Title: A Dose-Ranging, Randomized, Parallel, Placebo-Controlled Study to Assess the Effect of TAK-954 on Gastrointestinal and Colonic Transit in Patients With Diabetic or Idiopathic Gastroparesis

NCT Number: NCT03281577

Protocol Approve Date: 19 December 2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Dose-Ranging, Randomized, Parallel, Placebo-Controlled Study to Assess the Effect of TAK-954 on Gastrointestinal and Colonic Transit in Patients With Diabetic or Idiopathic Gastroparesis

Effect of TAK-954 on Gastrointestinal and Colonic Transit in Diabetic or Idiopathic Gastroparesis Patients

Sponsor:	Takeda Development Center Americas, Inc.		
Study Number:	TAK-954-2003		
IND Number:	114408	**EudraCT Number:**	Not Applicable
Compound:	TAK-954		
Date:	19 December 2018	**Version/Amendment Number:**	05

Amendment History:

Date	Amendment Number	Region
28 July 2017	Initial version	Global
06 November 2017	01	Global
28 February 2018	02	Global
26 April 2018	03	Global
11 September 2018	04	Global
19 December 2018	05	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center Americas, Inc. (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	United States Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance, Takeda Development Center Americas, Inc.
Medical Monitor (medical advice on protocol and study drug)	Medical Director, Clinical Science
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Medical Director, Clinical Science

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also 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, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

PPD

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 study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study 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 serious adverse events defined in Section 10.2 of this protocol.

Terms outlined in the study site agreement.

Responsibilities of the Investigator (Appendix A and Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D 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)

1.3 Protocol Amendment 05 Summary of Changes

Rationale for Amendment 05

This document describes the changes in reference to the protocol incorporating Amendment 05. The primary reason for this amendment is the elimination of 1 dosing arm based on the results of the interim analysis. The opportunity was taken to make additional changes.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix F.

Changes in Amendment 05

1. Revised number of subjects based on the findings of the interim analysis.
2. Decreased the number of active treatment arms.
3. Revised the type of vital sign procedures collected and clarified the timing in relation to pharmacokinetic (PK) blood draws.
4. Elimination of optional PK samples.
5. Revised the timing of vital sign measurements.
6. Eliminated instruction of the timing of PK sampling and electrocardiogram procedures.
7. Revised information related to interim analysis.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-954	
Title of Protocol: A Dose-Ranging, Randomized, Parallel, Placebo-Controlled Study to Assess the Effect of TAK-954 on Gastrointestinal and Colonic Transit in Patients With Diabetic or Idiopathic Gastroparesis	**IND No.:** 114408	**EudraCT No.:** Not applicable
Study Number: 2003	**Phase:** 2a	

Study Design:

This is a phase 2a, dose-ranging, randomized, parallel group, double-blind, placebo-controlled study evaluating the effects of TAK-954 on gastrointestinal (GI) and colonic transit in diabetic subjects reporting symptoms of gastroparesis with previously documented delay in gastric emptying or in subjects with diagnosis of idiopathic gastroparesis. The study will evaluate 12 subjects per treatment group.

This study consists of 3 periods and a Follow-up: a Screening Visit, a Baseline Period (between Day -14 and Day -1), Treatment Period (Days 1 to 4), and Follow-up Phone Call (Days 10 to 14).

Subjects will have an initial Screening Visit, then will undergo a baseline gastric emptying assessment with scintigraphy scans acquired at 0, 1, 2, 3 and 4 hours after radiolabeled meal, between Day -14 and Day -1 (Baseline Visit). The Screening and Baseline Visits may be performed on the same day.

If eligibility criteria are fulfilled, subjects will be randomized on Day 1 to TAK-954 0.1, 0.3, or 1 mg, or placebo. Based upon the results of the preplanned interim analysis, the number of active treatment arms has been decreased from 3 to 2. The specific dose deleted is not specified in order to maintain the blind of the study team. This change was not necessitated by safety findings.

Subjects will receive TAK-954 or placebo as a 60-minute intravenous (IV) infusion (at any time in the morning prior to 12:00) once a day for 3 days starting on Day 1. Following the infusion on Day 2, subjects will undergo scintigraphic assessment of gastric, small bowel, and colonic transit of solids over a 48-hour time period while on treatment.

The subjects will have pharmacokinetic (PK) samples collected as follows:

- Day 1: prior to dosing (0 hour), 1 (end of infusion), 2, and 4 hours after start of infusion.
- Day 2: prior to dosing (0 hour), 1 (end of infusion), 2, 5, 7, and 9 hours after the start of the infusion.
- Day 3: prior to dosing (0 hour), 1 (end of infusion) and 2 hours after start of infusion.
- Day 4: 25 hours after the start of the infusion on Day 3 (48 hours after the administration of the radiolabeled meal on Day 2, same time as the 48-hour geometric center measurement).

All participating subjects will have a 6-hour Holter monitor placed at the Baseline Visit. On Day 1, subjects will have continuous monitoring with a Holter monitor which will be placed prior to the first dose until the morning of Day 3. 12-lead ECG will be performed on Days 1, 2, and 3 prior to each IV infusion; within 30 minutes postinfusion and prior to discharge; and at the Final Visit on Day 4 or Early Termination Visit. In addition, a 12-lead ECG will be performed when needed, if a subject develops symptoms or clinical signs suggestive of cardiovascular origin (eg, dizziness, lightheadedness, chest pain, chest heaviness, palpitations, shortness of breath, tachycardia).

During the study, subjects will complete a daily diary to record their bowel habits. The subjects will assess their global GI symptom score using the GCSI at Screening. The On-study Bowel Habit Diary Card will be dispensed at Screening, to be completed daily from Screening and through the Treatment Period. The completed Bowel Habit Diary Card will be collected at the conclusion of the study.

Primary Objective:

To evaluate the dose-dependent effects of TAK-954 on gastric emptying time of solids in subjects with diabetic or idiopathic gastroparesis assessed by scintigraphy.

Secondary Objectives:

1. To evaluate the PD effects of TAK-954 on intestinal and colonic transit time assessed by scintigraphy.
2. To evaluate the PK of TAK-954 in subjects with gastroparesis.
3. To assess the safety and tolerability of multiple doses of TAK-954.

Subject Population: Diabetic subjects reporting symptoms of gastroparesis with a previously documented delay in stomach emptying or subjects with a diagnosis of idiopathic gastroparesis.

Number of Subjects:	**Number of Sites:**
Approximately 36 to 41 subjects (maximum of 12 per group)	Estimated total: 1 site in the United States
Dose Level(s):	**Route of Administration:**
TAK-954 0.1, 0.3, and 1 mg once daily (QD) Placebo	TAK-954 (IV) Placebo (IV)
Duration of Treatment:	**Period of Evaluation:**
3 days	Up to 28 days

Main Criteria for Inclusion:

Males and nonpregnant, nonbreastfeeding females who are aged 18 to 65 years, inclusive, with a body mass index (BMI) ≥16 and ≤40 kg/m^2. Subjects must have diabetes mellitus with symptoms of gastroparesis and previously documented gastric emptying delay or previously documented idiopathic gastroparesis in the last 5 years.

Main Criteria for Exclusion:

Subjects who:

- Have glycosylated hemoglobin (HbA1c) >12%.
- Have other structural diseases/conditions that affect the GI system.
- Are unable to withdraw drugs known to alter GI transit 48 hours prior to the study.
- Have clinically significant abnormal baseline safety labs.
- Have clinical evidence of significant cardiovascular, respiratory, moderate or severe renal insufficiency, hematological, neurological, or psychiatric disease, or other disease that interferes with the objectives of the study.
- Have preexisting hepatic disease that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points), see Appendix E.
- Are without known preexisting hepatic disease who have 1 or more of the following:
    - AST or ALT >2 times the ULN.
    - Bilirubin >1.5 times the ULN unless due to Gilbert's syndrome.
    - International normalized ratio (INR) >1.5 unless on anticoagulation therapy.
- Have QTcF (QT interval with Fredericia correction method) interval ≥460 msec or with other factors that increase the risk of QT prolongation or arrhythmic events at screening. Note: Subjects with bundle branch block and a prolonged QTc interval, or with QTcF between 450 and 460 msec, should be reviewed by the medical

monitor for potential inclusion.

- Have cardiac history that includes conditions requiring heart rate control (eg, atrial fibrillation, atrial flutter).
- Have second or third degree atrioventricular (AV) block; AV disassociation; >5 beats of non-sustained VT at a rate >120 bpm; ECG changes consistent with acute myocardial ischemia or infarction.
- If female, are pregnant or lactating or intending to become pregnant before participating in this study, during the study, and 4 to 5 days (5 half-lives) PLUS 30 days after last dose of the study drug; or intending to donate ova during such time period.
- Are considered by the investigator to be alcoholics not in remission or known substance abusers. Have a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is half-emptying time ($T_{1/2}$) of gastric emptying of solids.

The secondary endpoints for this study are:

- Colonic geometric center at 4, 24, and 48 hours after radiolabeled meal.
- Colonic filling at 6 hours (measure of small bowel transit time) after radiolabeled meal.
- $T_{1/2}$ of ascending colon emptying.
- The plasma PK parameters (area under the concentration-time curve during a dosing interval [AUC_{τ}], maximum observed concentration [C_{max}], and observed concentration at the end of a dosing interval [C_{trough}]) of TAK-954.

The safety endpoints for this study are:

- The percentage of subjects who experience at least 1 treatment-emergent adverse event.
- The percentage of subjects who discontinue due to an adverse event (AE).
- The incidence of subjects who meet the markedly abnormal criteria for safety laboratory tests postdose.
- The incidence of subjects who meet the markedly abnormal criteria for vital sign measurements postdose.
- The percentage of subjects who meet the markedly abnormal criteria for safety 12-lead ECG parameters and Holter monitor postdose.

Statistical Considerations:

The effects of the TAK-954 treatment on the primary PD endpoint will be assessed using analysis of covariance (ANCOVA). The secondary response measures will also be assessed using ANCOVA (with suitable transformation for skewness in the distributions of measured volumes), and, if necessary, nonparametric methods will be used. The covariates considered for inclusion in the analyses will be age, gender, BMI, and the baseline measurement of the respective PD measure. Two-sided 95% CI will be presented for the comparison of each dose of TAK-954 against placebo, both multiplicity adjusted and unadjusted CIs will be presented.

