEs including TEAEs, AEs leading to trial drug discontinuation, and SAEs.

11.1.4.2 Clinical Laboratory Evaluation

Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized by regimen. All clinical laboratory data will be provided in the data listings.

11.1.4.3 Vital Signs

Baseline, postdose, and changes from Baseline in vital sign measurements will be summarized. All vital sign data will be provided in the data listings.

11.1.4.4 ECGs

Baseline, postdose, and changes from Baseline in quantitative ECG parameters will be summarized by regimen. Shift tables for each will be generated to show the investigator's ECG interpretations at each postdose collection by the interpretation at Baseline.

All ECG data will be provided in the data listings.

11.2 Interim Analysis and Criteria for Early Termination

No formal interim analyses will be conducted.

11.3 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.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Trial-Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and trial site guarantee access to source documents by the sponsor or its designee and by the IRB or IEC.

All aspects of the trial and its documentation will be subject to review by the sponsor or the sponsor's designee, including but not limited to the Investigator's Binder, trial drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary trial assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all trial documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix A](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the trial (ie, before shipment of the sponsor-supplied drug or trial-specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB or IEC, and submission of the investigator’s final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial. The informed consent form and the subject information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject must be given ample opportunity to: (1) inquire about details of the trial, and (2) decide whether or not to participate in the trial. If the subject determines he or she will participate in the trial, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and before the subject entering into the trial. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Two copies of the informed consent are signed by the subject, 1 of which, along with the subject authorization form (if applicable) and subject information sheet (if applicable), will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

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

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the trial. During and after the trial, only the sponsor may make trial information available to other trial investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical trial site agreement, any public disclosure (including publicly accessible websites) related to the protocol or trial results, other than trial recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the trial (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of the trial, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical trial insurance against the risk of injury to trial subjects. Refer to the trial site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Trial Contact Information

Contact Type/Role	Contact
SAE and pregnancy reporting	PPD

15.0 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section [10.2.10](#) of this protocol.
- Terms outlined in the trial site agreement.
- Responsibilities of the Investigator ([Appendix A](#)).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix C](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

15.1.1 Trial-Related Responsibilities

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

15.1.2 List of Abbreviations

5-HT4	serotonin type 4
β-hCG	β-human chorionic gonadotropin
C Cl	
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC _{last}	area under the concentration-time curve from time 0 to the last measurable time point.
AUC _t	area under the concentration-time curve from time 0 to time t.
AUC _∞	area under the concentration-time curve from time 0 to infinity.
BMI	body mass index
CFR	Code of Federal Regulations
CCI	
C _{max}	maximum observed concentration
CRU	clinical research unit
CT	computed tomography
CV	coefficient of variation
CPAP	clinical pharmacology analysis plan
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
C PDA	
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HR	heart rate
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
PD	pharmacodynamic(s)
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
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
C T U	[REDACTED]
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

16.0 DATA HANDLING AND RECORDKEEPING

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

16.1 eCRFs

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

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

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

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

eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

16.2 Record Retention

The investigator agrees to keep the records stipulated in Section 16.1 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source

documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

17.0 REFERENCES

1. Barton RG. Nutrition support in critical illness. American Society for Parenteral and Enteral Nutrition 1994;168:659-64.
2. Harrington L. Nutrition in critically ill adults: key processes and outcomes. Crit Care Nurs Clin North Am 2004;16(4):459-65.
3. Slone DS. Nutritional support of the critically ill and injured patient. Crit Care Clin 2004;20(1):135-57.
4. Beattie DT, Armstrong SR, Vickery RG, Tsuruda PR, Campbell CB, Richardson C, et al. The Pharmacology of TD-8954, a Potent and Selective 5-HT(4) Receptor Agonist with Gastrointestinal Prokinetic Properties. Front Pharmacol 2011;2:25.

