Title: A Single-Sequence, Open-Label, 2-Period Crossover Trial to Evaluate the Effect of the Potent Cytochrome P-450 3A4 Inhibitor Itraconazole on the Pharmacokinetics of TAK-954 in Healthy Adult Subjects

NCT Number: NCT03173170

Protocol Approve Date: 03 May 2017

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Single-Sequence, Open-Label, 2-Period Crossover Trial to Evaluate the Effect of the Potent Cytochrome P-450 3A4 Inhibitor Itraconazole on the Pharmacokinetics of TAK-954 in Healthy Adult Subjects

Sponsor:	Takeda Development Center Americas, Inc.
Trial Number:	TAK-954-1004
Compound:	TAK-954

Date:	03 May 2017	**Version/Amendment Number:**	Initial Version

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1.0 TRIAL SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** TAK-954
Study Number: TAK-954-1004	**Phase:** 1
Protocol Title: A Fixed Sequence, Open-Label, 2-Period Crossover Trial to Evaluate the Effect of the Potent Cytochrome P-450 3A4 Inhibitor Itraconazole on the Pharmacokinetics of TAK-954 in Healthy Adult Subjects	
Trial Design: This is a phase 1, single-sequence, open-label, 2-period crossover trial in approximately 10 healthy male and female (non–childbearing potential) subjects aged 18 and 55 years (inclusive). The trial is designed to investigate the effect of a potent cytochrome P-450 (CYP) 3A4 inhibitor (itraconazole) on the pharmacokinetics (PK) of TAK-954. TAK-954 will be administered as a single 60-minute intravenous (IV) infusion. The trial will include a Screening Visit, Trial Period 1 (6 days), a washout (a minimum of 7 days between doses in Period 1 Day 1 and Period 2 Day 1), Trial Period 2 (9 days), and a Follow-up Visit. Eligible subjects will be allocated to the trial treatment by non-random assignment on Day 1 of Trial Period 1 and will receive a 0.2 mg single dose TAK-954 IV on this day and on Day 4 of Trial Period 2 at approximately the same time (between 0600 and 0900). In Trial Period 2, subjects will receive 200 mg once daily (QD) itraconazole orally on Days 1 to 8 at approximately the same time (between 0600 and 0900) and a single dose of 0.2 mg TAK-954 on Day 4. Itraconazole will be administered as 2 x 100 mg capsules. After completion of the trial (or after subject withdrawal), all subjects will return for a Follow-up Visit 10 to 14 days after their last dose of trial drug.	
Primary Objective: • To evaluate the effect of the potent CYP3A4 inhibitor itraconazole on the single-dose PK of TAK-954. **Secondary Objectives:** • To evaluate the safety of a single IV dose of TAK-954 in the presence and absence of a potent CYP3A4 inhibitor.	
Subject Population: Healthy male and female (non–childbearing potential) subjects.	
Number of Subjects: Approximately 10 subjects will complete this trial.	**Number of Sites:** 1 site
Dose Levels: • TAK-954 0.2 mg • Itraconazole 200 mg QD	**Route of Administration:** • TAK-954 IV • Itraconazole oral
Duration of Treatment: Two doses of TAK-954. Eight doses of itraconazole.	**Period of Evaluation:** Approximately 7 to 8 weeks
Main Criteria for Inclusion: Healthy male and female (non–childbearing potential) subjects who are aged 18 to 55 years, inclusive, with a body mass index (BMI) between 18 to 30 kg/m^2, and a body weight >50 kg.	
Main Criteria for Exclusion: 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 (maximum observed concentration [C_{max}] and area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration [AUC_{∞}]) for TAK-954 will be analyzed on Day 1 of Trial Period 1 and on Day 4 of Trial Period 2.

Safety endpoints:

Safety and tolerability will be assessed through physical examinations, electrocardiograms (ECGs), vital signs, and laboratory assessments as well as collection of spontaneous adverse events.

Statistical Considerations:

Pharmacokinetics:

The PK parameters of TAK-954 (and metabolites, if possible) will be summarized by regimen using descriptive statistics. Linear and semilogarithmic 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.