Information on the global score using the GCSI, as well as bowel movement frequency per day and average stool consistency on the Bristol stool form scale, will be tabulated and analyzed respectively.

Sample Size Justification: Below summarizes data for the primary and secondary PD response measures and uses the (relative) percent coefficient of variation, (%CV) to estimate the effect size detectable with 80% power based on a 2 sample z-test (ie, assuming the variation values are known) at a two-sided alpha level of 0.05. The effect size is the difference in group means as a percentage of the overall mean for each response and assumes 12 subjects per group. The ANCOVA should provide 80% power to detect similar (pairwise) differences using a pooled estimate of variation across all 3 groups and potentially even smaller effect sizes by adjusting for important covariates. An effect size of at least 30% for the primary endpoint is considered to be clinically important. The data from the scintigraphic transit studies are unpublished but based on the same methods proposed for this study.

Assuming n=12/Group 4-GROUP DESIGN (Based on ANCOVA α=0.05)

Response Type	Mean	SD	%CV	Effect Size (%) Detectable with 80% Power (α=0.05)
Gastric emptying of solids $T_{1/2}$ min (N=319)	122	29.8	24.5	34.2
Colonic filling at 6 h, % (N=63)	44	29	66	79
Geometric center at 24 h (N=220)	2.4	0.9	36	52
Ascending colon $T_{1/2}$ h (N=50)	15.0	8.0	53	63

An interim analysis was conducted when approximately half of the subjects have completed the study. Efficacy and safety data was reviewed to determine if the study should be modified based on the interim analysis results.

An executive committee within Takeda composed of a senior clinician, a senior statistician, a senior clinical pharmacologist, and a senior pharmacovigilance scientist not involved in the study have reviewed the interim analysis results and made recommendations for changes to the study. All members of the study team and the investigative team will remain blinded to treatment arm assignment and treatment arm results until the completion of the study.

Based upon the results of the preplanned interim analysis, 1 of the TAK-954 doses was dropped. The specific dose dropped is not specified in order to maintain the blind of the study team. The sample size for the remaining treatment arms will not change.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 List of Abbreviations

5HT4	serotonin
CCI	[redacted]
^{99m}Tc	technetium-99m
^{111}In	indium chloride isotope
AC	ascending
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{24,ss}$	area under the concentration-time curve from time 0 to time 24, at steady state
AUC_{τ}	area under the concentration-time curve during a dosing interval
AV	atrioventricular
BP	blood pressure
BMI	body mass index
%CV	percent coefficient of variation
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration during a dosing interval, at steady state
C_{trough}	observed concentration at the end of a dosing interval
CYP	cytochrome P450
DC	Descending colon
eCRF	electronic case report form
ECG	electrocardiogram
EFI	enteral feeding intolerance
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCSI	Gastroparesis Cardinal Symptom Index
GGT	γ-glutamyl transferase
GI	gastrointestinal
HbA1c	glycosylated hemoglobin
hCG	human chorionic gonadotropin
HR	heart rate
ICH	International Conference on Harmonisation
ICU	intensive care unit
INR	international normalized ratio
IRB	institutional review board

IUD	intrauterine device
IV	intravenous
kcal	kilocalorie
LFT(s)	liver function test(s)
MTD	maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect-level
PD	pharmacodynamic(s)
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PPS	per protocol set
RS	rectosigmoid colon
PTE	pretreatment event
QD	once daily
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SUSARs	suspected unexpected serious adverse reactions
SVT	supraventricular tachycardia
$T_{1/2}$	half-emptying time
TC	transverse colon
ULN	upper limit of normal
VT	ventricular tachycardia

3.3 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

TAK-954 is a highly selective and potent 5-HT_4 receptor agonist that has shown prokinetic activity throughout the gastrointestinal (GI) tract in experimental models and is in development for short-term (acute) use in the treatment of critically ill patients with enteral feeding intolerance (EFI). Critically ill patients who require enteral feeding frequently have reduced GI motility including delayed gastric emptying, develop enteral feeding intolerance, which can lead to several complications including not meeting daily calorie and protein requirements [1]. 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].

Nonclinical studies completed to date include intravenous (IV) and oral single-dose studies in rats, oral single-dose studies in dogs, and oral 28-day and 13-week repeat-dose studies in rats and dogs. TAK-954 was also tested in vitro and in vivo genotoxicity studies, embryo-fetal toxicity studies in rats and rabbits, and ex vivo and in vivo local tolerance studies. Toxicokinetic analysis of TAK-954 plasma levels was conducted in the Good Laboratory Practice repeat-dose studies.

Studies of TAK-954 on central nervous system and respiration showed no effect at clinically relevant doses. In the cardiovascular safety pharmacology study in dogs, dose-dependent increases in mean heart rate (HR) and non-dose-dependent increases in diastolic blood pressure and mean arterial blood pressure were observed (61-fold margin at dog no-observed-effect level (NOEL) versus healthy human maximum observed concentration [C_{max}] at 1 mg, IV [extrapolation based on 2x0.5 mg, IV pharmacokinetics (PK); assumes linear PK between 0.5 and 1 mg dose]).

TAK-954 is a substrate of cytochrome P450 (CYP) 3A4, CYP2D6, CYP2C9/19, and P-glycoprotein. TAK-954 had no significant inhibitory effect on the activities of major human CYPs 1A2, 2C9, 2C19, 2D6, and 3A in human liver microsomes. No inhibitory effect of the metabolites, THRX-513466 and THRX-913682, were observed on the metabolic activities of CYP1A2, CYP2C19, and CYP3A, and only moderate inhibition (up to 42%) was observed on the metabolic activities of CYP2C9 and CYP2D6 at high TAK-954 concentrations of 10 μM. TAK-954 is moderately protein bound, exhibiting concentration-independent binding.

In repeat-dose toxicity studies, the key adverse findings attributed to TAK-954 administration were decreased body weight gains and food consumption at higher doses in rats, dogs, and rabbits, effects that were dose-limiting in these species. In the 13-week dog study, an approximately 10.5% increase in the QT interval with Fridericia correction method (QTcF) was noted only on Day 28 in males receiving 30 mg/kg/day (160-fold margin at dog NOEL at 10 mg/kg/day versus healthy human C_{max} at 1 mg, IV [extrapolation based on 2x0.5 mg, IV C_{max}]). Other notable effects of TAK-954 observed in the rat toxicity studies included phospholipidosis in the lung and vacuoles in scattered thyroid follicular cells of rats, and vacuolated macrophages in the spleen and an increase in the degree of mammary gland

development in female rats; these findings were all reversible but did not reach full resolution at the end of the recovery period (468-fold margin at rat no-observed-adverse-effect level [NOAEL] versus healthy human area under the concentration-time curve from 0 to 24 hours [AUC_{24}] at 1 mg, IV [extrapolation based on 2x0.5 mg, IV AUC_{24}]). TAK-954 did not exhibit genotoxic potential. The embryo-fetal toxicity studies in rats and rabbits demonstrated embryo-fetal effects characterized by lower fetal weights and increased skeletal variations (decreased ossification) limited to maternally toxic doses (250-fold margin at rabbit NOAEL versus healthy human AUC_{24} at 1 mg, IV [extrapolation based on 2x0.5 mg, IV AUC_{24}]).

TAK-954 was well-tolerated in local tolerance studies at concentrations up to 20 µg/mL and did not cause hemolysis or flocculation in rat, dog, or human whole blood.

TAK-954 has been evaluated in 4 clinical studies to date: 3 phase 1 studies in healthy subjects, and an exploratory phase 2 study in critically ill patients with enteral feeding intolerance (EFI).

After single ascending oral doses (0.1 to 20 mg) of TAK-954 in healthy subjects, the maximum tolerated dose (MTD) dose was 10 mg and resulted in a C_{max} of 94.4 ng/mL and area under the concentration time-curve from time 0 to infinity of 1017 ng•hr/mL. After multiple ascending oral doses (0.2 to 10 mg) once daily (QD) of TAK-954 in healthy subjects, the MTD dose was 5 mg and resulted in a maximum observed concentration during a dosing interval, at steady state ($C_{max,ss}$) of 27.72 ng/mL and area under the concentration-time curve from 0 to 24 hours at steady state ($AUC_{24,ss}$) of 386.515 ng•hr/mL. C_{max} and the area under the concentration-time curve (AUC) increased in a roughly dose-proportional manner. TAK-954 was not extensively converted to either metabolite (THRX-513466 or THRX-913682), as assessed by circulating levels in plasma and urine.

After multiple daily IV infusion dosing in healthy subjects, mean TAK-954 $C_{max,ss}$ was 7.07 and 7.6 ng/mL in Cohorts 1 (0.5 mg QD over 5 days) and 2 (0.1 mg on Day 1 and 0.5 mg QD Days 2 to 5), respectively. Mean TAK-954 $AUC_{24,ss}$ was 51.0 and 63.3 ng.h/mL in Cohorts 1 and 2, respectively. TAK-954 steady state was achieved by Day 3, with mean half-life ($t_{1/2}$) values ranging from 18.0 to 18.9 hours on Day 5. The increase in Day 1 exposure from the 0.1 to 0.5 mg IV dose was approximately dose proportional. Based on the principle of superposition, the predicted $C_{max,ss}$ and $AUC_{24,ss}$ for TAK-954 1 mg IV dosing were 15.2 ng/mL and 126.6 ng.h/mL, respectively, which are approximately 2 to 3-fold lower comparing to multiple oral doses of 5 mg. 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 approximately 30% lower to that observed in healthy subjects.

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 serious adverse events (SAEs) and the overall incidence of adverse events (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 HR remained in the normal range for all groups throughout the study. 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 1 AE related to BP (orthostatic hypotension in a subject who received 5 mg TAK-954).

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 suggested TAK-954 decreases gastric emptying time following a liquid meal.

The purpose of this dose-ranging, randomized, parallel group, double-blind, placebo-controlled study is to evaluate the pharmacodynamic (PD) effects of TAK-954 on gastric, intestinal, and colonic transit in diabetic subjects reporting symptoms of gastroparesis with previously documented delay in stomach emptying, or in subjects with a diagnosis of idiopathic gastroparesis.