18.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that trial-related procedures, including trial-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
6. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the trial, and document the date of consent in the subject’s medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject’s personal information (including personal health information) that will take place in connection with the trial. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject.
10. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years after notification by the sponsor that all investigations have been discontinued or that

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

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

Appendix B Elements of the Subject Informed Consent

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

1. A statement that the trial involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the trial.
7. A description of the subject's responsibilities.
8. A description of the conduct of the trial.
9. A description of the possible side effects of the treatment that the subject may receive.
10. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
11. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
12. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
13. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject is authorizing such access.
14. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
15. The anticipated prorated payment(s), if any, to the subject for participating in the trial.
16. The anticipated expenses, if any, to the subject for participating in the trial.
17. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
18. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

19. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
20. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
21. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
22. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the trial medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the trial to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that trial results are published.
24. Male subjects must use adequate contraception (as defined in the informed consent) from Screening, throughout the duration of the trial, and for 30 days after the dose of trial medication.

25. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to Use of Personal Information

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

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the trial and/or other clinical studies.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the trial medication.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Female Subjects and Their Male Partners

Female subjects of childbearing potential are excluded from this trial. If any subject is found to be pregnant during the trial, she should be withdrawn from the trial and any Takeda-supplied drug and should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the trial 30 days after the last dose should also be recorded following authorization from the subject's partner. All pregnancies, including female partners of male subjects, in subjects on active trial drug will be followed up to final outcome. The outcome of the pregnancy, including any premature termination, must be reported to the sponsor.

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the trial, and for 30 days after the dose of trial drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

** Sterilized males should be at least 1 year post–bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

1. Highly effective methods of contraception are defined as “those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this trial, where medications and devices containing hormones are included, females of childbearing potential who are partners of male subjects are advised to use additional contraception chosen from the list below:

- Nonhormonal methods:
 - Intrauterine device.
 - Bilateral tubal occlusion.
- Hormonal methods:
 - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of trial drug.
 - Oral.
 - Intravaginal (eg, ring).
 - Transdermal.
 - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of trial drug.

- Oral.
- Injectable.
- Implantable.

2. Since genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drug, additional effective methods of contraception (there may be a higher than 1% failure rate) that may be chosen by the female partner of a male subject are:
 - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams).
 - Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action.
3. Unacceptable methods of contraception are:
 - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
 - Spermicides only.
 - Withdrawal.
 - No method at all.
 - Use of female and male condoms together.
 - Cap/diaphragm/sponge without spermicide and without condom.
4. Male subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and sperm donation during the course of the trial.
5. Male subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the trial procedures. Such guidance should include a reminder of the following:
 - Contraceptive requirements of the trial.
 - Reasons for use of barrier methods (ie, condom) in males with partners of child-bearing potential.
 - Assessment of subject compliance through questions such as:
 - Have you used the contraception consistently and correctly since the last visit?
 - Have you forgotten to use contraception since the last visit?

Appendix E Detailed Descriptions of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarification of number of subjects.

The primary change occurs in [Section 6.1 Trial Design](#).

Initial A range of approximately 16 to 32 subjects will be enrolled in this trial (Table 6.a).
wording:

Amended Table 6.a displays the number of subjects who will participate in the study based on
or new design options:
wording:

Rationale for Change:

To clarify the number of subjects in the trial.

[Section 1 Clarification of number of subjects](#) also contains a change.

Change 2: Clarification of number of subjects.

Revision of postmenopausal criteria.

The change occurs in [Table 7.a](#) **Inclusion Criteria (footnote a):**

Initial – Is a female subject with no childbearing potential, defined by at least 1 of the following criteria:
wording: • Postmenopausal (for healthy subjects defined as 12 months of spontaneous amenorrhea in females aged >45 years or approximately 6 months of spontaneous amenorrhea in females aged ≤ 45 years with serum FSH levels >40 mIU/mL and for hepatically impaired subjects defined as 12 months of spontaneous amenorrhea in females with serum FSH levels >40 mIU/mL). Appropriate documentation of FSH levels is required.

Amended – Is a female subject with no childbearing potential, defined by at least 1 of the following criteria:
or new Postmenopausal (~~for healthy subjects~~ defined as 12 months of amenorrhea without an alternative medical cause in females aged >45 years or approximately 6 months of spontaneous amenorrhea in females aged ≤ 45 years with serum FSH levels >40 mIU/mL). and for hepatically impaired subjects defined as 12 months of spontaneous amenorrhea in females with serum FSH levels >40 mIU/mL). Appropriate documentation of FSH levels is required.

