Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, 3-Period, Incomplete Block Design Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-954 in Healthy Adult Participants.

NCT Number: NCT03870555

Protocol Approve Date: 11 March 2019

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- 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 Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, 3-Period, Incomplete Block Design Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-954 in Healthy Adult Participants.

Study Identifier: TAK-954-1009

Compound: TAK-954

Date: 11 March 2019

Version/Amendment Number: Amendment 01

Amendment History:

Date	Amendment Number	Amendment Type	Region
07 February 2019	Initial Version		
11 March 2019	01	Not Applicable	United States

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, Massachusetts USA 02139 Telephone: +1 (617) 679-7000	TAK-954
Study Identifier: TAK-954-1009	**Phase:** 1

Protocol Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, 3-Period, Incomplete Block Design Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-954 in Healthy Adult Participants.

Study Design:

This is a double-blind, placebo-controlled, single ascending intravenous (IV) dose, 3-period, incomplete block design study to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of TAK-954 at higher IV doses than those previously studied. In this Phase 1 study, healthy adult participants will attend a screening visit within 28 days prior to the first dose.

Participants will be randomized to one of 3 treatment sequences as detailed in the table below. In each sequence, each participant will receive 2 doses of the active drug (out of 3 evaluated dose levels) in an ascending order and 1 dose of placebo. A sample size of 6 participants is proposed based on empirical considerations.

	Period 1		**Period 2**		**Period 3**	
Sequence	**Day 1 (Lead-in)**	**Day 2 (Treatment)**	**Day 1 (Lead-in)**	**Day 2 (Treatment)**	**Day 1 (Lead-in)**	**Day 2 (Treatment)**
Sequence 1 (n=2)	Placebo	Placebo	TAK-954	Treatment B	TAK-954	Treatment C
Sequence 2 (n=2)	TAK-954	Treatment A	Placebo	Placebo	TAK-954	Treatment C
Sequence 3 (n=2)	TAK-954	Treatment A	TAK-954	Treatment B	Placebo	Placebo

Lead-in TAK-954: 0.1 mg TAK-954 IV infusion.
Treatment A: 0.5 mg TAK-954 IV infusion.
Treatment B: 1 mg TAK-954 IV infusion.
Treatment C: 2 mg TAK-954 IV infusion.

On Day 1 of each period, each participant will receive a lead-in dose of 0.1 mg TAK-954 (if scheduled to receive a dose of active drug on Day 2 of that period as per the randomization schedule) or placebo (if scheduled to receive a placebo on Day 2 of that period as per the randomization schedule) as a 60 minutes IV infusion. On Day 2 of each period, participants will receive either a single dose of 0.5 mg, 1 mg, or 2 mg TAK-954 or placebo as a 60-minute infusion as per the randomization schedule.

Safety will be assessed by monitoring for adverse events (AEs), vital signs, orthostatic vital signs, electrocardiograms (ECGs), safety laboratory assessments, and physical examinations throughout each dosing period. Blood (for plasma) samples for assessment of TAK-954 concentrations will be collected at selected times from predose through to 9 hours after each lead-in dose (Day 1). Blood (for plasma) samples for assessment of TAK-954 concentrations will also be collected at selected times from predose through 336 hours (Day 16) after each Day 2 dose. Urine samples for assessment of TAK-954 concentrations will also be collected at selected times from predose through 36 hours (Day 3) after each Day 2 dose. CCI [redacted]. The time to first stool will be recorded following dosing on Day 1 until prior to dosing on Day 2 and following dosing on Day 2. The number of stools per day and stool form (Bristol Stool Form Scale) will be recorded following dosing on Day 1 until prior to dosing on Day 2, and for 36 hours following Day 2 dosing.

The last dose in the previous period and the first dose of the next period will be separated by a minimum of 16 days.

The starting dose of TAK-954 on Day 2 (Period 1) will be 0.5 mg, which is the highest dose previously used in a completed study following IV administration. Subsequent doses will be chosen based on emerging data; the currently proposed doses are 1 mg and 2 mg. Dose escalation to the next dose level (ie, next period) will not take place until the Investigator and the Sponsor have determined that adequate safety/tolerability from the previous period has been demonstrated to permit proceeding to the next dose level. Additional cohort(s) (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort.

Day 16 of Period 3 will also be considered as the follow-up visit for participants who complete the study. All participants who received at least 1 dose of study drug or placebo and withdraw from the study early will return for a follow-up visit, 10-14 days after the last dose administration.

Study Primary Objectives:

- To evaluate the safety and tolerability of single ascending IV doses of TAK-954.
- To evaluate the PK of single ascending IV doses of TAK-954.

Secondary Objective:

- To evaluate the PD effect of single ascending IV doses of TAK-954 on the gastrointestinal (GI) motility in healthy participants while in confinement.