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

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

4.2 Rationale for the Proposed Study

Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, pain, and bloating. Gastroparesis occurs in several clinical settings, particularly as a complication of diabetes mellitus, but also as a complication of upper GI surgery, neurological disease, collagen vascular disorders, viral infections, drugs, and so on. In the majority of cases, no underlying cause is found and gastroparesis is termed idiopathic. Several abnormalities in diabetes might result in gastric motor dysfunction including autonomic neuropathy, enteric neuropathy involving excitatory and inhibitory nerves, abnormalities of the interstitial cells of Cajal and acute fluctuations in blood glucose among others [4].

The underlying mechanism of delayed gastric emptying is common to both patients with gastroparesis and EFI, and the same products have been successfully studied and utilized in both populations to promote gastric emptying. This study will evaluate the prokinetic effect of TAK-954 on gastric emptying, intestinal and colonic transit in subjects with previously documented delay in gastric emptying.

Phase 1 studies have demonstrated acceptable PK characteristics and TAK-954 was well tolerated at all doses studied in the completed phase 1 and 2a studies. The TAK-954 IV doses to be used in the study, 0.1, 0.3 and 1 mg, were selected based on safety, tolerability, PK, and PD

(bowel movement, gastric emptying time, and HR) data from the healthy and critically ill subject studies. Based on a TAK-954 preliminary population-PK model using data from Phase 1 studies and in-vitro receptor saturation data, predicted subjects' trough 5-HT_4 receptor occupancy at steady state is estimated to be approximately 30%, 50% and 80% for 0.1, 0.3 and 1 mg doses, respectively. The dose range, 0.1, 0.3 and 1 mg, is expected to span the anticipated pharmacologically active dose range and is potentially considered well within the safety margin.

CCI

[redacted]

4.3 Benefit/Risk Profile

There is no expected clinical benefit to the study participants. Potential risks are based on TAK-954 clinical findings, the mechanism of action, nonclinical findings and the route of administration. The study involves the use of radiation that is within limits permissible for healthy volunteers and hence patients.

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

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to evaluate the dose-dependent effects of TAK-954 on gastric emptying time of solids in subjects with diabetic or idiopathic gastroparesis assessed by scintigraphy.

5.1.2 Secondary Objectives

The secondary objectives of this study are to:

Evaluate the PD effects of TAK-954 on intestinal and colonic transit time assessed by scintigraphy.

Evaluate PK of TAK-954 in subjects with gastroparesis.

Assess the safety and tolerability of multiple doses of TAK-954.

5.1.3 Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint for this study is half-emptying time ($T_{1/2}$) of gastric emptying of solids.

5.2.2 Secondary Endpoints

The secondary endpoints for this study are:

Colonic geometric center at 4, 24, and 48 hours after the radiolabeled meal.

Colonic filling at 6 hours (measure of small bowel transit time) after the radiolabeled meal.

$T_{1/2}$ of ascending colon emptying.

The following PK parameters of TAK-954:

- Area under the concentration-time curve during a dosing interval (AUC_{τ}), C_{max}, and observed concentration at the end of a dosing interval (C_{trough}).

5.2.3 Safety Endpoints

The safety endpoints for this study are:

- The percentage of subjects who experience at least 1 treatment-emergent adverse event.
- The percentage of subjects who discontinue due to an AE.

The incidence of subjects who meet the markedly abnormal criteria for safety laboratory tests postdose.

The incidence of subjects who meet the markedly abnormal criteria for vital sign measurements postdose.

The percentage of subjects who meet the markedly abnormal criteria for safety 12-lead ECG parameters and Holter monitor postdose.

5.2.4 Exploratory Endpoints

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2a dose-ranging, randomized, parallel group, double-blind, placebo-controlled study evaluating the effects of TAK-954 on gastric, small bowel, and colonic transit in diabetic subjects reporting symptoms of gastroparesis with previously documented delay in stomach emptying or in subjects with diagnosis of idiopathic gastroparesis. Twelve subjects per treatment group in diabetic subjects with symptoms of gastroparesis and previously documented delay in stomach emptying or in subjects with diagnosis of idiopathic gastroparesis will be evaluated.

This study consists of 3 periods and a Follow-up: a Screening Period, Baseline Period (between Day -14 and Day -1), Treatment Period (Days 1 to 4), and a Follow-up Phone Call (Days10 - 14). Women of childbearing potential will receive an additional Follow-up Phone Call (Days 38-43).

Subjects will have an initial Screening Visit, then will undergo a baseline gastric emptying assessment with scintigraphy scans acquired at 0, 1, 2, 3, and 4 hours after radiolabeled meal, between Day -14 and Day -1 (Baseline Visit). The Screening and Baseline Visits may be performed on the same day. Within 48 hours prior to baseline scintigraphy, female subjects must have a negative pregnancy test.

CCI

If eligibility criteria are fulfilled, subjects will be randomized on Day 1 to TAK-954 0.1, 0.3, or 1 mg, or placebo. Subjects will receive TAK-954 or placebo as a 60-minute intravenous (IV) infusion (at any time in the morning prior to 12:00) once a day (QD) for 3 days starting on Day 1. Following the TAK-954 infusion on Day 2, subjects will undergo scintigraphic assessment of gastric, small bowel, and colonic transit of solids during the Treatment Period.

At each visit, the fasting state of the subjects (8 hours) will be confirmed and fasting (finger stick) blood glucose obtained.

During the study, subjects will complete a daily diary to record their bowel habits. The subjects will assess their global GI symptom score using the GCSI at Screening. The On-Study Bowel Habit Diary Card will be dispensed at Screening to be completed daily from Screening and through the Treatment Period. The completed Bowel Habit Diary Card will be collected at the conclusion of the study.

The subjects will have PK samples collected as described in Section 9.1.14.1.

All participating subjects will have a 6-hour Holter monitor placed at the Baseline Visit. On Day 1, subjects will have continuous ECG monitoring for up to 4 hours after the infusion, and continuous monitoring with a Holter monitor which will be placed prior to the first dose on Day 1 until the morning of Day 3.

Participants will undergo follow-up safety monitoring by phone 7-10 days post last treatment dose. The study will be considered completed after the last subject's Follow-up Phone Call.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design

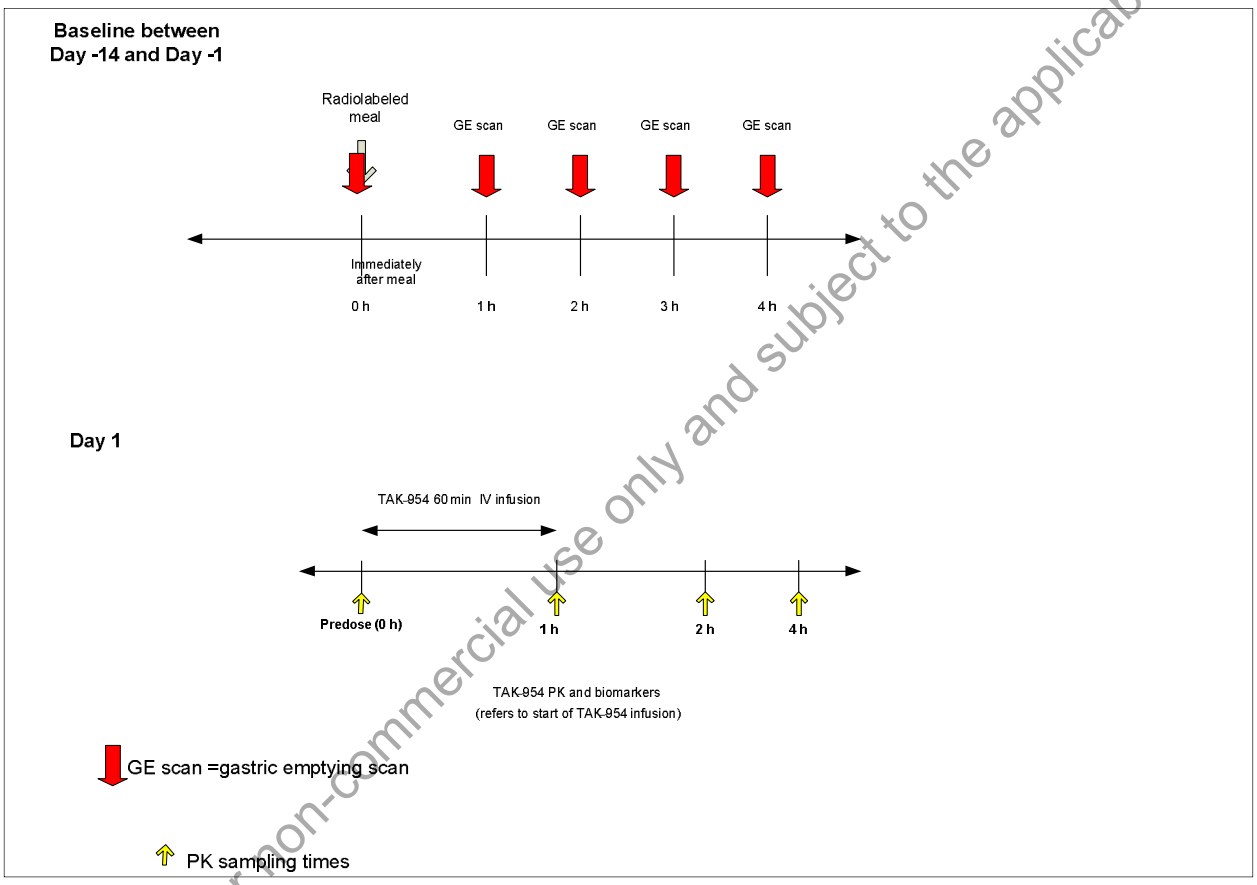


Figure 6.a Schematic of Study Design (continued)