For evaluation of potential effect of itraconazole on TAK-954 PK, paired t-tests and associated confidence intervals will be determined on the natural logarithms of C_{max} and AUCs to assess the exposure between regimens (TAK-954 alone and TAK-954 with itraconazole). The geometric mean of the relative bioavailability of the TAK-954 with itraconazole regimen relative to the TAK-954 alone regimen and the associated 90% confidence intervals will be determined by exponentiating the appropriate estimates for the difference between regimens in the log-transformed parameters.

Safety:

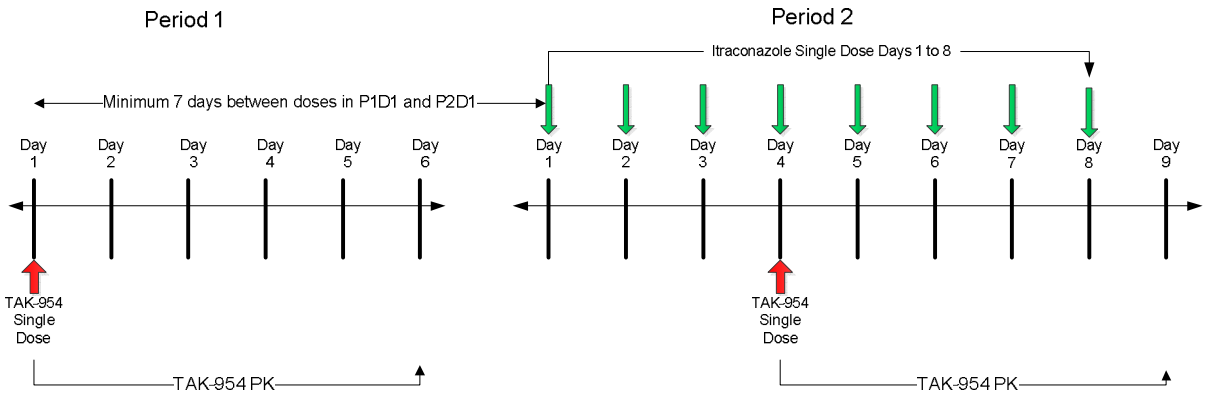
Safety data will be presented by regimen. Treatment-emergent adverse events (TEAEs) will be summarized by causal relationship to the trial drug and by intensity. Clinical laboratory variables, ECGS, and vital signs parameters (uncorrected and corrected QT intervals, PR, and QRS and heart rate) will be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

Sample Size Justification:

Approximately 10 subjects will complete this trial. With this sample size, a 2-sided 95.0% CI for the geometric mean ratio of C_{max} for TAK-954 when administered with and without itraconazole will have 90% probability of excluding 1.25 (the upper bound of the bioequivalence range) if itraconazole increases the C_{max} for TAK-954 by at least 50%. This calculation assumes that the CI is based on the t statistic, that the distance from the mean to the lower bound of the CI on the natural-log scale is 0.182, and that the true SD of differences on the natural-log scale is 0.187 as estimated from C_{max} values reported for Cohort 1 in Theravance Protocol No. 0095. Assuming the intrasubject variation observed for area under the concentration-time from 0 to t in that cohort (SD=0.129), a 2-sided 95.0% CI for the geometric mean ratio of AUC_{∞} for TAK-954 when administered with and without itraconazole will have greater than 99% probability of excluding 1.25 if itraconazole increases AUC_{∞} for TAK-954 by at least 50%.

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

2.0 TRIAL SCHEMATIC



PK=pharmacokinetic.

3.0 SCHEDULE OF TRIAL PROCEDURES

Assessment	Screening	Trial Period 1 (a)					Trial Period 2									Follow-up/Early Termination
Day	-28 to -2	-1	1	2	3	4 to 6	-1	1	2 to 3	4	5	6	7	8	9	10-14 days after last dose of trial drug
Administrative Procedures																
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Medical history/demographics	X															
Prior and concomitant medication review	----------Continuous review----------															
Clinic Procedures/Assessments																
Full physical examination	X	X														X
Semirecumbent vital signs (heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]	X		X (b)	X	X		X	X	X	X (b)	X	X			X	X
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature) rate	X		X (b)				X									
Height	X															
Weight	X															
Body mass index (BMI)	X															
Standard 12-lead electrocardiogram (ECG)	X		X (b)		X		X			X (b)					X	X
CCI	[redacted]															
Adverse event (AE) monitoring	----------Continuous review----------															
Laboratory Procedures/Assessments																
Serum chemistry	X	X			X		X							X		X
Hematology	X	X			X		X							X		X
Urinalysis	X	X			X		X							X		X
Serum follicle-stimulating	X															

