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

SAP Approve Date: 25 September 2018

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information 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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-954-2003

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

PHASE 2a

Version: 1.0

Date: 25 September 2018

Prepared by:

PPD

Based on:

Protocol Version: <Amendment 4>

Protocol Date: <11 September 2018>

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

1.0 TITLE PAGE 1
1.1 Approval Signatures 2
2.0 TABLE OF CONTENTS 3
3.0 LIST OF ABBREVIATIONS 5
4.0 OBJECTIVES 7
4.1 Primary Objectives 7
4.2 Secondary Objectives 7
4.3 Additional Objectives 7
4.4 Study Design 7
5.0 ANALYSIS ENDPOINTS 9
5.1 Primary Endpoint 9
5.2 Secondary Endpoints 9
5.3 Safety Endpoints 9
5.4 Exploratory Endpoints 9
6.0 DETERMINATION OF SAMPLE SIZE 10
7.0 METHODS OF ANALYSIS AND PRESENTATION 11
7.1 General Principles 11
7.1.1 Definition of Study Days and Study Visit Windows 11
7.1.2 Missing Data 14
7.2 Analysis Sets 15
7.3 Disposition of Subjects 15
7.4 Demographic and Other Baseline Characteristics 15
7.5 Medical History and Concurrent Medical Conditions 15
7.6 Medication History and Concomitant Medications 16
7.7 Study Drug Exposure and Compliance 16
7.8 Efficacy Analysis 16
7.8.1 Primary Efficacy Endpoint(s) 16
7.8.2 Secondary Efficacy Endpoint(s) 16
7.8.3 Additional Efficacy Endpoint(s) 16
7.9 Pharmacokinetic/Pharmacodynamic Analysis 17
7.9.1 Pharmacokinetic Analysis 17
7.9.2 Pharmacodynamic Analysis 17
7.9.2.1 Primary PD endpoint 17
7.9.2.2 Secondary PD endpoint 18

7.10 Other Outcomes 18
7.11 Safety Analysis 19
7.11.1 Adverse Events 19
7.11.2 Clinical Laboratory Evaluations 19
7.11.3 Vital Signs 20
7.11.4 12-Lead ECGs 20
7.11.5 Other Observations Related to Safety 21
7.12 Interim Analysis 21
7.13 Changes in the Statistical Analysis Plan 21
8.0 REFERENCES 22

LIST OF IN-TEXT TABLES

Table 6.a Summary of Detectable Effect Sizes for PD Endpoints 10

LIST OF IN-TEXT FIGURES

Figure 7.a Schematic of study design 12

LIST OF APPENDICES

Appendix A Clinical Laboratory Tests and Screening 23
Appendix B Criteria for Identification of Markedly Abnormal Laboratory Values 24
Appendix C Criteria for Abnormal Changes from Baseline of Vital Signs 26
Appendix D Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters 27

3.0 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
ANOVA	analysis of variance
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
BUN	blood urea nitrogen
%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
CPK	creatine phosphokinase
CRF	case report form
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
GC	geometric center
GCP	Good Clinical Practice
GCSI	Gastroparesis Cardinal Symptom Index
GGT	γ-glutamyl transferase
GI	gastrointestinal
HbA1c	glycosylated hemoglobin
HIV	human immunodeficiency virus
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
IVRS	Interactive Voice Response System
kcal	kilocalorie
LFT(s)	liver function test(s)
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MTD	maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect-level
PD	pharmacodynamics
PGx	pharmacogenomic(s)
PK	pharmacokinetics
PPS	per protocol set
PRO	patient-reported outcome
PTE	Pretreatment event
QD	Once daily
QOL	quality-of-life
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
RS	rectosigmoid colon
SAE	serious adverse event
SAP	statistical analysis plan
SDB	standard database
SUSARs	suspected unexpected serious adverse reactions
SVT	supraventricular tachycardia
T1/2	half-emptying time
TC	transverse colon
TLGs	tables, listings, and graphs
ULN	upper limit of normal
VT	Ventricular tachycardia
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

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.