Rationale for Change:

The Czech Competent Authority, State Institute for Drug Control, requested an amendment to the protocol for the postmenopausal criteria to be consistent with the Clinical Trial Facilitation Group “Recommendations related to contraception and pregnancy testing in clinical trials”.

Change 3: The addition of an exclusion criteria for subjects with QTcF >450 msec.

The primary change occurs in Table 7.b Exclusion Criteria.

Added text: The following exclusion criteria was added for all subjects:

Have a QTcF > 450 msec at Baseline.

Rationale for Change:

This standard exclusion criteria was inadvertently omitted during protocol development.

Change 4: The addition of an exclusion criteria for a positive human immunodeficiency virus (HIV) and hepatitis test for healthy subjects.

The primary change occurs in Table 7.b Exclusion Criteria:

Added text: The following exclusion criteria was added for Group 4 (healthy subjects only):

Have a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV), or HIV antibody/antigen, at Screening. Note: Subjects with positive HBV or HCV serology may be enrolled if quantitative PCR for HBV or HCV viral RNA is negative.

Rationale for Change:

This exclusion criteria was inadvertently omitted during protocol development.

Change 5: CCI

The primary change occurs in deleted Section 9.3.2 PD Assessments.

Deleted 9.3.2 – PD Assessments
text: CCI

Rationale for Change:

CCI

The following sections also contain this change:

- Section 3.0 Schedule of Trial Procedures.
- Section 5.1.3 Exploratory Objectives
- Section 5.2.3 Exploratory Endpoints.

- Section 6.1 Trial Design.
- Section 6.2.2.3 Exploratory Endpoints.
- Section 6.3 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters.

Change 6: Removal of “legal representative” language.

The primary change occurs in Section 13.2 Subject Information, Informed Consent, and Subject Authorization.

Deleted text: The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. ~~In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.~~

The subject, ~~or the subject's legally acceptable representative~~, must be given ample opportunity to: (1) inquire about details of the trial, and (2) decide whether or not to participate in the trial. If the subject, ~~or the subject's legally acceptable representative~~, determines he or she will participate in the trial, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, ~~or the subject's legally acceptable representative~~, at the time of consent and before the subject entering into the trial. The subject ~~or the subject's legally acceptable representative~~ should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Two copies of the informed consent are signed by the subject, 1 of which, along with the subject authorization form (if applicable) and subject information sheet (if applicable), will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects ~~or the relevant subject's legally acceptable representative~~ in the same manner as the original informed consent. The date the revised consent was obtained should be

recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Rationale for Change:

To address the following comment from the Czech Competent Authority (State Institute for Drug Control): It is required that only subjects who are able to provide an informed consent with participation in the trial and whose legal capacity is not restricted participate in the clinical trial. In compliance with Section 52 of Act No 378/2007 Coll. ("Act on Pharmaceuticals"), participation of persons with restricted capacity to carry out legal acts in a clinical trial is permissible only in cases where a preventive or therapeutic benefit from the trial is expected. The Institute requires that this information be included in the inclusion criteria as well as in chapter 13.2 "Subject Information, Informed Consent, and Subject Authorization" of the protocol. With respect to this comment, it is not possible for the Informed Consent to be signed by a legal guardian.

The following sections also contain this change:

- Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject.
- Appendix A Responsibilities of the Investigator.
- Appendix B Elements of the Subject Informed Consent.

Change 7: Addition of an exclusion criteria for subjects with legal incapacity or limited legal capacity.

The primary change occurs in [Table 7.b Exclusion Criteria](#).

Description Added exclusion criteria to all subjects: **Have legal incapacity or limited legal capacity.**
of change:

Rationale for Change:

To address request from the Czech Competent Authority (State Institute for Drug Control) to exclude subjects who cannot provide consent (see rationale for change above).

Change 8: Added information regarding pregnancy.

The primary change occurs in [Section 9.1.12 Pregnancy](#).