Assessment	Screening	Trial Period 1 (a)					Trial Period 2									Follow-up/Early Termination
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4 to 6**	**-1**	**1**	**2 to 3**	**4**	**5**	**6**	**7**	**8**	**9**	**10-14 days after last dose of trial drug**
hormone (FSH)																
Urine drug screen	X	X					X									
Urine alcohol test/alcohol breath test (d)	X	X					X									
HIV test	X															
Hepatitis panel	X															
Pharmacokinetics (PK) Evaluations																
Plasma samples for TAK-954 (e)			X	X	X	X				X	X	X	X	X	X	
Urine sample for TAK-954 PK (f)			X	X	X					X	X	X				
Pharmacogenomic (PGx) Evaluations																
Blood sample for DNA PGx			X													
Blood sample for RNA PGx			X													
Drug Administration																
TAK-954 dosing			X							X						
Itraconazole dosing								X	X	X	X	X	X	X		
Other																
Confinement		X	X	X	X			X	X	X	X	X	X			
Meals		X	X	X	X		X	X	X	X	X	X	X			

(a) A minimum of 7 days between doses in Period 1 Day 1 and Period 2 Day 1.
(b) Assessments at predose (within 30 minutes), 1, 2, 4, 8, and 12 hours postdose (relative to TAK-954 start of infusion).
(c) CCI [redacted]
(d) An alcohol breath test may be performed at the discretion of the investigator.
(e) 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, 96, and 120 hours postdose (relative to TAK-954 start of infusion).
(f) Urine collected at predose, 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours relative to TAK-954 infusion start in Trial Periods 1 and 2.

4.0 INTRODUCTION

4.1 Background

Critically ill patients who require enteral feeding frequently have reduced gastrointestinal (GI) motility, develop enteral feeding intolerance, 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 and hospital stay, and ultimately higher mortality [2,3].

TAK-954 is being developed for short-term use with enteral feeding to treat critically ill patients with enteral feeding intolerance. TAK-954 is a highly selective and potent serotonin type 4 (5-HT4) receptor agonist that exhibits prokinetic activity throughout the GI tract [4].

TAK-954 has been investigated in healthy subjects at single oral doses from 0.1 to 20 mg, multiple oral doses from 0.2 to 10 mg daily for 10 days, and multiple intravenous (IV) doses from 0.1 to 0.5 mg daily for 5 days. TAK-954 has been shown to undergo oxidative metabolism in vitro in human liver microsomes, although it was relatively stable when incubated with cryopreserved human hepatocytes (half-life [$t_{1/2}$]) >17 hours).

The purpose of this trial is to investigate the effect of a potent CYP3A4 inhibitor on the PK of IV TAK-954 in healthy males and females. Itraconazole has been chosen as it is recommended by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a suitable potent cytochrome P-450 (CYP) 3A4 inhibitor for use in drug-drug interaction (DDI) studies. An IV dose of 0.2 mg TAK-954 daily has been selected as a dose that is predicted to be within the clinically relevant range, but is lower than the maximum multiple IV dose (0.5 mg) that has been investigated so far, to allow for any increases in exposure that may be observed with metabolic inhibition.

Please refer to the TAK-954 Investigator's Brochure for complete information on the investigational product and the most recent itraconazole product insert for the appropriate region.

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, single-sequence, open-label, 2-period crossover trial in 10 healthy male and female (non–childbearing potential) subjects. The trial is designed to investigate the effect of a potent CYP3A4 inhibitor (itraconazole) on the PK of TAK-954. TAK-954 will be administered as a single 60-minute IV infusion.

4.3 Benefit/Risk Profile

As this is a trial in healthy subjects, there is no expected clinical benefit to the trial participants. Potential risks are based on clinical findings, the mechanism of action, and nonclinical findings.

There is minimal risk associated with trial procedures including 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, and the specified monitoring procedures. Overall, the risk:benefit 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 the potent CYP3A4 inhibitor itraconazole on the single-dose PK of TAK-954.

5.1.2 Secondary Objective

The secondary objectives of the trial are to evaluate the safety of single-dose IV doses of TAK-954 in the presence and absence of a potent CYP3A4 inhibitor.