4.2 Secondary Objectives

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

4.3 Additional Objectives

CCI

[redacted]

4.4 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 will be evaluated.

This study consists of 3 periods and a Follow-up: a Screening Period, a Baseline Period (between Day -14 and Day -6), a Treatment Period (Days 1 to 4), and a Follow-up Phone Call (Days 10 to 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 -6 (Baseline Visit). At least 48 hours prior to baseline scintigraphy, female subjects must have a negative urine pregnancy test.

If eligibility criteria are fulfilled, subjects will be randomized on Day 1 to 1 of 4 treatment arms: 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.

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

- Day 1: prior to dosing (0 hour) and at 0.5, 1 (end of infusion), 1.5, 2, and 4 hours after start of infusion.
- Day 2: prior to dosing (0 hour,), 0.5, 1 (end of infusion), 1.5, 2, 5, 7, and 9 hours after the start of the infusion.
- Day 3: prior to dosing (0 hour), 0.5, 1 (end of infusion), 1.5, and 2 hours after start of infusion, with an optional 4-hour sample.
- 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).

During the study, subjects will complete a daily diary to record their bowel habits and as well as their global score using the GCSI. 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.

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, then 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.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- The primary endpoint for this study is half-emptying time (T1/2) of gastric emptying of solids.

5.2 Secondary Endpoints

- 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.
- T1/2 of ascending colon emptying.
- The following PK parameters of TAK-954:
  - Area under the concentration-time curve during a dosing interval (AUCτ), Cmax, and observed concentration at the end of a dosing interval (Ctrough).

5.3 Safety Endpoints

- 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.

5.4 Exploratory Endpoints

PPD

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Table 6.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 6.a Summary of Detectable Effect Sizes for PD Endpoints

Assuming n=12/Group in Each of the 4 Dose Groups				
Response Type	Mean	SD	%CV	Effect Size (%) †
Gastric emptying of solids T1/2 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 T1/2 h (n=50)	15.0	8.0	53	63

† Detectable with 80% power, α=0.05.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Statistical analysis will be performed using the SAS System, Version 9.4.

Categorical data will be summarized as the number and percentage of subjects in each category. Continuous data will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. The coefficient of variation (%CV) and geometric mean will be included in the summary of continuous data where indicated.

Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate. Where applicable, confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate and p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

All statistical tests and confidence intervals (CIs) will be 2-tailed at α=0.05 level for significance unless otherwise stated. All study-related raw data for enrolled subjects, including derived data, will be presented in data listings.

7.1.1 Definition of Study Days and Study Visit Windows

Study Day 1 is defined as the date of the first dose of study drug. Other study days are defined relative to Study Day 1, with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: [date of assessment/event – date of first dose of study drug]. Study days on or after the first dose of study drug will be calculated as: [date of assessment/event – date of first dose of study drug + 1]. Unless specified otherwise, for all PD, symptom assessment, and safety endpoints, baseline is defined as the last non-missing measurement prior to the first dose of study drug.

Scintigraphy will be performed at 0, 1, 2, 3, and 4 hours post-radiolabeled meal on baseline visit (Days -14 to Day -6); on Day 2 at every 0.5 hour for first 4 hours post radiolabeled meal, then hourly until 9 hours post start of infusion; on Day 3 at 1 hour post start of infusion; and on Day 4 at 25 hours post start of infusion on Day 3.