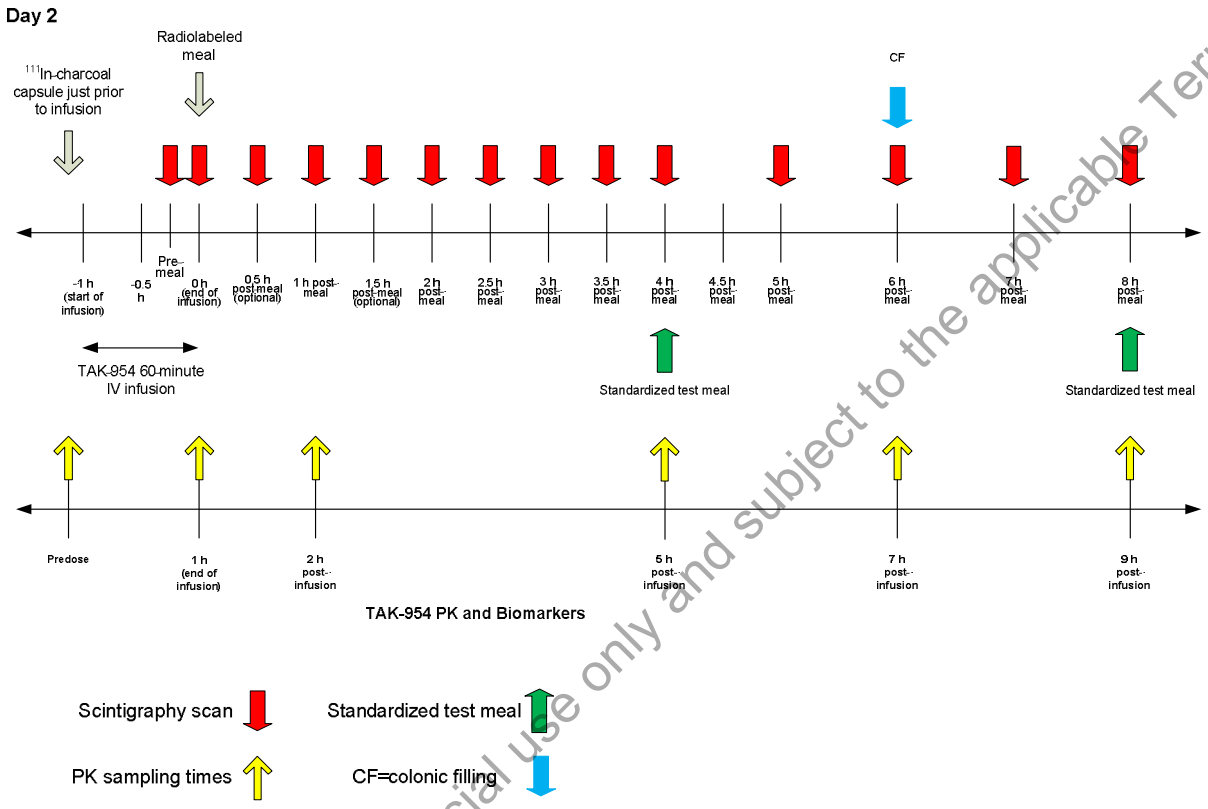
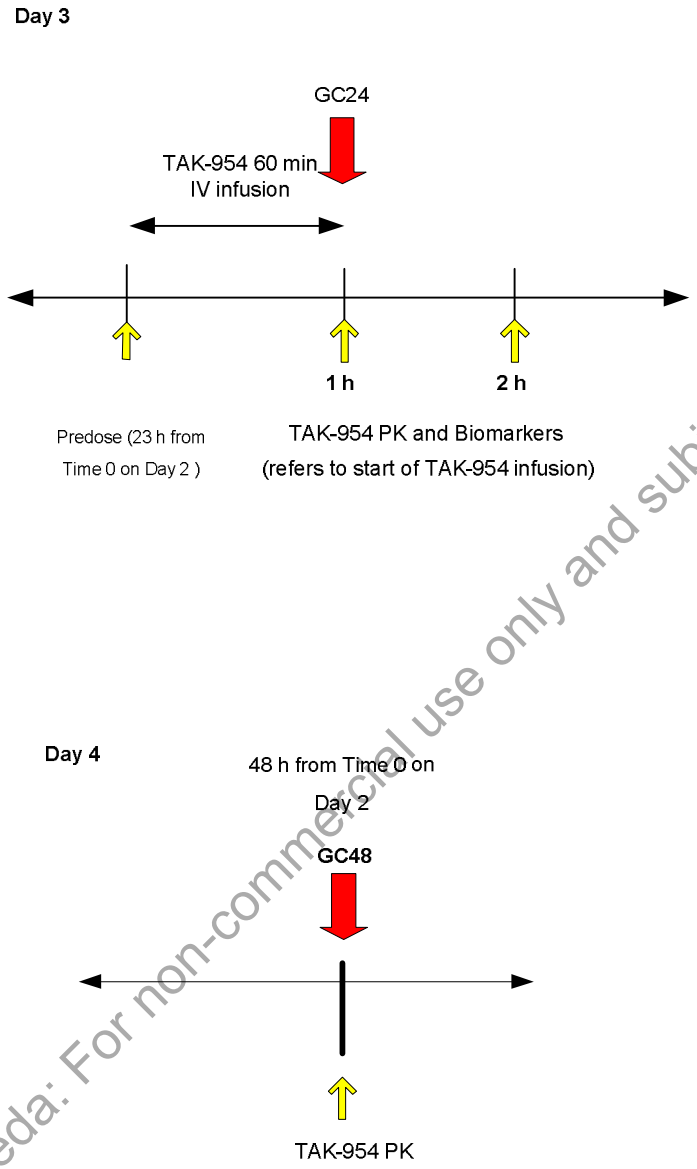


Figure 6.a Schematic of Study Design (continued)



GC=geometric center

6.2 Justification for Study Design, Dose, and Endpoints

The TAK-954 IV doses to be used in the study, 0.1, 0.3 and 1 mg, were selected based on safety, tolerability, PK and PD (bowel movement, gastric emptying time, HR) data from the healthy and critically ill subject studies. Based on unbound TAK-954 plasma concentrations using a preliminary population-PK model and in-vitro receptor saturation, predicted subjects' trough 5-HT_4 receptor occupancy at steady state are estimated to be approximately 30%, 50% and 80% for 0.1, 0.3 and 1 mg doses, respectively. The dose range, 0.1, 0.3 and 1 mg, is expected to span the anticipated pharmacologically active dose range and is considered well within the safety margin.

Measurement of gastric emptying of solids as measured by $T_{1/2}$ is endorsed by national societies [9] for use in clinical practice to identify gastric motor function abnormalities as in conditions associated with slow or accelerated gastric emptying, to investigate pathophysiological mechanisms that may be associated with patients' symptoms or syndromes, and to evaluate the effects of treatment such as prokinetic agents [4]. Therefore scintigraphy assessment of gastric emptying is the most appropriate tool to evaluate the pharmacodynamic properties of TAK-954 in upper GI motility and to assess its potential in both gastroparesis and enteral feeding intolerance.[4]

The study's secondary endpoints include colonic geometric center at 4, 24, and 48 as a measure of colonic transit time and colonic filling at 6 hours as an indirect measure of intestinal transit time that will help to obtain a complete picture of the prokinetic effect of TAK-954 by assessing its effects on the lower GI tract. This assessment is relevant not only because it can help to evaluate TAK-954's potential application in other conditions associated with delayed intestinal motility such as postoperative ileus, intestinal pseudo obstruction or constipation; but also because it can help to determine the right dose for use in future trials in critically ill patients at high risk of malnutrition and EFI as accelerated bowel and colonic transit time can increase the risk of diarrhea and malabsorption.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-954, such that the risk is no longer acceptable for subjects participating in the study.

Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study 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 study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has diabetes mellitus with symptoms of gastroparesis and previously documented gastric emptying delay or previously documented idiopathic gastroparesis in the last 5 years.
4. The subject is a male or nonpregnant, nonbreastfeeding female and aged 18 to 65 years, inclusive.
5. The subject has a body mass index (BMI) ≥16 and ≤40 kg/m^2 at the Screening Visit.
6. A female subject of childbearing potential* must agree to use highly effective contraception during the course of the study.

> *Definitions and highly effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has participated in another interventional clinical study within the past 30 days.
2. The subject is an immediate family member, investigational team member, or is in a dependent relationship with an investigational team member who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
3. The subject has HbA1c >12%.
4. The subject has other structural diseases/conditions that affect the GI system.
5. The subject has a history of hypersensitivity or allergies to TAK-954.
6. The subject is unable to withdraw any of the following medications listed in Table 7.a 48 hours prior to the study.
7. The subject has a clinically significant abnormal baseline safety laboratory value.
8. The subject has preexisting hepatic disease that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points), see Appendix E.

9. Subjects without known preexisting hepatic disease who have 1 or more of the following:
    - AST or ALT >2 times the ULN.
    - Bilirubin >1.5 times the ULN unless due to Gilbert's syndrome.
    - International normalized ratio (INR) >1.5 unless on anticoagulation therapy.
10. The subject has QTcF interval ≥460 msec or with other factors that increase the risk of QT prolongation or arrhythmic events at screening. Note: Subjects with bundle branch block and a prolonged QTc interval, or with QTcF between 450 and 460 msec, should be reviewed by the medical monitor for potential inclusion.
11. Subjects who have second or third degree atrioventricular (AV) block; AV disassociation; >5 beats of non-sustained VT at a rate >120 bpm; ECG changes consistent with acute myocardial ischemia or infarction.
12. The subject has a cardiac history that includes conditions requiring HR control (eg, atrial fibrillation, atrial flutter, ventricular tachycardia, or other tachyarrhythmias).
13. The subject has clinical evidence (including physical examination, ECG, clinical laboratory value and review of the medical history) of significant cardiovascular, respiratory, moderate or severe renal insufficiency (creatinine clearance ≤60 mL/min), hematological, neurological, psychiatric, or other disease that interferes with the objectives of the study.
14. If female, are pregnant or lactating or intending to become pregnant before participating in this study, during the study, and within 4 to 5 days (5 half-lives) PLUS 30 days after last dose of the study drug; or intending to donate ova during such time period.
15. If male, the subject intends to donate sperm during the course of this study or for 4 to 5 days (5 half-lives) PLUS 30 days thereafter.
16. The subject is considered by the investigator to be an alcoholic not in remission or known substance abuser; have a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
17. A subject, who in the determination of the investigator, possesses any condition that the investigator believes would put the subject at risk or would preclude the subject from successfully completing all aspects of the study.