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[redacted]

Study Participant Population: Healthy male and female participants aged 18 to 55 years inclusive. Body Mass Index (BMI) 18.0-32.0 kg/m^2, inclusive, body weight ≥50 kg.

Planned Number of Participants:	**Planned Number of Sites:**
6 Additional cohort(s) (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort.	1
Dose Levels: **Day 1 (Lead-in):** 0.1 mg TAK-954 (100 mL x 0.001 mg/mL TAK-954 solution for IV administration) Placebo will be administered as 100 ml saline solution for IV infusion. Lead-in treatment (ie, TAK-954 or placebo) will match the scheduled treatment (TAK-954 or placebo) to be received on Day 2 of that period as per the randomization schedule.	**Route of Administration:** IV

Day 2 (Treatment): Treatment A: 0.5 mg TAK-954 (100 mL x 0.005 mg/mL TAK-954 solution for IV administration) Treatment B: 1 mg * TAK-954 (100 mL x 0.01 mg/mL TAK-954 solution for IV administration) Treatment C: 2 mg * TAK-954 (100 mL x 0.02 mg/mL TAK-954 solution for IV administration) Placebo will be administered as 100 ml saline solution for IV infusion. * Dose levels may be changed based on emerging data	
Duration of Treatment: On Day 1 of each period, each participant will receive a lead-in dose of 0.1 mg TAK-954 or placebo as a 60-minute IV infusion. On Day 2 of each period, participants will receive a single dose of either TAK-954 (if received the lead-in dose of TAK-954 on Day 1 of that period) or placebo (if received placebo on Day 1 of that period) as a 60-minute infusion.	**Planned Study Duration:** Approximately 73 days including screening period and follow-up visit.

Criteria for Inclusion:

In order to be eligible for study participation, participants must:

1. Healthy, adult, male or female, 18-55 years of age, inclusive, at screening.
2. Body mass index (BMI) ≥18 and ≤ 32.0 kg/m2, weighing ≥50 kg at screening.
3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, orthostatic vital signs, or ECGs, as deemed by the Investigator or designee.
4. Continuous nonsmoker who has not used nicotine- containing- products for at least 3 months prior to the first dose and throughout the study based on participant self-reporting.
5. For a male or female of childbearing potential, use an acceptable birth control methods as indicated in Appendix D.
6. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol.

Criteria for Exclusion:

The participant must be excluded from participating in the study if the participant:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.
6. History or presence of:
   - risk factors for Torsade de Pointes (eg, heart failure, unexplained syncope, cardiomyopathy, or family

history of Long QT Syndrome);

- family history of sudden death;
- sick sinus syndrome, second or third degree atrioventricular (AV) block, myocardial infarction, pulmonary congestion, symptomatic or significant cardiac arrhythmia, prolonged heart rate corrected QT interval by Fredericia (QTcF) interval, or conduction abnormalities;
- cholecystectomy;
- orthostatic hypotension or orthostatic vital sign results at screening with a decrease in systolic >20 mmHg or decrease in diastolic >10 mmHg, and increase in pulse of >20 bpm.

7. Female participants with a positive pregnancy test or who are lactating.
8. Positive urine drug or alcohol results at screening or first check in-.
9. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
10. Seated blood pressure is less than 100/60 mmHg or greater than 140/90 mmHg at screening.
11. QTcF interval is >450 msec (males and females) or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening or first check-in, including:
    - T wave forms which make accurate QT measurement difficult;
    - Absence of regular atrial or the presence of junctional rhythm;
    - Abnormal sinus rhythm (heart rate <55 bpm or >100 bpm);
    - PR interval >210 msec, or QRS complex >110 msec.
12. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to the first dosing and throughout the study. After randomization, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Acceptable birth control methods as described in Appendix D will be allowed.
    - Any drugs known to be significant inducers of Cytochrome P450 (CYP) 3A4 enzymes and/or P-gp, including St. John's Wort, for 28 days prior to the first dosing and throughout the study.
    - Serotonin antagonists, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, gamma-aminobutyric acid antagonists, and N-methyl-D-aspartate receptor antagonists for 14 days prior to the first dosing and throughout the study.
    - Serotonin agonists for 28 days prior to the first dosing and throughout the study.

    Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/PD interaction with study drug.
13. Participant has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
14. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks of first dosing.
15. Has been on a diet incompatible with the on study- diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
16. Donation of blood or significant blood loss within 56 days prior to the first dosing.
17. Plasma donation within 7 days prior to the first dosing.
18. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study are:

The following safety parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period:

- Treatment emergent AE (TEAE) assessments.
- Vital signs.
- 12-lead ECG.
- Clinical laboratory testing (hematology, serum chemistry and urinalysis).

The following plasma PK parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period:

- AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
- AUC_{0-inf}: Area under the plasma concentration-time curve from time 0 to infinity.
- Ceoi: Observed plasma concentration at the end of infusion.
- CL: Clearance.
- Vz: Volume of distribution.