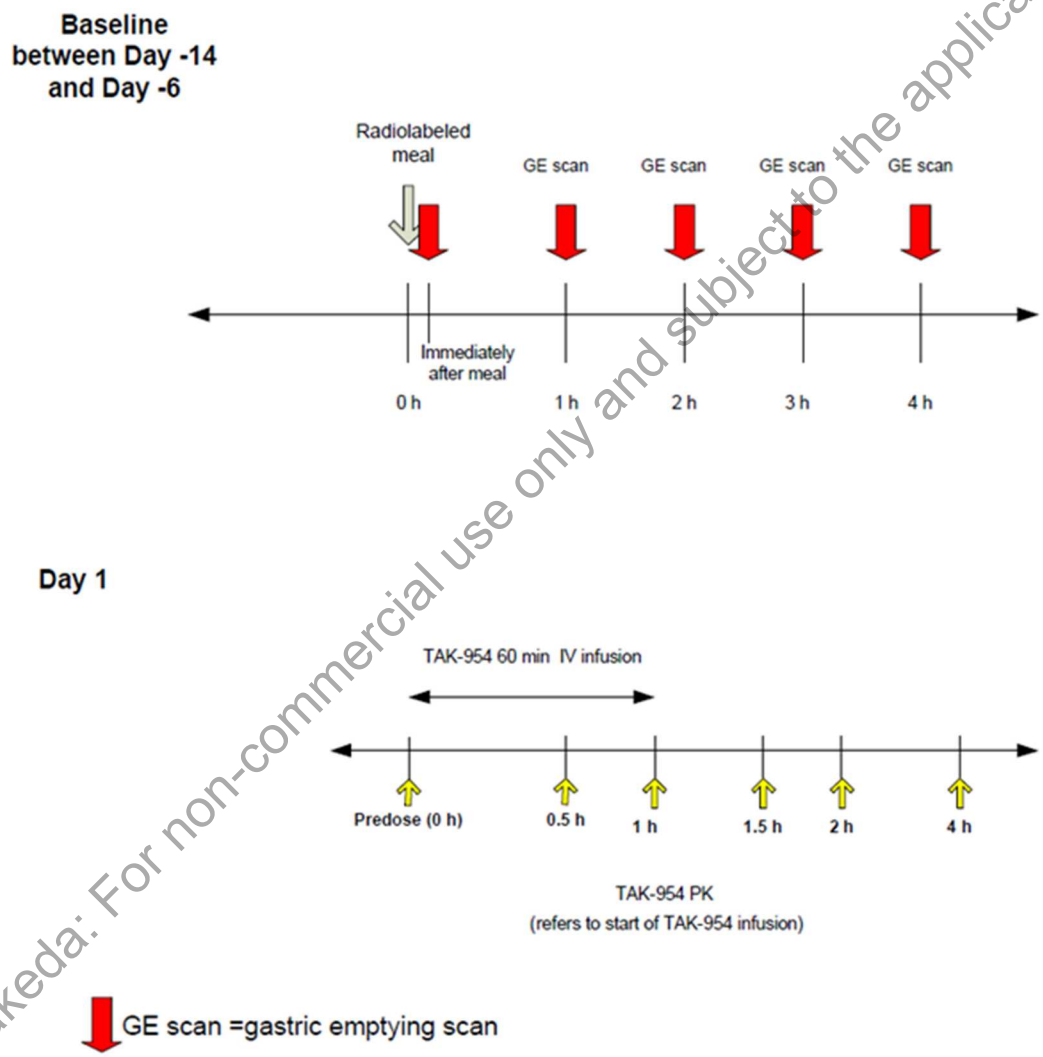
PK timepoints will be collected on Day 1 prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, and 4 hours after start of infusion; on Day 2 prior to dosing (0 hour,), 0.5, 1, 1.5, 2, 5, 7, and 9 hours after the start of the infusion; on Day 3 prior to dosing (0 hour), 0.5, 1, 1.5, and 2 hours after start of infusion, with an optional 4-hour sample; and on Day 4 at 25 hours post start of infusion on Day 3.