5.1.3 Exploratory Objectives

Exploratory objectives of this trial include:

CCI [redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint of the trial is the following PK parameters on Day 1 of Trial Period 1 and Day 4 of Trial Period 2:

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

5.2.2 Safety Endpoints

Safety endpoints include the following:

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

5.2.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

PK parameters:

CCI [redacted]

CCI

[redacted]

Pharmacodynamic parameters:

CCI

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 1, single-sequence, open-label, 2-period crossover trial in approximately 10 healthy male and female (non–childbearing potential) subjects. The trial is designed to investigate the effect of a potent CYP3A4 inhibitor (itraconazole) on the PK of TAK-954. TAK-954 0.2 mg will be administered as a single 60-minute IV infusion.

The trial will include a Screening Visit, Trial Period 1 (6 days), a washout (a minimum of 7 days between doses in Period 1 Day 1 and Period 2 Day 1), Trial Period 2 (9 days), and a Follow-up Visit. Blood samples for assessment of TAK-954 concentrations will be collected before each dose of TAK-954 and at intervals up to 120 hours after the last dose of trial drug in each trial period. Samples may be assayed for TAK-954 metabolites. TAK-954 and its metabolites will also be assayed in urine, data permitting and if deemed possible.

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

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

CCI [redacted]

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

6.2 Rationale for Trial Design, Dose, and Endpoints

6.2.1 Rationale of Trial Design and Dose

TAK-954 is a small molecule, 5-HT4 agonist. TAK-954 has been investigated in healthy subjects at single oral doses from 0.1 to 20 mg, multiple oral doses from 0.2 to 10 mg once daily (QD) for 10 days, and multiple IV doses from 0.1 to 0.5 mg QD for 5 days. A single IV dose of 0.5 mg TAK-954 has also been investigated in critically ill patients with enteral feeding intolerance and compared with metoclopramide. After multiple IV infusion dosing in healthy subjects (0.1 and 0.5 mg with a 1-hour infusion), TAK-954 concentrations declined in a biphasic manner, with mean $t_{1/2}$ values ranging from 18.0 to 18.9 hours on Day 5. TAK-954 steady state was achieved by Day 3 with minimal accumulation of TAK-954 after multiple IV dosing of 0.5 mg. The increase in exposure from the 0.1 mg to 0.5 mg IV dose was approximately dose proportional, and the mean amount of TAK-954 excreted unchanged in urine on Day 5 ranged from 27.7% to 31.6%. In subjects who were critically ill and received 0.5 mg by IV infusion, the PK exposure was slightly lower relative to that observed in healthy subjects.

Two active metabolites were identified nonclinically, but TAK-954 was not extensively metabolized to either of these metabolites after oral dosing (mean C_{max} and area under the concentration-time curve from time 0 to 48 hours metabolite to parent ratios ranged from 0.0008 to

0.004). Renal excretion of these metabolites was also low with concentrations in urine generally below the limit of detection. Evidence of GI prokinetic activity in healthy subjects (increased bowel movement frequency, looser stool consistency, and decreased time to first bowel movement) was observed at all dose levels after receiving single and multiple doses (oral and IV). In 7 subjects who were critically ill, scintigraphy data qualitatively suggest TAK-954 decreases gastric emptying time after a liquid meal.

After multiple oral doses in healthy subjects, TAK-954 was generally well tolerated at doses up to 5 mg QD for 10 days. There were no SAEs and the overall incidence of AEs reported for the TAK-954 dose groups was similar to that for the placebo group. All AEs were mild or moderate. The most commonly reported treatment-related AEs in TAK-954 subjects overall were headache and diarrhea. No dose-related trends were evident in the AE data across the 0.2, 1, or 5 mg dose groups, but 2 of 3 subjects receiving 10 mg were discontinued because of an AE (mild intermittent atrioventricular dissociation, which resolved without intervention). There were no safety signals in the clinical laboratory or respiratory rate data after multiple dose administration. Mean blood pressure (BP) and heart rate (HR) remained in the normal range for all groups throughout the trial. However, there was a trend toward lower BP and elevated HR in the standing position for TAK-954 subjects, but no dose response was apparent. In addition, there was one AE related to BP (orthostatic hypotension in a subject who received 5 mg TAK-954).