The following urine PK parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period

- Ae: Amount of drug excreted in urine.
- fe: Fraction of IV dose excreted in urine.
- CLR: Renal clearance.

The secondary endpoints will be assessed through evaluation of the following parameters:

The following PD parameters derived after a single dose of TAK-954 on Day 2 of each treatment period

- Time to first stool.
- Number of stools per day.
- Stool form (Bristol Stool Form Scale).

The exploratory endpoints will be assessed through evaluation of the following parameters:

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Statistical Considerations:

Safety:

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

Pharmacokinetics:

Individual TAK-954 CCI plasma and urine concentration data, as appropriate, and PK parameters will be listed by participant and treatment, and summarized by treatment (TAK-954 plasma concentrations and PK parameters) and nominal time (TAK-954 plasma concentrations).

Statistical analyses of additional plasma PK parameters may be performed, if appropriate.

Dose proportionality will be assessed graphically.

Pharmacodynamics:

Time to first stool, number of stools per day, and stool consistency (form) will be reported using descriptive and summary statistics.

Sample Size Justification:

Approximately 6 participants will be enrolled in this study. This sample size is based on empirical considerations and is considered adequate for the objectives of this study.

2.0 STUDY SCHEMATIC

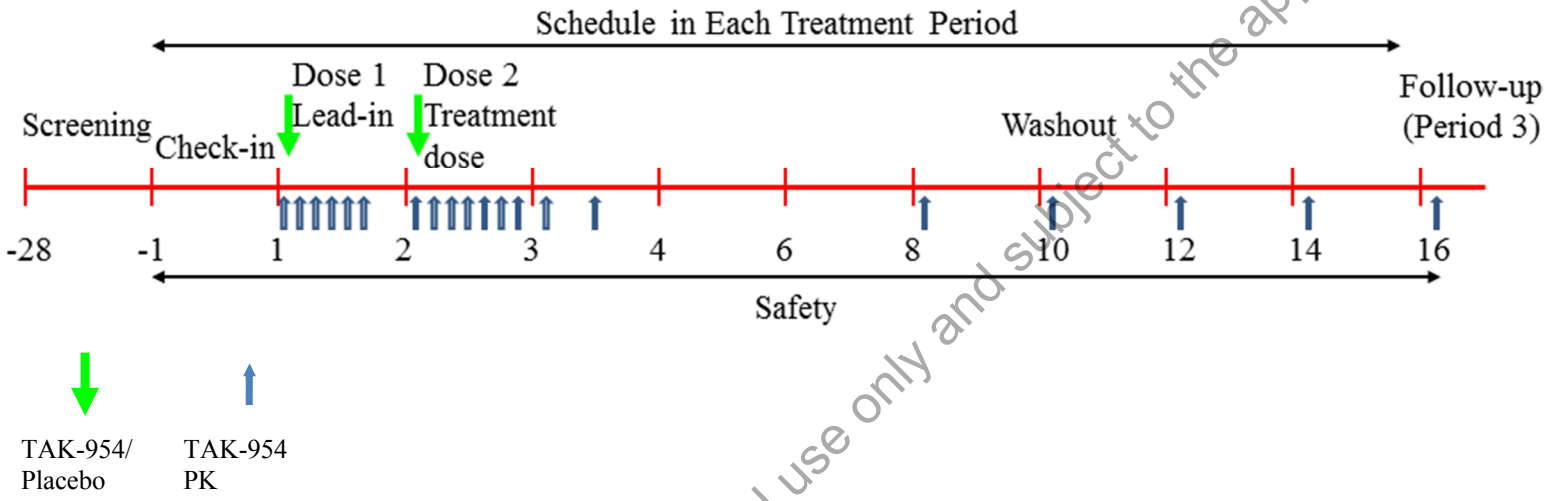
Pretreatment	**Treatment Periods 1-3**						
Screening	**Check-in and Predose Assessments**	**Lead-in Dose and Study Assessments**	**Treatment Dosing and Study Assessments**	**Safety and PK Assessments**		**Study Exit (a)**	**Follow Up (b)**
Within 28 days prior to first dosing	Day -1	Day 1	Day 2	Day 3	Days 4-16	Day 16 of Treatment Period 3	14 days after last dose
Outpatient Visit	◄- - - - - - - -	Confinement (a) (c)		- - - - - - - - ►		Outpatient Visits (c)	

(a) At all times, a participant may be required to remain at the clinical research unit for longer at the discretion of the Investigator or designee.

(b) Day 16 of Period 3 will also be considered as the follow-up visit for participants who complete the study. All participants who received at least 1 dose of study drug or placebo and withdraw from the study early will return for a follow-up visit 10-14 days after the last dose administration.