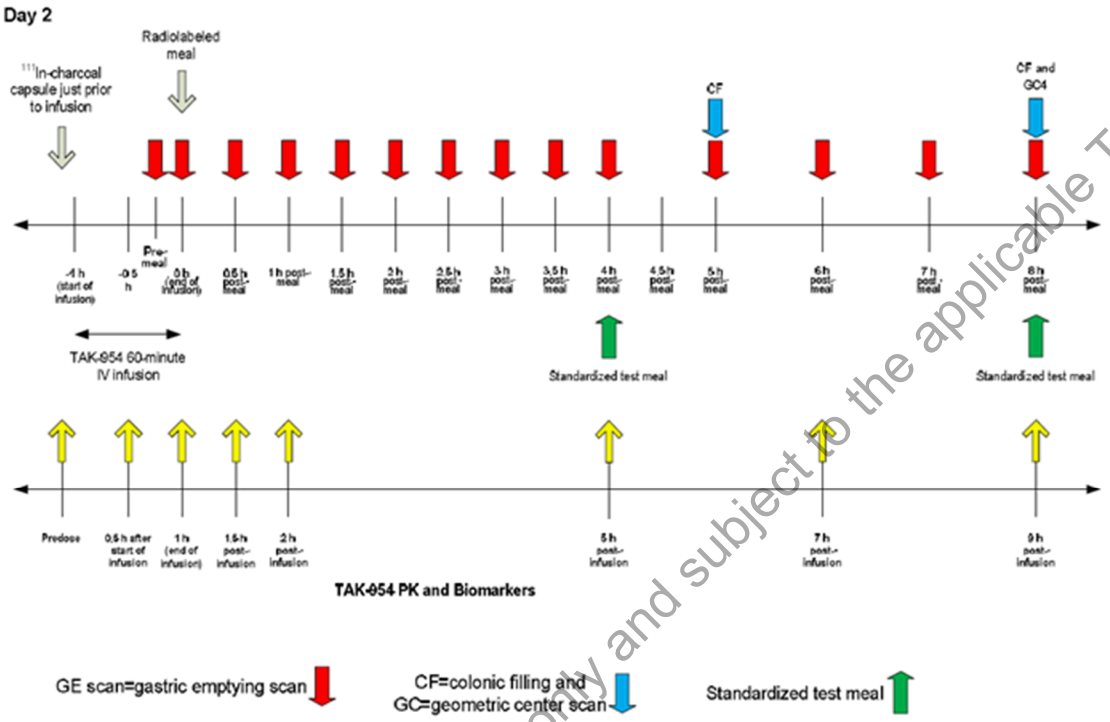
Vital signs will be collected upon arrival and departure from the Clinical Research and Trials Unit and at the time of the PK. Physical examination will be conducted prior to dosing on Days 1, 2, and 3. 12-lead ECG will be performed prior to each IV infusion, within 30 minutes post infusion, and at discharge on Days 1, 2, and 3; and at the Final Visit on Day 4 or Early

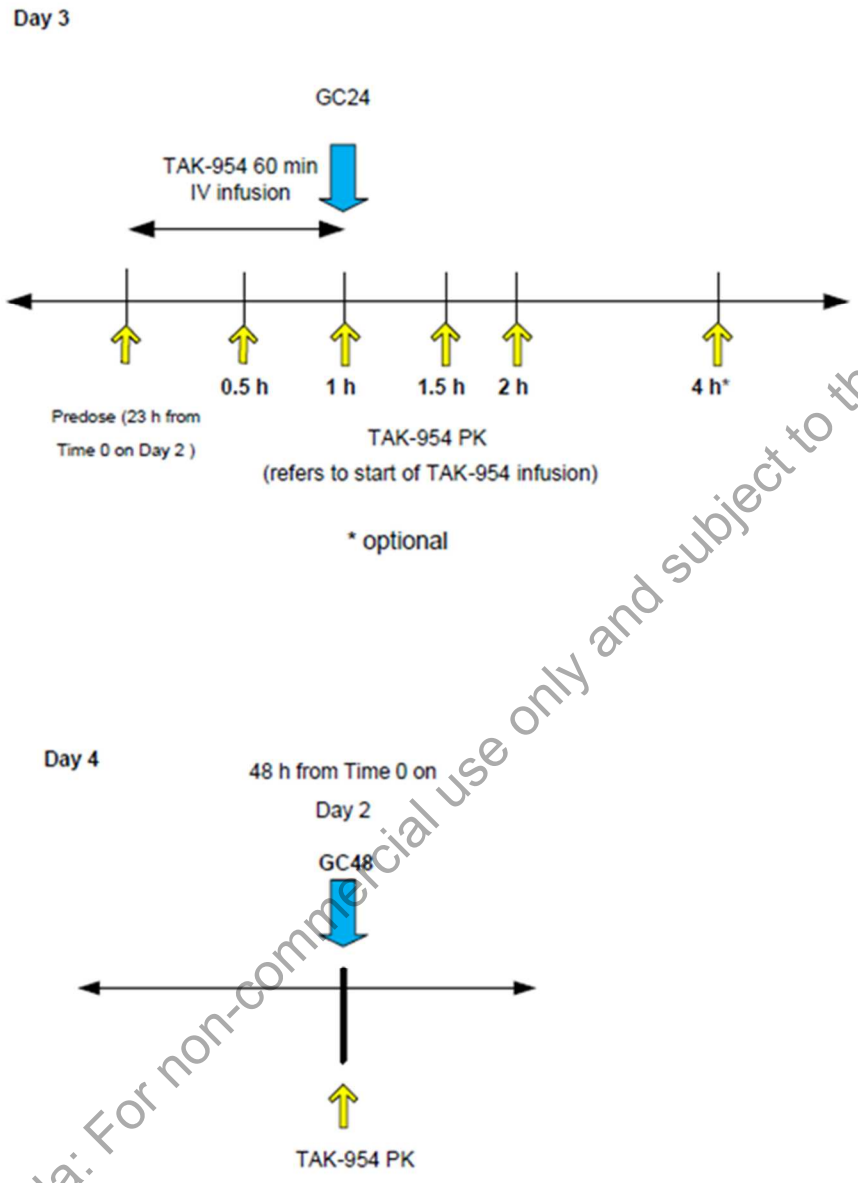
Termination Visit. In addition, a 12-lead ECG will be performed when needed, if a subject develops symptoms suggestive of cardiovascular origin (eg, dizziness, chest pain).