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

TAK-954 has been shown to undergo oxidative metabolism in vitro in human liver microsomes, though it was relatively stable when incubated with cryopreserved human hepatocytes ($t_{1/2}$ >17 hours).

The purpose of this trial is to investigate the effect of a potent CYP3A4 inhibitor on the PK of IV TAK-954 in healthy subjects. Itraconazole has been chosen as it is recommended by the FDA and EMA as a suitable potent CYP3A4 inhibitor for use in DDI studies. An IV dose of 0.2 mg TAK-954 has been selected as a dose that is predicted to be within the clinically relevant range, but is lower than the maximum multiple IV dose (0.5 mg) that has been investigated so far, to allow for any increases in exposure that may be observed with metabolic inhibition.

6.2.2 Rationale for Endpoints

6.2.2.1 PK

The primary endpoint for this trial consists of standard PK variables (C_{max} and AUC_{∞}) to determine the effect of itraconazole on the PK of TAK-954 in healthy subjects.

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

CCI

[redacted]

6.2.3 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.

6.3 Trial Beginning and End/Completion

6.3.1 Definition of Beginning of the Trial

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

6.3.2 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).

6.3.3 Definition of Trial Discontinuation

Trial discontinuation because of nonsafety reasons, such as:

- A finding (eg, PK, PD, 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.

6.3.4 Criteria for Premature Termination or Suspension of the Trial

6.3.4.1 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.

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

In the event that the sponsor, an institutional review board (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:

1. Understand the trial procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all trial procedures and restrictions.
3. Be a man or woman (with no child bearing potential) aged 18 to 55 years, inclusive, at the Screening Visit.
4. Have a BMI ≥18 and ≤30 kg/m^2 and a body weight >50 kg at the Screening Visit.
5. Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before administration of the initial dose of trial drug/invasive procedure.
6. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and before administration of the initial dose of trial drug.
7. Meet the following birth control requirements:
   - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from trial drug administration on the first day of the first dose until 5 half-lives plus 90 days after administration of the last dose of trial drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1 year post–bilateral vasectomy procedure before trial drug administration on the first day of the first dose. A male subject whose vasectomy procedure was performed less than 1 year before trial drug administration on the first day of the first dose must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
   - Is a male subject who agrees to not donate sperm from trial drug administration on the first day of the first dose until 5 half-lives plus 90 days after administration of the last dose of trial drug.
   - Is a female subject with no childbearing potential, defined by at least 1 of the following criteria:
     a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years, 6 months of spontaneous amenorrhea in females aged >45 years with serum FSH levels >40 mIU/mL). Appropriate documentation of FSH levels is required.
     b) Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

c) Had a tubal ligation with appropriate documentation of surgical procedure.

d) Has a congenital condition resulting in no uterus.

7.2 Exclusion Criteria

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

1. Has 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.
2. Has 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.
3. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of the sponsor.
4. Has a history of cancer (malignancy).
5. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
6. Has a positive alcohol or drug screen.
7. Is a lactating/nursing woman.
8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 8 weeks of the first dose of trial drug.
9. Has a known hypersensitivity to any component of the formulation of TAK-954 or related compounds, or to itraconazole (see Product Insert).
10. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of trial drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit. There may be certain medications that are permitted, see Section 7.3.
11. Has 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).
12. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
13. Has a substance abuse disorder.

7.3 Excluded Medications, Supplements, and Dietary Products

Use of excluded agents (prescription or nonprescription) or dietary products is outline in Table 7.a.

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

Category	Between Screening and Enrollment (Days -28 to Predose [Day 1])	Randomization Post-Enrollment (Day 1) to Follow-up Visit
Tobacco- and nicotine-containing products	Completely restricted	Completely restricted
Cannabis products	Completely restricted	Completely restricted
Alcohol	Completely restricted 7 days before dosing	Completely restricted 7 days before dosing At all other times no more than 3 units/day
Xanthine and/or caffeine	Completely restricted 24 hours before dosing	Completely restricted 24 hours before dosing At all other times no more than 6 units/day
Medications	Completely restricted 7 days before dosing	Completely restricted (a)
Food substance		
Grapefruit /grapefruit juice	Completely restricted 7 days before dosing	Completely restricted
Fruit	No restriction	No restriction
Fruit juice	No restriction	Dosing will occur without consumption of fruit juice. Fruit juice is restricted 4 hours after dosing.
Mustard green (b)	Completely restricted 7 days before dosing	Completely restricted
Charbroiled meat	Completely restricted 7 days before dosing	Completely restricted

(a) If medications are required to treat an AE, certain medications may be allowed after discussion and agreement between the sponsor and principal investigator.
(b) Mustard green family includes kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, and mustard.