(c) Participants will start the confinement on Day -1 and be released from confinement after Day 3 study assessments are complete and will return to the study site for subsequent safety and PK assessments as per the scheduled of study procedures (Section 3.0); There will be a washout period of at least 16 days between the last dose in the previous period and the first dose of the next period.

Figure 2.a Schematic of Study Design



3.0 SCHEDULE OF STUDY PROCEDURES

3.1 Screening and Period 1

		Study Period 1 [b]																	
		Day -1	Day 1							Day 2								Day 3	
			Hours relative to start of infusion on Day 1							Hours relative to start of infusion on Day 2									
	Screening [a]	Check-in	Predose	0	1	1.083	1.25	3	9	Predose	0	0.5	1	2	4	6	12	24	36
Administrative Procedures																			
Informed Consent (including Future Biomedical Research)	X																		
Inclusion/Exclusion Criteria	X																		
Medical History	X																		
Prior/Concomitant Medication Review	X---------- Continuous ----------X																		
Clinic Procedures/Assessments																			
Full Physical Examination	X																		
Abbreviated Physical Examination		X																X	
Height	X																		
Weight	X																	X	
12-Lead ECG	X	X	X		X			X		X			X	X		X		X	
Orthostatic Vital Signs (HR, BP)	X	X			X			X		X			X	X		X		X	
Vital Signs (HR, BP)			X																
Vital signs (RR and T)	X		X							X								X	
TAK-954 / Placebo Administration				X							X								
Adverse Events Monitoring	X---------- Continuous ----------X																		
Laboratory Procedures/Assessments																			
Hematology, Chemistry [c], Urinalysis	X	X								X								X	
Serum FSH - if applicable	X																		
Urine Drug Screen	X	X																	

		Study Period 1 [b]																	
		Day -1	Day 1							Day 2								Day 3	
			Hours relative to start of infusion on Day 1							Hours relative to start of infusion on Day 2									
	Screening [a]	Check-in	Predose	0	1	1.083	1.25	3	9	Predose	0	0.5	1	2	4	6	12	24	36
Urine Alcohol Screen	X	X																	
HIV/Hepatitis Screen	X																		
Blood for DNA analysis (optional)					X[d]														
Serum Pregnancy Test (hCG) – Female Participants Only	X	X																	
Pharmacokinetic Evaluations																			
Blood for Plasma TAK-954 (C [redacted]) Cl			X		X[e]	X	X	X	X	X		X	X[e]	X	X	X	X	X	X
Urine for Urinary TAK-954 CC [redacted] l			X---------- Continuous [f] ----------X																
Pharmacodynamic Evaluations																			
Time to Onset of Defecation				X---------- Continuous ---------- X							X ---------- Continuous ---------- X								
Number of Stools per Day				X---------- Continuous ---------- X							X ---------- Continuous ---------- X								
Stool Form (Bristol Stool Form Scale)				X---------- Continuous ---------- X							X ---------- Continuous ---------- X								
Other																			
Confinement		X---------- Continuous ----------X																	
Visit and Return Visits	X																		

	Study Period 1				
	Day 8	**Day 10**	**Day 12**	**Day 14**	**Day 16**
	Hours relative to start of infusion on Day 2				
	144	**192**	**240**	**288**	**336**
Administrative Procedures					
Prior/Concomitant Medication Review	X---------- Continuous ----------X				
Clinic Procedures/Assessments					
12-Lead ECG	X	X	X	X	
Orthostatic Vital Signs (HR, BP)	X	X	X	X	
Adverse Events Monitoring	X---------- Continuous ----------X				
Pharmacokinetic Evaluations					
Blood for Plasma TAK-954 CCI	X	X	X	X	X
Other					
Visit and Return Visits	X	X	X	X	X

a. Within 28 days prior to the first study drug administration.

b. There will be a washout period of at least 16 days between the last dose in the previous period and the first dose of the next period.

c. Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to the serum chemistry sample is taken.

d. DNA sample should be obtained after dosing (or with the next scheduled blood draw) on randomized participants only.

e. To be performed at the end of infusion.

f. Urine will be collected at predose (spot sample) and from 0-12, and 12-24 hours postdose on Day 1 and from 0-12, 12-24, and 24-36 hours on Day 2.