A schematic of the study design is included as Figure 7.a.

Figure 7.a Schematic of study design







7.1.2 Missing Data

There will be no imputation of incomplete or missing data unless otherwise indicated.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarizing concentration values and deriving of PK parameters. These values will be flagged in the data listings.

7.2 Analysis Sets

The Full Analysis Set (FAS) will include all randomized subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment they were randomized to receive.

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.

The Safety Analysis Set (SAF) will include all subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment that was actually received. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

The PK Analysis Set is defined as all subjects who receive at least 1 dose of study drug and have sufficient blood sampling to allow for PK evaluation.

7.3 Disposition of Subjects

A subject disposition summary will be provided. Subjects' study completion data, including reasons for premature termination, will be provided in listings and also summarized.

Significant protocol deviations will be summarized.

A summary of screening failures will also be provided.

7.4 Demographic and Other Baseline Characteristics

For continuous variables (age, weight, height, and body mass index [BMI]), summary statistics will be generated. BMI (in kg/m^2) will be calculated using the subject's baseline height and weight measurements and summarized.

For categorical variables, the number and percentage of subjects in each category will be presented.

There will be no inferential analysis of demographic and baseline characteristics.

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that resolved at or prior to the time of informed consent. Concurrent medical conditions are defined as significant ongoing conditions or diseases that are present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the latest version of MedDRA, and will be summarized by treatment and overall using System Organ Class (SOC) and MedDRA preferred term (PT). The table will include number and percentages of subjects, and will be sorted in alphabetical order by SOC. Within an SOC, PTs are sorted in decreasing frequency based on the total number of subjects. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms. Summaries will be based on the safety set. There will be no inferential analysis of medical history and concurrent medical conditions.

All medical history and concurrent medical condition data will be presented in data listing.

7.6 Medication History and Concomitant Medications

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. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug), and summarized by giving the number and percentage of subjects by preferred medication name within each therapeutic class, with therapeutic class sorted in alphabetical order and preferred term sorted in decreasing frequency based on the total number of subjects. If a subject report taking 2 drugs belonging to the same class, he/she will only be counted once within that class. Summaries of medication history and concomitant medication will be based on the safety set. There will be no inferential analysis of medication history and concomitant medications.