7.3 Excluded Medications

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator. Use of excluded agents (prescription or nonprescription) is outline in Table 7.a.

Table 7.a Excluded Medications

Medication	
Drugs known to alter GI transit including laxatives, magnesium or aluminum-containing antacids, prokinetics, erythromycin, narcotics, anticholinergics, tricyclic antidepressants.	Monoamine oxidase inhibitors.
Selective serotonin reuptake inhibitors: escitalopram, citalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, and newer antidepressants.	Serotonin and norepinephrine reuptake inhibitors: venlafaxine, duloxetine, desvenlafaxine, milnacipran, levomilnacipran.
Analgesic drugs including opiates, nonsteroidal antiinflamatories, cyclooxygenase-2 inhibitors.	Benzodiazepines.
Antidiabetes treatment with pramlintide or glucagon-like peptide-1 receptor agonists.	N-methyl-D-aspartate receptor antagonist. phencyclidine, ketamine, tiletamine, methoxetamine, dextromethorphan, pethidine, levorphanol, methadone, dextropropoxyphene, tramadol, ketobemidone.
Gamma-aminobutyric acidergic (GABAergic) agents: bicuculline, securinine, metrazol, flumazenil.	5-HT agonist.

Note: Low stable doses of thyroid replacement, estrogen replacement, aspirin for cardioprotection, and birth control pills or depot injections; metformin, dipeptidyl peptidase-IV inhibitors, and insulin for diabetes are permissible.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form eCRF using the following categories. For screen failure subjects, refer to Section 9.1.15.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or 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 PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study 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 9.1.8), if the following circumstances occur at any time during study drug treatment:

   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × 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 INR >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 (postrandomization) 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 after 3 attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the 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 due to an AE should not be recorded in the "voluntary withdrawal" category.
6. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. 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. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 TAK-954

The drug product, TAK-954 Injection (Concentrate for Solution for Infusion), consists of a clear colorless solution of TAK-954 free base in clear Type I glass vials fitted with a rubber stopper and sealed with an aluminum cap. The drug product is formulated as 0.1 mg/mL of TAK-954 free base equivalent dissolved in water for injection, adjusted to pH 5.0 with hydrochloric acid and/or sodium hydroxide. Each glass vial contains 5.5 mL of sterile TAK-954 solution designed to deliver nominally 5.0 mL of the solution. The drug product solution is intended to be diluted to the required concentration with a diluent for IV infusion. The placebo IV infusion solution is the diluent only and prepared in the same manner as the active. Please see the pharmacy manual for preparation and administration instructions.

TAK-954 cartons and vials will be affixed with clinical labels that are in accordance with all regulatory requirements.

8.1.1.2 Ancillary Materials

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.

8.1.2 Storage

The required storage condition for TAK-954 study drug is refrigeration between 2°C and 8°C.

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The subjects will be randomized to TAK-954 0.1, 0.3, or 1 mg; or placebo and will receive TAK-954 or placebo as a 60-minutes infusion IV once a day for 3 days starting on Day 1. The number of active treatment arms decreased based upon the prespecified interim analysis. To maintain the blinding of the study team, the specific treatment arm is not identified. This change was not necessitated by safety findings.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

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. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive their treatment according to the randomization schedule allocated to the study site.

8.3 Randomization Code Creation and Storage

Randomization personnel or the designee of the sponsor will generate the randomization table/schedule and will provide it to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The study drug blind is maintained through a randomization schedule held by authorized persons only.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed locally.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee or destroyed locally.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received, dispensed and remaining at the conclusion of the study. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for clinical study drug accountability, return and/or destruction.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, ethnicity, race as described by the subject, height, weight, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 48 hours prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system looking for hyperreflexia, hypertonicity and clonus; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then BMI=79.2/1.76^2=25.56818 kg/m^2

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2. However, if the BMI is used as entry criteria based on 40 kg/m^2 cut-off point, then this determination must be made after rounding.

9.1.5 Vital Sign Procedure

Vital signs will include sitting/supine blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute).

When vital signs are scheduled at the same time as PK blood draws, the PK blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC WBC with differentials Hemoglobin Hematocrit Platelets	ALT AST Albumin Alkaline phosphatase Total bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase γ-glutamyl transferase (GGT) Potassium Sodium Glucose HbA1c (a) TSH (a)	pH Specific gravity Protein Glucose Blood Nitrite Microscopic analysis (RBC/high power field, WBC/high power field, epithelial cells, casts, etc.) to be performed if abnormal.

Other:

Serum	Urine	Coagulation
Hepatitis panel, including HBsAg and anti-HCV Female subjects only: Beta human chorionic gonadotropin ([hCG] for pregnancy) **Follicle-stimulating hormone (FSH)** If menopause is suspected.	Beta hCG (female subjects only)	INR

HbsAg=hepatitis B virus surface antigen, HCV=hepatitis C virus, RBC=red blood cell, WBC=white blood cell.
(a) HbA1c and TSH to be collected at Screening only.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 3 days and preferably within 48-72 hours after the abnormality was noted. (Refer to Section 7.4 and Section 10.2.3 for the appropriate guidance on reporting abnormal LFTs.)

If ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3).

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 4 to 5 days (5 half-lives) PLUS 30 days after last dose of study 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. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below.

9.1.9.2 Female Subjects and Their Male Partners

Animal studies for TAK-954 have demonstrated embryotoxicity and there is a lack of adequate reproductive toxicity data in humans; therefore, female subjects should be instructed to use highly effective methods of contraception.

From signing of informed consent, throughout the duration of the study, and for 4 to 5 days (5 half-lives) PLUS 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list below).

Methods:

Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation.

- Oral.
- Intravaginal.
- Transdermal.

Progestogen-only hormonal contraception associated with inhibition of ovulation.

- Oral.
- Injectable.
- Implantable.

IUD.

Bilateral tubal occlusion.

In addition, they must be advised not to donate ova during this period.

9.1.9.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

*A woman is considered a woman of childbearing potential (fertile) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those < 45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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

The following procedures apply for contraception and pregnancy avoidance.

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 study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

   Nonhormonal Methods:

   – IUD.

   – Bilateral tubal occlusion.

   Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound and concomitant medications, which may reduce the efficacy of the contraception method (Evaluate on compound-by-compound and protocol-by-protocol basis and obtain clinical pharmacology justification).

   – Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
     - Oral.
     - Intravaginal (eg, ring).
     - Transdermal.

   – Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug in combination with a barrier method (male condom, female condom, or diaphragm);
     - Oral.

- Injectable.
- Implantable.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly 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, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular serum/urine hCG pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c) Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes").
      iv. Is there a chance you could be pregnant?
5. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses); a negative serum hCG pregnancy test prior to the first dose of study medication (Day 1; if a negative serum hCG pregnancy test was obtained on Day -1, then the serum pregnancy test on Day 1 can be discontinued); and a negative urine pregnancy test within 48 hours prior to consuming a radiolabeled meal. A serum hCG test may substitute for a urine pregnancy test as long as the timing of the test as required is appropriately maintained.

9.1.9.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

Contraceptive requirements of the study.

Reasons for use of barrier methods (ie, condom) in males with partners of childbearing potential.

Assessment of subject compliance through questions such as:

- Have you used the contraception consistently and correctly since the last visit?
- Have you forgotten to use contraception since the last visit?
- Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")?
- Is there a chance you could be pregnant?

9.1.10 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and TAK-954 should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 4 to 5 days (5 half-lives) PLUS 30 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, from Day 1 up to 4 to 5 days (5 half-lives) PLUS 30 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. 12-lead ECG will be

performed on Days 1, 2, and 3 prior to each IV infusion; within 30 minutes postinfusion and prior to discharge; and at the Final Visit on Day 4 or Early Termination Visit. In addition, a 12-lead ECG will be performed when needed, if a subject develops symptoms or clinical signs suggestive of cardiovascular origin (eg, dizziness, lightheadedness, chest pain, chest heaviness, palpitations, shortness of breath, tachycardia).

The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QT and QTcF.

All participating subjects will have a 6-hour Holter monitor placed at the Baseline Visit. On Day 1, subjects will have continuous monitoring with a Holter monitor which will be placed prior to the first dose until the morning of Day 3. Interpretation of the Holter monitor recording will be performed by a Mayo cardiologist.

9.1.12 Scintigraphy Procedure

An adaptation of the Mayo Clinic's established scintigraphic method will be used to measure GI transit. A radiolabeled meal of ^{99m}Tc (technetium-99m)-sulfur colloid added to 2 scrambled eggs will then be eaten with 1 slice of whole wheat bread and 1 glass of skim milk. This meal facilitates measurement of gastric and small bowel transit. ^{111}In (indium chloride isotope)-absorbed on activated charcoal particles will be delivered to the colon by means of a methacrylate-coated, delayed-release capsule.

At the Baseline Visit (between Days -14 and -1), subjects will ingest the radiolabeled standardized test meal followed by scans after ingestion at 0, 1, 2, 3 and 4 hour timepoints.

On Day 2, subjects will ingest the radiolabeled (^{111}In) charcoal capsule just prior to the 60-minute infusion of TAK-954. The radiolabeled breakfast for scintigraphic study will be given at the end of the TAK-954 infusion. Relative to the time of completion of the breakfast meal ingestion, abdominal images are obtained pre-meal, immediately following the radiolabeled meal, and every 30 minutes following the meal for the first 4 hours and then hourly until 8 hours (5 and 9 hours post start of infusion on Day 2), then at 24 and 48 hour timepoints post breakfast meal on Day 2 (1 hour and 25 hours post start of infusion on Day 3). Following the first day of study drug administration on Day 1, subjects will return the next 2 days (Days 2 and 3) for IV administration of study medication. On Days 3 and 4, subjects will return in the morning for the 24- and 48-hour abdominal images, respectively. The performance characteristics of this test are summarized in Scintigraphy: Gastric Emptying, Small Bowel, and Colonic Transit SOPs by Enteric Physiology and Imaging Facility.

All subjects on treatment will consume the same test meal as above followed by standardized test meals at lunch and afternoon snack at 4 and 8 hours after the radio labeled meal, respectively.