3.2 Periods 2 and 3

	Study Periods 2 and 3 [a]																	
	Day -1	Day 1							Day 2								Day 3	
		Hours relative to start of infusion on Day 1							Hours relative to start of infusion on Day 2									
	Check-in	Predose	0	1	1.083	1.25	3	9	Predose	0	0.5	1	2	4	6	12	24	36
Administrative Procedures																		
Prior/Concomitant Medication Review	X---------- Continuous ----------																----------X	
Clinic Procedures/Assessments																		
Abbreviated Physical Examination	X																X	
Weight	X																X	
12-Lead ECG	X	X		X			X		X			X	X		X		X	
Orthostatic Vital Signs (HR, BP)	X			X			X		X			X	X		X		X	
Vital Signs (HR, BP)		X																
Vital signs (RR and T)		X							X								X	
TAK-954 / Placebo Administration			X								X							
Adverse Events Monitoring	X---------- Continuous ----------																----------X	
Laboratory Procedures/Assessments																		
Hematology, Chemistry [b], Urinalysis	X								X								X	
Urine Drug Screen	X																	
Urine Alcohol Screen	X																	
Serum Pregnancy Test (hCG) – Female Participants Only	X																	
Pharmacokinetic Evaluations																		
Blood for Plasma TAK-954 [CCI redacted])		X		X [c]	X	X	X	X	X		X	X [c]	X	X	X	X	X	X
Urine for Urinary TAK-954 [CCI redacted])		X---------- Continuous [d] ----------															----------X	

	Study Periods 2 and 3 [a]																
	Day -1	Day 1							Day 2							Day 3	
		Hours relative to start of infusion on Day 1							Hours relative to start of infusion on Day 2								
	Check-in	Predose	0	1	1.083	1.25	3	9	Predose	0	0.5	1	2	4	6	12	24	36
Pharmacodynamic Evaluations																	
Time to Onset of Defecation			X---------- Continuous ---------- X							X ---------- Continuous ---------- X								
Number of Stools per Day			X---------- Continuous ---------- X							X ---------- Continuous ---------- X								
Stool Form (Bristol Stool Form Scale)			X---------- Continuous ---------- X							X ---------- Continuous ---------- X								
Other																	
Confinement	X---------- Continuous ----------X																

	Study Periods 2 and 3 [a]					Follow-up (Day 16 of Period 3 / 10-14 days post last dose) / Early Term
	Day 8	Day 10	Day 12	Day 14	Day 16	
	Hours relative to start of infusion on Day 2					
	144	192	240	288	336	
Administrative Procedures						
Prior/Concomitant Medication Review	X---------- Continuous ----------X					
Clinic Procedures/Assessments						
Full Physical Examination						X
Weight						X
12-Lead ECG	X	X	X	X		X
Orthostatic Vital Signs (HR, BP)	X	X	X	X		X
Vital signs (HR, BP)						X
Vital signs (RR, and T)						X
Adverse Events Monitoring	X---------- Continuous ----------X					
Pharmacokinetic Evaluations						
Blood for Plasma TAK-954 CCI [redacted]	X	X	X	X	X	
Other						
Visit and return visits	X	X	X	X	X	

a. There will be a washout period of at least 16 days between the last dose in the previous period and the first dose of the next period.

b. Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to the serum chemistry sample is taken.

c. To be performed at the end of infusion.

d. Urine will be collected at predose (spot sample) and from 0-12, and 12-24 hours postdose on Day 1 and from 0-12, 12-24, and 24-36 hours on Day 2.

4.0 INTRODUCTION

4.1 Background

TAK-954 is a small molecule 5-hydroxytryptamine receptor 4 (5-HT4) agonist that exhibits prokinetic activity throughout the GI tract and is being developed for the treatment of disorders of reduced GI motility to accelerate GI recovery post-surgery (post-operative gastrointestinal dysfunction).

TAK-954 has been investigated in healthy participants at single oral doses from 0.1 to 20 mg, multiple oral doses from 0.2 to 10 mg QD for 10 days, a single IV infusion over 60 min of 0.2 mg in each of two periods in a crossover drug-drug interaction study and a single IV infusion of 0.1 mg followed by multiple doses of 0.5 mg for 3 days and multiple IV doses of 0.5 mg QD for 5 days. After single and multiple IV infusion dosing in healthy participants (0.2 mg and 0.1 single dose and 0.5 mg multiple doses over 1 hour), TAK-954 concentrations declined in a biphasic manner, with mean $t_{1/2}$ value of 22.6 hours, CL values of 7.17 L/h (119.5 mL/min) and Vz values of 230.37 L following single 0.2 mg dose. TAK-954 steady state was achieved by Day 3, with minimal accumulation of TAK-954 after multiple IV dosing of 0.5 mg. The increase in exposure from the 0.1 mg to 0.5 mg IV dose was approximately dose proportional, and the mean amount of TAK-954 excreted unchanged in urine on Day 5 ranged from 27.7% to 31.6%. A single IV dose of 0.5 mg TAK-954 has also been investigated in critically ill patients with enteral feeding intolerance and compared to metoclopramide. In patients who were critically ill and received 0.5 mg by IV infusion, the exposure was slightly less (C_{max} 5040 pg/mL and AUC_{0-24} 23,200 pg·h/mL) compared to that observed in healthy participants (C_{max} 6920 pg/mL and AUC_{0-24} 41,500 pg·h/mL) following administration of a single 0.5 mg IV infusion.