7.4 Diet, Fluid, and Activity

7.4.1 Diet and Fluid

Subjects must abstain from all food and drink (except water) at least 8 hours before any safety laboratory evaluations.

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

Subjects will receive a standard (moderate-fat) breakfast 1.5 hours before TAK-954 dosing in Trial Period 1 and 30 minutes before itraconazole dosing in Trial Period 2. Lunch will be provided approximately 4 hours after TAK-954 dosing or 5.5 hours after itraconazole dosing, as applicable, on all days. Dinner will be provided approximately 9 or 10 hours after TAK-954 or itraconazole dosing, respectively, on all days. An evening snack will also be permitted. The caloric content and composition of meals will be the same in each trial period. After the 24-hour postdose (Day 1 of Trial Period 1 and Day 4 of Trial Period 2) procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

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. Liver Function Test (LFT) Abnormalities

   In multidose studies, trial drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 10.2.9.4), if the following circumstances occur at any time during trial drug treatment:

   – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 times the upper limit of normal (ULN), or

   – ALT or AST >5×ULN and persists for more than 2 weeks, or

   – ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or international normalized ratio >1.5, or

   – ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
3. 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.
4. 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.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the electronic case report form (eCRF).

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 of 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, Compounding Instructions, 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.

Itraconazole will be supplied by the trial site.

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 6.3.4.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject entering 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. 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.

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

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=kg/m^2). Body weight and height will be obtained with the subject's shoes off and jacket or coat removed.

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.

Before each trial period, 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. Changes in subject health status from baseline assessment to trial drug administration should be captured in the subject's medical history. A complete description of AE collections and procedures is provided in Section 10.0.

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	3,4-methylenedioxy-methamphetamine (MDMA)
Barbiturates	Methadone/metabolite
Benzodiazepines	Opiates
Buprenorphine/metabolite	Oxycodone/oxymorphone
Cannabinoids	Phencyclidine
Cocaine/metabolites	

Alcohol Screen

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

9.2.1.2 Screening

Serum

Serum evaluations will include the following tests:

HIV test	FSH (females only)
	Hepatitis panel, including HBsAg and anti-HCV

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 300 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	Mandatory
Blood sample for RNA PGX	Blood	RNA	PGx measurements	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.

The following plasma PK parameters for TAK-954 will be calculated on Day 1 of Trial Period 1 and Day 4 of Trial Period 2:

- C_{max}
- AUC_{∞}
- $t_{1/2}$

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 date and time of the dosing and sample collection is noted on eCRF.

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[redacted]

9.3.2 PGx Measurements

9.3.2.1 Blood Sample for DNA and RNA PGx Measurements

When sampling of whole blood for PGx analysis occurs, every subject must sign an informed consent/be consented in order to participate in the trial. PGx is a component of the trial; participation is mandatory.

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), pharmacodynamics (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 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 PD 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 non-random assignment on Day 1 of Trial Period 1 and will receive a 0.2 mg single-dose TAK-954 IV on this day and on Day 4 of Trial Period 2 at approximately the same time (between 0600 and 0900). In Trial Period 2, subjects will receive 200 mg QD itraconazole orally on Days 1 to 8 at approximately the same time (between 0600 and 0900). Itraconazole will be administered as 2 x 100 mg capsules and witnessed by the investigator and/or trial staff. The bioavailability of itraconazole when administered as capsules is increased under fed compared with fasted conditions and therefore, itraconazole will be administered after a standard (moderate-fat) breakfast (consumed within 30 minutes before dosing). The TAK-954 infusion will start 1 hour after itraconazole administration on Day 4 of Trial Period 2. To maintain similar conditions in each trial period, subjects will also receive a standard (moderate-fat) breakfast 1.5 hours before TAK-954 IV administration in Trial Period 1.