Description A section was added to further clarify dealing with pregnancy.
of change:

Added text: **9.1.12 Pregnancy**

Women of childbearing potential will not be included in this trial.

Male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in Appendix D containing highly effective contraception.

If any subject is found to be pregnant during the trial, she should be withdrawn from the trial and any Takeda-supplied drug and should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the trial 30 days after the last dose should also be recorded following authorization from the subject's partner. All pregnancies, including female partners of male subjects, in subjects on active trial drug will be followed up to final outcome. The outcome of the pregnancy, including any premature termination, must be reported to the sponsor.

Rationale for Change:

Text added to further clarify contraception and dealing with pregnancy.

Change 9: Added pregnancy test at check-in on Day -1.

The primary change occurs in Section 3.0 Schedule of Trial Procedures.

Description Urine pregnancy test (hCG) was added to the check-in (Day -1) Visit.
of change:

Section 9.2.1.2 Screening also contains this change.

Rationale for Change:

Routine/standard test omitted from the initial protocol.

Change 10: Revised exclusion criteria based on bilirubin levels.

The primary change occurs in Table 7.b Exclusion Criteria.

Description Changed exclusion criteria for hepatically impaired subjects: Have bilirubin levels
of change: above 5 times the upper limit of normal (ULN) at Screening or Day -1 for Groups 1
and 2 and 4 (no limit for Group 3).

Added exclusion criteria for healthy subjects: **Have bilirubin levels above 1.5 times the ULN at Screening or Day -1.**

Rationale for Change:

To clarify the normal range in healthy volunteers which is different than levels allowed for subjects with hepatic impairment.

Section 1.0 TRIAL SUMMARY also contains this change.

Change 11: Pregnancy and contraception wording changed.

The primary change occurs in Appendix D Pregnancy and Contraception.

Initial *Female Subjects and Their Male Partners*

wording: Female subjects of childbearing potential are excluded from this trial; there are no requirements for contraception or pregnancy avoidance.

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the trial, and for 5 half-lives PLUS 90 days after the dose of trial drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

Amended *Female Subjects and Their Male Partners*

or new wording: Female subjects of childbearing potential are excluded from this trial; there are no requirements for contraception or pregnancy avoidance. **If any subject is found to be pregnant during the study, she should be withdrawn from the study and any Takeda-supplied drug and should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study 30 days after the last dose should also be recorded following authorization from the subject's partner. All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome. The outcome of the pregnancy, including any premature termination, must be reported to the sponsor.**

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the trial, and for 5 half-lives ~~PLUS 90~~ 30 days after the dose of trial drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective

contraception below.

Rationale for Change:

- 1) Text added to further clarify dealing with pregnancy.
- 2) Period for male subjects to use barrier contraception: Given that TAK-954 did not exhibit genotoxic potential in the standard battery of genotoxicity assays and the short half-life, 30 days is considered acceptable. This is in line with the CTFG “Recommendations related to contraception and pregnancy testing in clinical trials” that only require contraception during treatment and until the end of relevant systemic exposure in the male subject plus a 90 day period in case of genotoxicity findings (and no additional time required in case of no genotoxicity).

The following sections also contain this change:

- [Table 7.a Inclusion Criteria](#) (footnote a).
- [Appendix B Elements of the Subject Informed Consent](#).

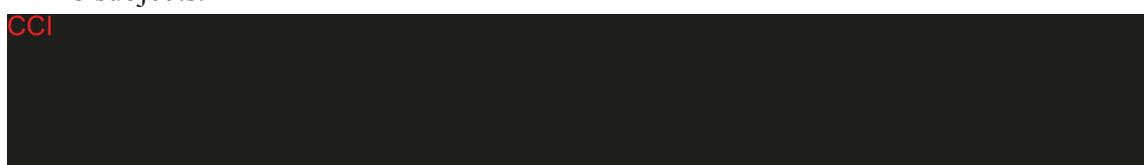
Change 12: Clarification to altering the trial design.