Clinical Safety

TAK-954 was generally well tolerated at doses of up to 10 mg (oral single dose) and multiple doses of up to 5 mg (orally for 10 days) or doses of 0.5 mg (IV for 5 days). No serious adverse events (SAEs) were reported across all Phase 1 studies. The most common AEs in participants receiving TAK-954 regardless of dose were headache, nausea, vomiting, diarrhea, and postural dizziness (IV dose only) with no clear exposure response. No clinically relevant trends in clinical laboratory data, physical examinations, or ECGs (including QT interval data) were observed after single or repeat oral or IV dosing. Although there were transient asymptomatic increases in heart rate associated with TAK-954 administration all events resolved spontaneously, none were considered clinically significant by the investigator, and a dose response was not evident. Adverse events associated with cardiovascular systems were dizziness, postural hypotension, and tachycardia. These were usually of short duration and resolved spontaneously. In the single ascending oral dose study, junctional rhythm was reported in 4 participants: 2 receiving 1 mg (isolated occurrences at 24 hours and 36 hours after dosing), and 2 receiving 20 mg (isolated occurrence at 24 hours and in 1 of the 2, multiple occurrences starting at 8 hours after dosing). ECGs were collected at the following time points: 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dosing. There appeared to be a lack of an obvious dose related effect, the findings were far removed from time to maximum concentration (1-2 hours postdose), and in 3 of the 4 participants

the finding was isolated to a single ECG time point. Dose escalation in the study was stopped at 20 mg, according to the protocol-specified stopping rules, because of the occurrence of two AEs of moderate orthostatic hypotension. In the multiple ascending oral dose study, no ECG findings of significance were reported in the first 3 cohorts (0.2 mg, 1 mg, and 5 mg, or placebo for 10 days). However, in Cohort 4 (10 mg), asymptomatic intermittent AV dissociation was reported in 2 of 3 participants. The two participants had bradycardia approximately 50 bpm at baseline. One hour after receiving the first dose of TAK-954, both participants developed intermittent AV dissociation. They both received additional doses on study day 2 before being discontinued from the study.

Refer to the Investigator's Brochure (IB) for detailed background information on TAK-954 [1].

4.2 Rationale for the Proposed Study

The IV formulation of TAK-954 was assessed at doses ranging from 0.1 to 0.5 mg with 0.5 mg for 5 days being the maximum IV dose investigated to date. TAK-954 was generally well tolerated.

This study will further explore the safety, tolerability, PD, and PK of IV doses of TAK-954 at higher dose levels to guide the selection of a supratherapeutic dose. This information is needed in order to design a future study investigating the potential of TAK-954 to prolong the QTc interval.

4.3 Benefit/Risk Profile

The doses of TAK-954 administered in this study are not anticipated to induce any potential risk or benefit to participants participating in this study, as the predicted exposure levels are expected to be lower than the exposure levels found safe and well tolerated following oral dose administration of TAK-945 (see Section 6.3.2).

The safety monitoring practices employed by this protocol (ie, AE questioning, 12-lead ECG, vital signs, orthostatic vital signs, clinical laboratory tests, and physical examinations) are adequate to protect the participants' safety and should detect all expected TEAEs. In addition, a lead-in dose on Day 1 will be administered prior to receiving the full dose on Day 2 in order to reduce postural hypotension adverse event. Based on the observation in a previous multiple dose IV study (Theravance 0095), AE's (moderate postural dizziness) seen on Day 1 after the 0.5 mg dose were not found when the Day 1 dose was reduced to 0.1 mg followed by 0.5 mg doses on Days 2 through 5.

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy participants enrolled in this study is the free medical tests received at screening and during the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

TAK-954 will be sufficiently safe and well-tolerated to permit continued clinical investigation.

5.2 Study Objectives

5.2.1 Study Primary Objectives

The primary objectives of the study are:

- To evaluate the safety and tolerability of single ascending IV doses of TAK-954.
- To evaluate the PK of single ascending IV doses of TAK-954.

5.2.2 Study Secondary Objective

The secondary objective of the study is:

- To evaluate the PD effect of single ascending IV doses of TAK-954 on the GI motility in healthy participants while in confinement.

5.2.3 Study Exploratory Objectives

CCI

[redacted]

5.3 Endpoints

5.3.1 Primary Endpoints

The primary endpoints of the study are:

The following safety parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period:

- TEAE assessments.
- Vital signs.
- 12-lead ECG.
- Clinical laboratory testing (hematology, serum chemistry and urinalysis).

The following plasma PK parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period:

- AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.

- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
- Ceoi: Observed plasma concentration at the end of infusion.
- CL: Total clearance after intravenous administration, calculated using the observed value of the last quantifiable concentration.
- Vz: Volume of distribution during the terminal disposition phase after intravenous administration, calculated using the observed value of the last quantifiable concentration.