9.5 Confinement

Period 1:

Subjects will report to the clinical research unit (CRU) on Day -1, the day before the scheduled day of administration of the trial drug at the discretion of the investigator. Subjects will remain in the unit until after the PK sample collection at 48 hours after TAK-954 dosing (the morning of Day 3) and will return to the clinic for PK sample collection at 72, 96, and 120 hours. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

Period 2:

Subjects will report to the CRU on Day -1, the day before the scheduled day of administration of the trial drug at the discretion of the investigator. Subjects will remain in the unit until after the PK sample collection at 72 hours after TAK-954 dosing (the morning of Day 7). Subjects will return to the clinic for PK sample collection at 96 and 120 hours and itraconazole administration at 96 hours (Day 8). At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

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, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, 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 last dose of trial drug. 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

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

If a subject is noted to have ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported 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 10.2.10).

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

11.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects. 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

Concentrations of TAK-954 and any measured metabolites will be summarized by regimen over each scheduled sampling time using descriptive statistics.

The amount of TAK-954 and any measured metabolites excreted in urine will be summarized by regimen using descriptive statistics.

Individual plasma and urine concentration versus time data will be presented in a data listing.

Plasma and urine PK parameters of TAK-954 and any measured metabolites will be summarized by regimen using descriptive statistics.

For evaluation of potential effect of itraconazole on TAK-954 PK, paired t-tests and associated CIs will be determined on the natural logarithms of C_{max} and area under the concentration-time curses to assess the exposure between regimens (TAK-954 alone and TAK-954 with itraconazole). The geometric mean of the relative bioavailability of the TAK-954 with itraconazole regimen relative to the TAK-954 alone regimen and the associated 90% CIs will be determined by exponentiating the appropriate estimates for the difference between regimens in the log-transformed parameters.

A more detailed analysis will be presented in the SAP. Additional analyses will be included, if appropriate.

11.1.4 Safety Analysis

The safety set will be used for all summaries of safety parameters. These summaries will be presented by TAK-954 alone, itraconazole alone, and TAK-954 with itraconazole.

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). Treatment-emergent adverse events (TEAEs) with onset occurring within 30 days (onset date minus last date of dose +1≤30) after the last 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. 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

Approximately 10 subjects will complete this trial. With this sample size, a 2-sided 95.0% CI for the geometric mean ratio of C_{max} for TAK-954 when administered with and without itraconazole will have 90% probability of excluding 1.25 (the upper bound of the bioequivalence range) if itraconazole increases the C_{max} for TAK-954 by at least 50%. This calculation assumes that the CI is based on the t statistic, that the distance from the mean to the lower bound of the CI on the natural-log scale is 0.182, and that the true SD of differences on the natural-log scale is 0.187 as estimated from C_{max} values reported for Cohort 1 in Theravance Protocol No. 0095. Assuming the intrasubject variation observed for area under the concentration-time curve from time 0 to time t in that cohort (SD=0.129), a 2-sided 95.0% CI for the geometric mean ratio of AUC_{∞} for TAK-954 when administered with and without itraconazole will have greater than 99% probability of excluding 1.25 if itraconazole increases AUC_{∞} for TAK-954 by at least 50%.

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 in Trial Period 1.

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. 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.

Once signed, the original informed consent form, 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.

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	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 224-554-1052

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
AE	adverse event
Ae_t	amount of drug excreted in urine from time 0 to time t
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
CL_R	renal clearance
C_{max}	maximum observed concentration
CRU	clinical research unit
CV	coefficient of variation
CYP	cytochrome P-450
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
EFI	enteral feeding intolerance
EMA	European Medicines Agency
f_e	fraction of administered dose of drug excreted in urine
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
IRB	institutional review board
IV	intravenous

LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
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 or the subject's legally acceptable representative.
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 or the subject's legally acceptable representative is authorizing such access.
14. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
15. The anticipated prorated 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 or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the 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 5 half-lives plus 90 days after last 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; 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 last 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 pregnant partners.
   - 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?

A Single-Sequence, Open-Label, 2-Period Crossover Trial to Evaluate the Effect of the Potent Cytochrome P-450 3A4 Inhibitor Itraconazole on the Pharmacokinetics of TAK 954 in Healthy Adult Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	04-May-2017 22:28 UTC
	Clinical Pharmacology Approval	05-May-2017 11:32 UTC
	Clinical VP Approval	05-May-2017 16:05 UTC