All medication history and concomitant medications data will be presented in data listing.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects. No summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

Not applicable

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable

7.8.3 Additional Efficacy Endpoint(s)

Not applicable

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 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:

- AUC_{τ}: Area under the concentration-time curve during a dosing interval (Day 1 to 3).
- C_{max}: Maximum observed concentration (Day 1 to 3).
- $C_{through}$: Observed concentration at the end of a dosing interval (Day 2 and 3).

The plasma concentration of TAK-954 will be summarized by treatment group over each scheduled sampling time point using descriptive statistics (N, arithmetic mean, SD, SE, CV%, median, minimum and maximum). In addition, the figures for mean plasma concentrations of TAK-954 versus time (linear and semi-log scale) will be generated, in overall population and by treatment group.

Additional plasma PK parameters may be calculated if necessary, in accordance with the Clinical Pharmacology Analysis Plan (CPAP).

7.9.2 Pharmacodynamic Analysis

The analyses and summaries for PD will be based on the FAS.

7.9.2.1 Primary PD endpoint

The primary PD endpoint is the half-emptying time (T1/2) 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$T_{1/2}$ 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.

Analysis of covariance (ANCOVA) methods will be used to assess the effect of treatment on the half-emptying time of gastric emptying of solids, including gastroparesis type (diabetic or idiopathic), age, gender, BMI, and the baseline measurement of gastric emptying $T_{1/2}$ as covariates. Dunnett's test will be used to compare each treatment arm to placebo. Multiplicity adjusted and unadjusted 95% 2-sided confidence intervals will be presented. Normality will be tested using the Shapiro Wilk W test with criteria <0.01. If normality is not achieved, a natural

log transformation may be done, and normality testing will be repeated. If normality is not achieved, a non-parametric test (such as Kruskal Wallis) may be use.

7.9.2.2 Secondary PD endpoint

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 x 1 + %TC x 2 + %DC x 3 + %RS x 4 + %stool x 5)/100 = 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 effect of treatment on 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. Dunnett's test will be used to compare each treatment arm to placebo. Multiplicity adjusted and unadjusted 95% 2-sided confidence intervals will be presented. Normality will be tested using the Shapiro Wilk W test with criteria <0.01. If normality is not achieved, a natural log transformation may be done, and normality testing will be repeated. If normality is not achieved, a non-parametric test (such as Kruskal Wallis) may be use.

7.10 Other Outcomes

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 by each day.

7.11 Safety Analysis

Safety analyses include adverse events (AEs), clinical laboratory parameters, vital sign parameters, 12-lead electrocardiogram (ECG) results.

All summaries of safety data are based on subjects in the Safety Set.

7.11.1 Adverse Events

All AE verbatim terms will be coded by SOC and PT using the latest version of MedDRA dictionary. SOCs will be sorted by alphabetical order. Within a SOC, PTs will be sorted in descending order based on the total number of subjects with AEs. For each category and overall, subjects reporting more than 1 occurrence for a term (SOC or PT) being summarized will be counted only once using the most extreme incident (most severe for the intensity tables and related for the relationship to study drug tables).

A treatment-emergent adverse event (TEAE) will be defined as an AE or serious adverse event (SAE) that started or worsened after first study drug administration and within 30 days of last dose of study drug (onset date – date of last dose + 1 ≤30). AEs with missing onset dates will be summarized with TEAEs regardless of severity and relationship to study medication.

TEAEs will be summarized by giving the number and percentage (N [%]) of subjects reporting any event for each term. The following is a list of TEAE summary tables to be generated.

- Overview of TEAEs (at both subject and event level).
- TEAEs by SOC and PT (at both subject and event level).
- Subject Mappings for TEAEs.
- TEAEs by SOC and PT by underlying disease condition (DG and IG).
- TEAEs by PT.
- Relationship of TEAEs to Study Drug by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.
- TEAEs leading to study discontinuation by SOC and PT.
- Treatment-emergent SAEs by SOC and PT.

An AE of Special Interest (serious or non-serious) is one 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.

7.11.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include hematology, serum chemistries, and urinalysis tests. Refer to Appendix A for the list of all clinical laboratory tests.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical safety laboratory variables will be summarized for baseline, postbaseline values, and change from baseline by treatment group and overall at each measurement. Only the scheduled measurements will be included in the summary. No inferential analysis will be performed.