The following urine PK parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period

- Ae: Amount of unchanged drug excreted in urine.
- fe: Fraction of IV dose excreted in the urine.
- CLR: Renal clearance.

5.3.2 Secondary Endpoints

The secondary endpoint includes:

The following PD parameters derived after a single dose of TAK-954 on Day 2 of each treatment period

- Time to first stool.
- Number of stools per day.
- Stool form (Bristol Stool Form Scale).

5.3.3 Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a double-blind, placebo-controlled, single ascending IV dose, 3-period, incomplete block design study to investigate the safety, tolerability and PK, and PD of TAK-954 at higher IV doses than those previously studied. In this Phase 1 study, healthy adult participants will attend a screening visit within 28 days prior to the first dose.

Participants will be randomized to one of 3 treatment sequences as detailed in the table below. In each sequence (see Section 9.1.1.1), each participant will receive 2 doses of the active drug (out of 3 evaluated dose levels) in an ascending order and 1 dose of placebo. A sample size of 6 participants is proposed based on empirical considerations.

On Day 1 of each period, each participant will receive a lead-in dose of 0.1 mg TAK-954 (if scheduled to receive a dose of active drug on Day 2 of that period as per the randomization schedule) or placebo (if scheduled to receive a placebo on Day 2 of that period as per the randomization schedule) as a 60-minute IV infusion. On Day 2 of each period, participants will receive either a single dose of 0.5 mg, 1 mg, or 2 mg TAK-954 or placebo as a 60-minute infusion as per the randomization schedule.

Safety will be assessed by monitoring for AEs, vital signs, orthostatic vital signs, ECGs, safety laboratory assessments, and physical examinations throughout each dosing period. Blood (for plasma) samples for assessment of TAK-954 concentrations will be collected at selected times from predose through to 9 hours after each lead-in dose (Day 1). Blood (for plasma) samples for assessment of TAK-954 concentrations will also be collected at selected times from predose through 336 hours (Day 16) after each Day 2 dose. Urine samples for assessment of TAK-954 concentrations will also be collected at selected times from predose through 36 hours (Day 3) after each Day 2 dose. CCI [redacted]. The time to first stool will be recorded following dosing on Day 1 until prior to dosing on Day 2 and following dosing on Day 2. The number of stools per day and stool form (Bristol Stool Form Scale) will be recorded following dosing on Day 1 until prior to dosing on Day 2, and for 36 hours following Day 2 dosing.

The last dose in the previous period and the first dose of the next period will be separated by a minimum of 16 days.

The starting dose of TAK-954 on Day 2 (Period 1) will be 0.5 mg, which is the highest dose previously used in a completed study following IV administration. Subsequent doses will be chosen based on emerging data; the currently proposed doses are 1 mg and 2 mg (see Table 6.a). Dose escalation to the next dose level (ie, next period) will not take place until the Investigator and the Sponsor have determined that adequate safety/tolerability from the previous period has been demonstrated to permit proceeding to the next dose level. Additional cohorts (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort. For dose escalation and stopping rules see Section 6.2.

Day 16 of Period 3 will also be considered as the follow-up visit for participants who complete the study. All participants who received at least 1 dose of study drug or placebo and withdraw from the study early will return for a follow-up visit, 10-14 days after the last dose administration.

Table 6.a Planned TAK-954 and Placebo Doses

	Dose	Infusion Duration
Lead-in	0.1 mg (100 mL x 0.001 mg/mL)	60 min
Treatment A	0.5 mg (100 mL x 0.005 mg/mL)	60 min
Treatment B (a)	1 mg (100 mL x 0.01 mg/mL)	60 min
Treatment C (a)	2 mg (100 mL x 0.02 mg/mL)	60 min
Placebo	100 mL	60 min

(a) The starting dose on Day 2 of Period 1 will be 0.5 mg, which is the highest dose previously used in a completed study following IV administration. Subsequent doses will be chosen based on emerging data; the currently proposed doses are 1 mg and 2 mg. Dose escalation to the next dose level (ie, next period) will not take place until the Investigator and the Sponsor have determined that adequate safety/tolerability from the previous period has been demonstrated to permit proceeding to the next dose level. Additional cohort(s) (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort. For dose escalation see Section 6.2.

6.2 Dose Escalation

A decision to proceed to the next higher dose administration (next period) will be made by the Investigator and Sponsor representative(s) who will review all pertinent blinded safety/tolerability (eg, physical examinations, vital signs assessments, orthostatic vital signs, 12-lead ECGs, clinical laboratory tests, and AEs) data through at least 10 days following Day 2 dosing in each period for at least 75% of participants from the current period and those from all previous periods, as applicable.