The primary change occurs in [Section 6.3 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters](#):

Initial wording: This is a phase 1 assessment of TAK-954 in humans, and the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 clinical trials. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

- Decrease the dose of the trial drug administered.
- A planned PK data review may be eliminated if agreed to by Sponsor and investigator and if no further increases in total daily dose occur.
- Addition of a PK data review.
- The number of subjects in the severe hepatically-impaired cohort may be less than 8 subjects.

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Up to an additional 50 mL of blood may be drawn for PK and/or PD analyses. This may include repeat samples or modified PK/PD time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial.

The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, PK, or PD data (eg, to obtain data closer to the time of peak plasma concentrations). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatinine kinase to serum chemistry panel that was already drawn).

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at the discretion of the investigator.

Amended or new wording: This is a phase 1 assessment of TAK-954 in humans, and the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 clinical trials. ~~Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.~~

- Decrease the dose of the trial drug administered.
- A planned PK data review may be eliminated if agreed to by Sponsor and investigator ~~and if no further increases in total daily dose occur.~~
- Addition of a PK data review.
- The number of subjects in the severe hepatically-impaired cohort may be less than 8 subjects.

~~The PK/PD sampling scheme currently outlined in the protocol may be modified during the trial based on newly available PK or PD data (eg, to obtain data closer to the time of peak plasma concentrations). Based on emerging PK data, the actual PK sampling times may change but the number of samples will remain the same.~~ If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional PD markers.

Up to an additional 50 mL of blood may be drawn for PK and/or PD analyses. This may include repeat samples or modified PK/PD time points based on emerging **data from previous subjects/cohorts in the study as per protocol**. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume ~~during his/her participation in the entire trial~~.

The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) currently outlined in the protocol may be modified during the trial based ~~on newly available safety, tolerability, PK, or PD data as it is analysed per protocol from previous subjects/cohorts in the study~~ (eg, to obtain data closer to the time of peak

~~plasma concentrations~~). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatinine kinase to serum chemistry panel that was already drawn).

It is understood that the current trial may employ some or none of the alterations described above. **Any alteration made Any of these per protocol alterations (part of trial design to this protocol to meet the trial objectives its objectives) must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at the discretion of the investigator. Any other changes, if considered substantial, will be documented in a protocol amendment which will require approval before they are implemented.**

Rationale for Change:

This section has been revised to clarify changes that can be done within the remit of the protocol and those that would require a protocol amendment. Wording pertinent to oral dosing (time of peak plasma concentrations) has also been removed given that is not applicable to the TAK-954 formulation used in the study.

Change 13: Additional vital sign measurements added.

The primary change occurs in Section 3.0 Schedule of Trial Procedures.

Description Additional blood pressure and heart rate assessments were added on Day 1 at 0.5 and of change: 12 hours after the start of the infusion and on Day 5.

Rationale for Change:

The additional vital sign measurements added are aligned with PK measurements taken at same timepoints and will add to the evaluation of any potential tachycardia or hypotension.

Change 14: Added exclusion criteria for restricted concomitant medications.

The primary change occurs in Section 7.2 Exclusion Criteria.

Description Added the following exclusion criteria for Groups 1 through 3: **Are unable to refrain** of change: **from or anticipates the use of:**

- **strong CYP3A4 inhibitors or inducers**
- **serotonin agonists or antagonists**
- **monoamine oxidase inhibitors**
- **noradrenergic agonists**
- **selective serotonin reuptake inhibitors**
- **gamma—aminobutyric acid antagonists**
- **N-methyl-D-aspartate receptor antagonists**

beginning approximately 7 days before administration of the trial drug,

throughout the trial, until the Follow-up Visit.

Rationale for Change:

Restricted concomitant medications (in Section [7.3 Excluded Medications, Supplements, and Dietary Products](#) and others added to minimize the risk of serotonin syndrome) were inadvertently omitted from exclusion criteria in the original protocol.

Section [7.3 Excluded Medications, Supplements, and Dietary Products](#) also contains this change.

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	09-Oct-2017 10:57 UTC
	Statistical Approval	09-Oct-2017 13:47 UTC
	Pharmacovigilance Approval	09-Oct-2017 14:23 UTC
	Clinical Science Approval	09-Oct-2017 19:11 UTC