Prior to the 4-hour scan on Day 2, a standard meal (chicken, potato, pudding "Stanghellini" meal), 550 kilocalorie (kcal) will be ingested. Hourly images will be taken until 8 hours post-radiolabeled meal, when the second standard roast beef sandwich "Greydanus" 750 kcal

snack is ingested 15 minutes prior to the scheduled 8-hour scan. The subject will leave the study center at the end of the afternoon. They will be asked to return the following days fasting (Days 3 and 4), for IV administration of study medication (Day 3 only) and the image at 24 (Day 3) and 48 hours (Day 4) after the ingestion of radiolabeled meal on Day 2.

All efforts will be made to obtain the scintigraphy scans at the exact nominal time relative to dosing. However, samples obtained within 10 to 15 minutes of the nominal time from dosing will not be captured as a protocol deviation, as long as the exact time of dosing and time of scan is noted on eCRF.

9.1.13 Pharmacogenomic and Biomarker Sample Collection

CCI

[redacted]

9.1.13.1 Biomarker Sample Collection

CCI

[redacted]

CCI

9.1.14 PK Sample Collection and Analysis

9.1.14.1 Collection of Plasma for PK Sampling

The subjects will have PK samples collected as follows:

Days 1: prior to dosing (0 hour), 1 (end of infusion), 2, and 4 hours after start of infusion.

Day 2: prior to dosing (0 hour), 1 (end of infusion), 2, 5, 7, and 9 hours after the start of the infusion.

Day 3: prior to dosing (0 hour), 1 (end of infusion), and 2 hours after start of infusion.

Day 4: 25 hours after the start of infusion on Day 3 (48 hours after the administration of the radiolabeled meal and capsule on Day 2, same time as the 48-hour geometric center measurement).

PK samples collected during the infusion will be drawn from the opposite arm from where the infusion is delivered. All efforts will be made to obtain the PK and PD 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 dosing (start and ending of infusion) and the sampling collection is noted on eCRF.

Primary specimen collection parameters are provided in Table 9.b.

Table 9.b Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Plasma sample for TAK-954 PK	Plasma	Pharmacokinetic measurements	Mandatory
CCI			
CCI			
CCI			

If indicated, these collected samples may also be assayed for metabolites and/or additional PD markers.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the Screening Visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

PTE/AE.

Did not meet inclusion criteria or did meet exclusion criteria. <specify reason>

Significant protocol deviation.

Lost to follow-up.

Voluntary withdrawal (specify reason).

Study termination.

Other study-specific.

Other (specify reason).

Subject identification numbers assigned to subjects who fail screening should not be reused.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

On Day 1, if they fulfill eligibility criteria, the subjects will be randomized to TAK-954 (0.1, 0.3, or 1 mg) or placebo.

9.1.17 Blood Volume

The maximum volume of blood at any single day is approximately 50 mL, and the approximate total volume of blood for the study is 250 mL.

Direct venipuncture is the preferred method of blood collection.

9.2 Monitoring Subject Treatment Compliance

All supplies used to administer study drug to the subject will be recorded on the eCRFs.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.4 Biological Sample Retention and Destruction

In this study, blood, and blood derived samples for biomarker measurement will be collected as described in Section 6.1. Any leftover biomarker samples if not utilized will be preserved and retained at sponsor selected for long term storage facility for up to 15 years from the end of study. After that time, the samples will be destroyed.

The pharmacogenomic (PGx) samples will be initially stored at a vendor/comparable lab, under contract to Takeda, with validated procedures in place, and then preserved and retained at a sponsor-selected long-term storage facility, for up to but not longer than 15 years, from the end of the study when the study report is signed, or if less, the maximum period permitted under applicable law or until consent is withdrawn.

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

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

Subjects who consented and provided a PGx sample for DNA 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.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)

Necessitate therapeutic intervention.

Require an invasive diagnostic procedure.

Require discontinuation or a change in dose of study drug or a concomitant medication.

Be considered unfavorable by the investigator for any reason.

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs 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 a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

Changes in laboratory values or ECG findings are only considered to be PTEs or 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 or ECG retest and/or continued monitoring of an abnormal value or finding is 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 a PTE or as an AE.

Pre-existing conditions:

Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. I Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").

If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").

If the subject experiences a worsening or complication of an AE after any change in study drug, 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 intensity of AEs /serious PTEs:

If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the

condition should be recorded as a PTE or 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 PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Management of Specific AEs

10.1.5.1 Cardiovascular Disorders

Cardiovascular events:

Tegaserod, a nonselective 5-HT_4 agonist, was withdrawn from the market in 2007 based on pooled clinical trial results that suggested increased risk of cardiovascular ischemic events. Alternatively, TAK-954, highly selective 5-HT_4 agonist, did not demonstrate significant AEs related to cardiovascular events in studies to date. In TAK-954 clinical studies, 1 subject received TAK-954 0.5 mg IV in the intensive care unit (ICU) following an emergency evacuation of a spontaneous posterior fossa intraparenchymal hemorrhage. This patient died due to her underlying admitting diagnosis.

The medical monitor should be contacted within 24 hours if a subject develops cardiovascular events that include ischemic heart disease, cerebrovascular accident (eg, transient ischemic attack and stroke), venous or arterial thromboembolic events, and heart failure.

QT Prolongation

Cisapride, a nonselective 5-HT_4 agonist and a potent human ether-à-go-go–related gene blocker, was withdrawn from the market due to the risk of prolonged QT interval and sudden death.

In TAK-954 clinical studies, only 1 subject in Study 0082 had QTcF over 450 msec. This subject received TAK-954 0.5 mg IV was in the ICU following an emergency evacuation of a spontaneous posterior fossa intraparenchymal hemorrhage. She had medical history of atrial

fibrillation on warfarin, mitral valve replacement, and biventricular pacemaker, and on Screening, her QTcF was 461 msec. She had a maximum QTcF of 496 msec on Day 1 and she was not treated for this finding.

If a subject develops QT prolongation (QTcF) longer than 480 msec, study drug should be discontinued, levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range, and concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects. In addition, the medical monitor should be contacted within 24 hours. Heart-rate corrected QT interval will be calculated using Fredericia's formula ($QTcF=QT/RR^{1/3}$).

AV Dissociation/Heart Block

In Study 0061, 2 subjects receiving TAK-954 10 mg orally developed intermittent mild AEs of AV dissociation. The finding resolved without treatment.

If subjects develop new onset first degree heart block, medical monitor will need to be contacted to discuss within 24 hours. Treatment with study drug should be discontinued with the occurrence of any second or third degree heart block and the medical monitor should be contacted within 24 hours.

Treatments with study drug may be continued in second degree heart block Mobitz I (Wenckebach) after medical monitor review.

Supraventricular Tachycardia (SVT)

In Study 0061, there was a trend toward lower blood pressure and elevated HR in the standing position for TAK-954 subjects, but no dose response was apparent. One subject (Study 0095, TAK-954 0.5 mg dose) had the AE of postural tachycardia reported on Day 1, with HR values in the standing position ranging from 100 to 116 bpm from 1 to 4 hours postdose. No other subject had HR values that were reported as AEs.

Treatment should be discontinued if a subject develops SVT at rest irrespective of the seriousness and the medical monitor should be contacted within 24 hours.

Hypotension

Asymptomatic increases in both supine and standing HR were observed at all doses of TAK-954, and mean changes in supine and standing blood pressure were variable with no discernible pattern across the dose ranges. The dose escalation in the single ascending dose study was stopped at 20 mg, according to the protocol-specified stopping rules, because of the occurrence of 2 AEs of moderate orthostatic hypotension.

If subjects develop significant hypotension, treatment with study drug should be permanently discontinued.

10.1.5.2 Serotonin Syndrome

Serotonin syndrome, a potentially life threatening adverse drug reaction, may result from drugs that increase the serotonergic activity in the central nervous system. The most commonly implicated classes of drugs are selective serotonin reuptake inhibitors. The clinical features may include agitation, confusion, diarrhea, hyperthermia, tachycardia, hypertension, mydriasis, hypertonicity, and hyperreflexia.

If a subject develops any of the following clinical features (Hunter's criteria):

- Spontaneous clonus.
- Inducible clonus PLUS agitation or diaphoresis.
- Ocular clonus PLUS agitation or diaphoresis.
- Tremor PLUS hyperreflexia.
- Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus.

Discontinue treatment with study drug. In addition, review the subject medications and discontinue any medication(s) that may be associated with serotonin syndrome. Suspected serotonin syndrome should be reported to the sponsor as an SAE with 24 hours.

Should any of these events occur in a subject, study drug should be discontinued.

10.1.5.3 AESI

An AE of Special Interest (serious or nonserious) is 1 of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. If there are any significant cardiovascular events, please contact the medical monitor to discuss management of these events.

10.1.6 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

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.

10.1.7 Causality of AEs

The relationship of each AE to study drug(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 cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications 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 medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Drug

Drug withdrawn – a study drug is stopped due to the particular AE.

Dose not changed – the particular AE did not require stopping a study drug.

Unknown – only to be used if it has not been possible to determine what action has been taken.

Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.

Dose reduced – the dose was reduced due to the particular AE.

Dose increased – the dose was increased due to the particular AE.

Dose interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

Recovered/resolved – Subject returned to first assessment status with respect to the AE/PTE.

Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE 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 study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".

Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.

Fatal – the AEs/PTEs which are considered as the cause of death.

Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Day 1) or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug Day 1). Routine collection of AEs will continue until the Follow-up Visit.

10.2.1.2 PTE and AE Reporting

At each study 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 study. Subjects experiencing a serious PTE 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. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug 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 PTEs and AEs will be documented in the PTE/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:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.1.3 AEs of Special Interest

AEs of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

An AE of special interest (serious or non-serious) is 1 of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

10.2.2 Collection and Reporting of SAEs

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

The investigator should submit the original copy of the SAE form to the sponsor.

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

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 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 10.2.2. 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 or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information 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.

10.3.1 Safety Reporting to Investigators, IRBs, 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, including investigators and IRBs. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report 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 a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 CRFs (Electronic and Paper)

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

The sponsor or its designee will supply study 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 study 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 to eCRFs 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 e-sign 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 study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study 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.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-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, International Conference on Harmonisation E6 Section 4.9.5 requires the investigator to retain essential documents specified in International Conference on Harmonisation (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 study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

Full Analysis Set: The full analysis set (FAS) will include all subjects randomized. Subjects in this set will be analyzed according to the original randomization. This will be the main analysis set for efficacy analyses.