Individual results for hematology laboratory tests and serum chemistry tests will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix B). All subjects that meet the MAV criteria will be presented in a data listing. If a subject has a MAV for a particular laboratory test, all values for that subject and for that parameter will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal laboratory test result will be presented by treatment group and overall. All postbaseline clinical lab results within 7 days of the last dose, including scheduled and unscheduled measurements will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

All clinical laboratory data will be presented in both SI and conventional units in the data listings. Laboratory data outside of the normal reference range will be flagged on the listing along with values meeting MAV criteria.

7.11.3 Vital Signs

Vital sign measurements include body temperature, heart rate, respiratory rate, and blood pressure.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of vital signs parameters will be summarized for baseline, postbaseline, and change from baseline at each scheduled time point. Only the vital signs collected at the scheduled visits or time points will be included in the summary. No inferential analysis will be performed.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix C) will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal vital sign measurement will be summarized. All postbaseline vital signs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

All vital sign data will be presented in the listings. Vital sign MAVs will be flagged in the listings.

7.11.4 12-Lead ECGs

The ECG parameters include heart rate, PR interval, QRS duration, QT interval, and QT interval with Fredericia's corrections (QTcF).

Descriptive statistics (N, mean, median, SD, minimum and maximum) of quantitative ECG data will be summarized for baseline, postbaseline, and change from baseline at each scheduled time point. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No inferential analysis will be performed for the observed ECGs.

For ECG interpretation data, shift tables will be provided as the number of subjects to assess interpretation status change from baseline to each scheduled postbaseline measurement.

All individual ECGs that meet Takeda's predefined criteria for markedly abnormal values (Appendix D) will be listed. The number and percentage of subjects with at least one markedly abnormal ECG measurement will be summarized. All post dose ECGs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects who meet the MAV criteria will be listed as a table.

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

7.11.5 Other Observations Related to Safety

Not applicable

7.12 Interim Analysis

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.

7.13 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

Appendix A Clinical Laboratory Tests and Screening

Chemistry

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

Hematology

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

Urinalysis

Protein	Glucose
Blood	Nitrite

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

Appendix B Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional SI	<100 x 10^3/μL <7100x 10^9/L	>450 x 10^3/μL >450 x 10^9/L

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

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Alkaline phosphatase	Both	--	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Total bilirubin	Conventional SI	-- --	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Albumin	Conventional SI	<3 g/dL <30 g/L	-- --
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional SI	--	>2.0 mg/dL >177 μmol/L
Blood urea nitrogen	Conventional SI		>30 mg/dL >10.7 mmol/L
Sodium	Conventional SI	<130 mEq/L <130 mmol/L	>150 mEq/L >150 mmol/L
Potassium	Conventional SI	<3.0 mEq/L <3.0 mmol/L	>5.5 mEq/L >5.5 mmol/L
Glucose	Conventional SI	<55 mg/dL <3 mmol/L	>180 mg/dL >10 mmol/L*
Chloride	Conventional SI	<75 mEq/L <75 mmol/L	>126 mEq/L >126 mmol/L

Parameter	Unit	Low Abnormal	High Abnormal
Calcium (corrected)	Conventional	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L
	SI	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	
Bicarbonate	Conventional	<8.0 mEq/L	
	SI	<8.0 mmol/L	

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

- Unless for patients who have Diabetic at baseline.

Appendix C Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<60	>120
Systolic blood pressure	mm Hg	<90	>140
Diastolic blood pressure	mm Hg	<60	>90
Body temperature	^{o}C	<35.6	>37.7
	^{o}F	<96.1	>99.9

Appendix D Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤120 milliseconds	≥200 milliseconds
QTcF Interval		≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤60 milliseconds	≥120 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	25-Sep-2018 19:52 UTC
	Statistical Approval	26-Sep-2018 02:02 UTC
	Clinical Pharmacology Approval	26-Sep-2018 15:24 UTC
	Pharmacovigilance Approval	27-Sep-2018 11:46 UTC
	Clinical Science Approval	28-Sep-2018 08:10 UTC