Per Protocol Set: The per protocol set (PPS) analysis set is a subset of the FAS. The PPS consists of all subjects who do not violate the terms of the protocol in a way that would significantly impact the efficacy assessment. All decisions to exclude subjects from the PPS dataset will be made prior to the unblinding of the study and subject to clinical review. This analysis set will be for efficacy analyses only and can be considered as a sensitivity analysis in support of the primary analysis based on the FAS.

Safety Set: The safety set (SAF) will include all subjects who have received at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment they actually received. This analysis set will be used for safety analyses only.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by each treatment group and overall. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age and weight) 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 characteristics data will be listed.

13.1.3 Pharmacokinetic Analysis

PK parameters will be determined from the concentration-time data for all evaluable subjects using non-compartmental analysis. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times for plasma PK parameters.

For TAK-954, the following PK parameters including, but not limited to, will be calculated as appropriate:

Day 1: AUC_{τ}, C_{max}.

Day 2: AUC_{τ}, C_{max}, C_{trough}.

Day 3: AUC_{τ}, C_{max}, C_{trough}.

Additional PK parameters may be calculated as appropriate. More detailed information will be given in the clinical pharmacology analysis plan.

13.1.4 PD Analysis

The PD effect of TAK-954 will be assessed using a number of scintigraphic parameters.

Primary PD endpoint

The primary PD endpoint will be the $T_{1/2}$ of gastric emptying of solids. Geometric mean of counts in anterior and posterior gastric regions of interest will be used to estimate by power exponential analysis, the proportionate emptying over time of counts from ^{99m}Tc solids and ^{111}In from the stomach. Gastric emptying from the power exponential analysis for the post injection period will be calculated and compared for the different treatments. The primary endpoint will be analyzed using analysis of covariance (ANCOVA) methods. The covariates considered for inclusion in the analyses will be gastroparesis type (diabetic or idiopathic), age, gender, BMI, and the baseline measurement of gastric emptying $T_{1/2}$. Dunnett's test will be used to compare each treatment arm to placebo. Multiplicity adjusted and unadjusted 95% 2-sided CIs will be presented.

The$T_{1/2}$ of gastric emptying of solids will be estimated by the linear interpolation using the slope of the 2 data points before and after 50% has emptied from the stomach. If less than 50% empty at 4 hours, the 3 data points at 180, 210, and 240 minutes will be used to project the time the $T_{1/2}$ value.

Secondary PD endpoints

The secondary PD endpoints will be:

Colonic geometric center at 4, 24, and 48 hours after the radiolabeled meal.

Colonic filling at 6 hours (measure of small bowel transit time) after the radiolabeled meal.

$T_{1/2}$ of ascending colon emptying.

Colonic geometric center at 4, 24, and 48 hours post meal will be estimated using geometric mean of counts in ascending, transverse, descending and rectosigmoid colon and stool (weighted by factors of 1 to 5, respectively). The geometric center is the weighted average of counts in the different colonic regions: ascending (AC), transverse (TC), descending (DC), rectosigmoid (RS), and stool. At any time, the portion of colonic counts in each colonic region is multiplied by its weighting factors as follows:

$$(\%AC \times 1 + \%TC \times 2 + \%DC \times 3 + \%RS \times 4 + \%stool \times 5)/100 = \text{geometric center}$$

Thus, a high geometric center implies faster colonic transit. A geometric center of 1 implies that all isotope is in the ascending colon, and a geometric center of 5 implies that all isotope is in the stool.

Colonic filling at 6 hours post meal will be estimated by determining the amount of identified ^{99m}Tc -labeled solid meal within the colon at 6 hours with the value corrected for downscatter of

radioactivity from the ^{111}Indium chloride isotope located within the same area appearing within the technetium window of analysis.

$T_{1/2}$ of ascending colon emptying will be estimated by power exponential analysis of the proportionate emptying over time of counts from the colon. The primary data for this analysis will be the proportion of decay and depth-corrected counts in the ascending colon on the hourly scans on the first day of transit measurement and the 24 hour data. The $T_{1/2}$ of ascending colon emptying is also estimated by plotting the activity-time curve for percent residing in the ascending colon; linear interpolation is used to connect points.

The secondary endpoints will also be assessed using an ANCOVA model. The covariates considered for inclusion in the analyses will be gastroparesis type (diabetic or idiopathic), age, gender, BMI, and the baseline measurement of the respective endpoint. The data may be transformed to correct for non-normality in the distributions of measured variables. If necessary, non-parametric ANCOVA will be used.

13.1.5 Biomarkers

Descriptive statistics, graphical methods, and statistical modeling as appropriate will be used to explore the relationship between baseline levels/response and the levels of various biomarkers.

13.1.6 Safety Analysis

AEs will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated. All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

Vital signs, ECGs, and laboratory parameters will also be tabulated.

13.1.7 Other Analyses

Patient Reported Outcomes:

Information on the global score using the GCSI, as well as bowel movement frequency per day and average stool consistency on the Bristol stool form scale, will be tabulated and analyzed respectively.

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis was conducted when approximately half of the subjects have completed the study. Efficacy and safety data was reviewed to determine if the study should be modified based on the interim analysis results.

An executive committee within Takeda composed of a senior clinician, a senior statistician, a senior clinical pharmacologist, and a senior pharmacovigilance scientist not involved in the study have reviewed the interim analysis results and made recommendations for changes to the study. All members of the study team and the investigative team will remain blinded to treatment arm assignment and treatment arm results until the completion of the study.

Based upon the results of the preplanned interim analysis, 1 of the TAK-954 doses was dropped. The specific dose dropped is not specified in order to maintain the blind of the study team. The sample size for the remaining treatment arms will not change.

13.3 Determination of Sample Size

Table 13.a below summarizes data for the primary response measures and uses the percent coefficient of variation, (%CV) to estimate the effect size detectable with 80% power based on a 2 sample z-test (ie, assuming the variation values are known) at a 2-sided alpha level of 0.05. The effect size is the difference in group means as a percentage of the overall mean for each response and assumes 12 subjects per group. Based on data acquired using the same methods in the laboratory, the sample size of 12 subjects per group provides 80% power to detect approximately 30% changes in the primary endpoints of the study: gastric emptying, and overall colonic transit. This magnitude of change is considered clinically significant. The ANCOVA should provide 80% power to detect similar (pairwise) differences using a pooled estimate of variation across all 3 groups and potentially even smaller effect sizes by adjusting for important covariates. The data from the scintigraphic transit studies are unpublished but based on the same methods proposed for this study.

Table 13.a Summary of Detectable Effect Sizes for PD Endpoints

Assuming n=12/Group in Each of the Dose Groups				
Response Type	**Mean**	**SD**	**%CV**	**Effect Size (%) †**
Gastric emptying of solids $T_{1/2}$ min (n=319)	122	29.8	24.5	34.2
Colonic filling at 6 h, % (n=63)	44	29	66	79
GC at 24 h (n=220)	2.4	0.9	36	52
Ascending colon $T_{1/2}$ h (n=50)	15.0	8.0	53	63

GC= geometric center, h=hour, min=minute.
† Detectable with 80% power, α=0.05.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study 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 guarantees access to source documents by the sponsor or its designee (contract research organization) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study 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, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). 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 study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study 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 study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study 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 study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study 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 ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study 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 B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB

IRBs 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. If any member of the IRB has direct participation in this study, 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 due to 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 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 for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study 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 notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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 study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB 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 and sponsor.

15.2 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 study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, 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 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 and the sponsor prior to 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.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, 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 prior to the subject entering into the study. 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 prior to subject entering into the study; 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 pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a subject 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 the monitor or the sponsor's designee, 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 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 study 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 15.2).

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).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

15.4.2 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 study, 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 study 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.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

Each subject in the study 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 study insurance against the risk of injury to study subjects. Refer to the study 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.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

Study Day	Screening (a)	Baseline (a)	Treatment Days 1	2	3	Final Visit or Early Termination Visit (b) 4	Follow-up Phone Call
Visit Windows (Days):	**-14 to -1**	**-14 to -1**					**10 - 14**
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Demographics	X						
Physical examination (c)	X		X	X	X	X	
Vital signs (d)	X	X	X	X	X	X	
Weight, height, and BMI	X						
Concomitant medications	X	X	X	X	X	X	X
Clinical laboratory tests (e)	X		X	X	X	X	
Fasting (finger stick) blood glucose (f)		X		X	X	X	
12-lead ECG (g)	X		X	X	X	X	
6-hour Holter monitor		X					
Holter monitoring (h)			X	X	X		
PTE	X	X					
Serum pregnancy test (hCG) (i)	X		X				
Urine pregnancy test (j)		X					
Randomization			X				
Medication history	X		X				
Concurrent medical conditions	X						X
Plasma sample for TAK-954 PK (k)			X	X	X	X	
CCI							
CCI							
CCI							
Gastroparesis Cardinal Symptom Index	X						
Bowel Habit Diary Card	X	X	X	X	X	X	
Hepatitis panel	X						
Scintigraphy (o)		X		X	X	X (p)	
Study drug dosing			X	X	X		
AE assessment		X	X	X	X	X	X
Radiolabeled meals (q)		X		X			
Charcoal administration (r)				X			

Footnotes are on last table page.

(a) Screening and Baseline Visit procedures may be done on the same day.
(b) Conduct Final Visit procedures for subjects discontinued early per Section 7.5. The end of study is defined as the date of the last visit (Day 4) of the last subject undergoing the study unless the study is stopped earlier by sponsor.
(c) Physical examination will be conducted prior to dosing on Days 1, 2, and 3.
(d) Vital signs will be collected at Screening and Baseline, and on Days 1, 2, 3 and 4 upon arrival and departure from the Clinical Research and Trials Unit, and on Day 1, 2, and 3 prior to dosing (0 hour), 1 (end of infusion), and 2 hours after start of infusion.
(e) Hematology, serum chemistries, and urinalysis tests. HbA1c and TSH will be assessed only at Screening.
(f) If the Screening and Baseline Visits are combined (same day), a fasting blood glucose (finger stick) will not be performed if blood glucose is performed.
(g) 12-lead ECG will be performed prior to each IV infusion, within 30 minutes post infusion, and at discharge on Days 1, 2, and 3; and at the Final Visit on Day 4 or Early Termination Visit. In addition, a 12-lead ECG will be performed when needed, if a subject develops symptoms or clinical signs suggestive of cardiovascular origin (eg, dizziness, lightheadedness, chest pain, chest heaviness, palpitations, shortness of breath, tachycardia).
(h) Holter monitor will be placed prior to dosing on Day 1 until the morning of Day 3.
(i) Women of childbearing potential. If a negative serum hCG pregnancy test was obtained on Day -1, then the serum pregnancy test on Day 1 can be discontinued.
(j) Urine pregnancy test will be conducted within 48 hours prior to consuming a radiolabeled meal in women of childbearing potential if screening serum pregnancy test was not completed within these 48 hours.
(k) PK timepoints will be collected as follows:
Day 1: prior to dosing (0 hour), 1 (end of infusion), 2, and 4 hours after start of infusion.
Day 2: prior to dosing (0 hour,), 1 (end of infusion), 2, 5, 7, and 9 hours after the start of the infusion.
Day 3: prior to dosing (0 hour), 1 (end of infusion), 2, and hours after start of infusion.
Day 4: 25 hours post start of infusion on Day 3 (48 hours after the administration of the radiolabeled meal on Day 2, same time as the 48-hour geometric center measurement).
(l) CCI [redacted]
(m) CCI [redacted]
(n) CCI [redacted]
(o) Scintigraphy:
Baseline at 0, 1, 2, 3, and 4 hours (240 min) post-radiolabeled meal on Days -14 to Day -1.
Day 2 at every 0.5 hour for first 4 hours post radiolabeled meal, ie, 5 hours post start of infusion, then hourly until 9 hours post start of infusion (8 hours post radiolabeled meal) on Day 3 at 1 hour post start of infusion (24 hours post radiolabeled meal on Day 2), and on Day 4 at 25 hours post start of infusion on Day 3 (48 hours post radiolabeled meal on Day 2).
(p) Scintigraphy will not be performed if this is an Early Termination Visit.
(q) Radiolabeled meals administered at Baseline (between Day -14 and Day -1) and Day 2 at the end of infusion (1 hour post start infusion).
(r) Radiolabeled charcoal capsule administered on Day 2 at predose (within 5 minutes of start of infusion).

Appendix B 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 study.

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB. 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 study. 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.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following 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.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

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

1. A statement that the study 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 study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. 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.
13. 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.
14. 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, 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.
15. 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.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB and whom to contact in the event of a research-related injury to the subject.

19. 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 or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. 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 study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. 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 study. 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;
    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 study drug(s), studying other therapies for subjects, 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 study 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 study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 4 to 5 days (5 half-lives) PLUS 30 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 4 to 5 days (5 half-lives) PLUS 30 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D 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.

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 study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- 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 study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study 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 E Hepatic Function Categories Based on Child-Pugh Score

Classification of clinical severity:
Mild (Class A): total score 5-6 points.
Moderate (Class B): total score 7-9 points.
Severe (Class C): total score 10-15 points.

Assessment Parameters	Points Scored for Observed Findings		
	1 point	**2 points**	**3 points**
Encephalopathy grade (a)	none	1 or 2	3 or 4
Ascites	absence	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Source:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.
(a) Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

Appendix F Detailed Descriptions of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 05 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Revised number of subjects based on the findings of the interim analysis.

The primary change occurs in Section 2.0 STUDY SUMMARY.

Initial wording:	**Number of Subjects:** 48 (12 per group)
Amended or new wording:	**Number of Subjects:** ~~48~~**Approximately 36 to 41 subjects** (**maximum of** 12 per group).

Rationale for Change:

One dosing arm was dropped based on conclusions obtained from the unblinded executive committee who performed the interim analysis.

Section 2.0 STUDY SUMMARY also contains this change.

Change 2: Decreased the number of active treatment arms.

The primary change occurs in Section 8.1.3 Dose and Regimen.

Initial wording:	The subjects will be randomized to 1 of 4 treatment arms: TAK-954 0.1, 0.3, or 1 mg; or placebo and will receive TAK-954 or placebo as a 60-minutes infusion IV once a day for 3 days starting on Day 1.
Amended or new wording:	The subjects will be randomized to ~~1 of 4 treatment arms:~~ TAK-954 0.1, 0.3, or 1 mg; or placebo and will receive TAK-954 or placebo as a 60-minutes infusion IV once a day for 3 days starting on Day 1. **The number of active treatment arms decreased based upon the prespecified interim analysis. To maintain the blinding of the study team, the specific treatment arm is not identified. This change was not necessitated by safety findings.**

Rationale for Change:

Based on conclusions obtained from the unblinded executive committee who performed the interim analysis.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1 Study Design.
- Section 9.1.16 Documentation of Randomization.
- 13.2 Interim Analysis and Criteria for Early Termination.
- Table 13.a.

Change 3: Revised the type of vital sign procedures collected and clarified the timing in relation to pharmacokinetic (PK) blood draws.

The primary change occurs in Section 9.1.5 Vital Sign Procedure.

Initial wording:	Vital signs will include body temperature (oral measurement), respiratory rate, sitting/supine blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute). When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.
Amended or new wording:	Vital signs will include ~~body temperature (oral measurement), respiratory rate,~~ sitting/supine blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute). When vital signs are scheduled at the same time as **PK** blood draws, the **PK** blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

Rationale for Change:

Decrease the number of procedures needed and clarify the timing in relation to PK blood draws.

Change 4: Elimination of optional PK samples.

The primary change occurs in Section 9.1.14.1 Collection of Plasma for PK Sampling.

Initial wording:	The subjects will have PK samples collected as follows: Days 1: prior to dosing (0 hour), and at 0.5 (optional), 1 (end of infusion), 1.5 (optional), 2, and 4 hours after start of infusion. Day 2: prior to dosing (0 hour), 0.5 (optional), 1 (end of infusion), 1.5 (optional), 2, 5, 7, and 9 hours after the start of the infusion. Day 3: prior to dosing (0 hour), 0.5 (optional), 1 (end of infusion), 1.5 (optional), 2, and 4 (optional) hours after start of infusion.
Amended or new wording:	The subjects will have PK samples collected as follows: Days 1: prior to dosing (0 hour), ~~and at 0.5 (optional),~~ 1 (end of infusion), ~~1.5 (optional),~~ 2, and 4 hours after start of infusion. Day 2: prior to dosing (0 hour), ~~0.5 (optional),~~ 1 (end of infusion), ~~1.5 (optional),~~ 2, 5, 7, and 9 hours after the start of the infusion. Day 3: prior to dosing (0 hour), ~~0.5 (optional),~~ 1 (end of infusion), ~~1.5 (optional),~~ **and** 2, ~~and 4 (optional)~~ hours after start of infusion.

Rationale for Change:

To decrease the amount of blood needed from subjects.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY also contains this change.

Figure 6.a Schematic of Study Design.

Table 9.b. Primary Specimen Collections.

Change 5 Revised the timing of vital sign measurements.

The primary change occurs in Appendix A Schedule of Study Procedures.

Initial wording:	(d) Vital signs will be collected upon arrival and departure from the Clinical Research and Trials Unit, and at the time of the PK samples.
Amended or new wording:	(d) Vital signs will be collected **at Screening and Baseline, and on Days 1, 2, 3, and 4** upon arrival and departure from the Clinical Research and Trials Unit, ~~and at the time~~ **and on Days 1, 2, and 3 prior to dosing (0 hour), 1 (end of** ~~the PK sample~~ **infusion), and 2 hours after start of infusion**.

Rationale for Change:

Correction of vital sign measurement timing.

Change 6: Eliminated instruction of the timing of PK sampling and electrocardiogram procedures.

The primary change occurs in Section 9.1.14.1 Collection of Plasma for PK Sampling.

Deleted text:	~~When a PK sample coincides with an ECG or vital signs measurement, the ECG will take priority over the vital signs measurement.~~

Rationale for Change:

As the drug is administered via IV infusion, it is important to have the PK sample obtained as soon as possible at the end of infusion in order to calculate the C_{max}. Waiting for an ECG measurement will significantly increase the variability across subjects. There is no safety issue for doing it either way.

Change 7: Revised information related to interim analysis.

The primary change occurs in Section 13.2 Interim Analysis and Criteria for Early Termination.

Initial wording:	An interim analysis will be conducted when approximately half of the subjects have completed the study. Efficacy and safety data will be reviewed to determine if the study should be modified based on the interim analysis results. If needed, the changes will be related to dose selection, sample size modification, or study termination. An executive committee within Takeda composed of a senior clinician, a senior statistician, a senior clinical pharmacologist, and a senior pharmacovigilance scientist not involved in the study will review the interim analysis results and make recommendations for changes to the study, if appropriate. All members of the study team and the investigative team will remain blinded to treatment arm assignment and treatment arm results until the completion of the study.
Amended or new wording:	An interim analysis ~~will be~~ **was** conducted when approximately half of the subjects have completed the study. Efficacy and safety data ~~will be~~ **was** reviewed to determine if the study should be modified based on the interim analysis results. ~~If needed, the changes will be related to dose selection, sample size modification, or study termination.~~ An executive committee within Takeda composed of a senior clinician, a senior statistician, a senior clinical pharmacologist, and a senior pharmacovigilance scientist not involved in the study ~~will~~ **have** ~~review~~ **reviewed** the interim analysis results and ~~make~~ **made** recommendations for changes to the study~~, if appropriate~~. All members of the study team and the investigative team will remain blinded to treatment arm assignment and treatment arm results until the completion of the study. **Based upon the results of the preplanned interim analysis, 1 of the TAK-954 doses was dropped. The specific dose dropped is not specified in order to maintain the blind of the study team. The sample size for the remaining treatment arms will not change.**

Rationale for Change:

Based on conclusions obtained from the unblinded executive committee who performed the interim analysis.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	20-Dec-2018 14:59 UTC
	Statistical Approval	20-Dec-2018 15:28 UTC
	Pharmacovigilance Approval	20-Dec-2018 15:30 UTC
	Clinical Pharmacology Approval	20-Dec-2018 18:55 UTC