Additional cohort(s) (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

6.3 Rationale for Study Design, Dose, and Endpoints

6.3.1 Rationale of Study Design

A randomized, double-blind, placebo-controlled design has been selected to allow for unbiased analysis of safety and tolerability data following single doses. A lead-in dose on Day 1 will be administered prior to receiving the treatment dose on Day 2 in order to reduce postural hypotension adverse event. The starting treatment dose (Day 2) was selected to ensure the safety of the participants and is supported by previous clinical studies. The different dose levels will be studied in a dose escalation study design, in order to define doses that are anticipated to be safe. Dose escalation will be based on safety and tolerability from previous periods.

Participants will be randomized to treatment sequences to minimize assignment bias and a crossover design is used to reduce the residual variability as every participant acts as their own control. However, an incomplete block design where the 4 treatment (3 active and 1 placebo) will be randomized to 3-period instead of 4-period is proposed; all participants will receive placebo treatment but will be randomized to receive 2 out of 3 treatment dose (see Table 9.a). This will provide the same information as full design but in a shorter timeframe. As safety and tolerability is the primary endpoint, the study will be double-blinded.

6.3.2 Rationale for Dose

6.3.2.1 Starting Dose for This Study

The starting dose (Day 2) in Period 1 of this study is 0.5 mg IV, which is the maximum IV dose of TAK-954 reported from a completed study to date. Ongoing clinical studies (TAK-954-2003) have administered 1 mg infusion of TAK-954 over 60 min. Results for these studies are pending.

A lead-in dose of 0.1 mg will be administered on Day 1 for participants randomized to receive TAK-954 on Day 2 to alleviate moderate postural dizziness as reported in previous studies.

6.3.2.2 Maximum Dose/Exposure for This Study

The maximum tolerated oral doses of TAK-954 were 10 mg single dose, and 5 mg QD multiple doses for 10 days. Single oral doses of 20 mg were associated with moderate orthostatic hypotension (2 of 6 participants), and 2 of 3 participants with bradycardia at baseline discontinued multiple oral doses of 10 mg QD due to intermittent AV dissociation AEs that started approximately one-hour post dosing on first day. Currently, the highest dose being investigated for the inpatient use only is 0.5 mg administered IV QD for up to 10 days (TAK-954-2004). In addition, 1 mg is being investigated in Study TAK-954-2003.

Mean (standard deviation [SD]) TAK-954 exposure parameters (C_{max} and AUC), from oral and IV doses are presented in Table 6.b. Exposures predicted from regression of IV data (Studies Theravance 0095 and TAK-954-1004) are also shown in Table 6.b. Assuming dose proportional PK, the predicted C_{max} and AUC parameters for TAK-954 following the proposed maximum dose (2 mg IV) in this study are lower than those observed at oral doses associated with dose-limiting arrhythmia events.

Table 6.b Mean (SD) Actual and Predicted Exposure Parameters for TAK-954 after Oral and IV dosing

Route	Study	N	Dose/Regimen	C_{max} (ng/mL)	AUC (ng•h/mL)
Oral	Theravance 0060	6	10 mg single dose	94.4 (47.0)	1017 (327)[a]
		6	20 mg single dose	223 (60.0)	2462 (617)[a]
	Theravance 0061	6	5 mg QD (Day 1)	19.0 (8.2)	211 (n=2)[a]
		5	5 mg QD (Day 10)	27.7 (5.2)	387 (830)[b]
		3	10 mg QD (Day 1)	56.5 (20.3)	498 (n=1)[a]
		1	10 mg QD (Day 10)	64.6	796 [b]
IV	Theravance 0095	6	0.1 mg (Day 1)	1.2 (0.3)	15.3 (n=1)
	TAK-954-1004		0.2 mg single dose	2.64 (0.4)	28.6 (6.6)[a]
	Theravance 0095		0.5 mg (Day 1)	6.9 (2.1)	50.6 (5.4) [c]
	Not applicable	*Predicted*	*2 mg single dose*	*~28*	*~171*[a]
		Predicted	*3 mg single dose*	*~41*	*~255* [a]

a $AUC_{0\text{-inf.}}$
b AUCtau.
c AUClast.

6.3.3 Rationale for Endpoints

6.3.3.1 Safety Endpoints

The key safety endpoints are typical for Phase 1 studies and will be assessed through monitoring of adverse events, vital signs, orthostatic vital signs, ECGs, laboratory assessments and physical examinations.

6.3.3.2 Pharmacokinetic Endpoints

The pharmacokinetic endpoints are standard for this type of study.

6.3.3.3 Pharmacodynamic Endpoints

Time to onset of defecation, number of stools per day, and stool consistency (form) are indicators of GI transit.

6.3.4 Future Biomedical Research

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

6.3.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the primary assessment is safety, tolerability, and PK. The blood collection for plasma concentrations for TAK-954 are required to be collected as close to the scheduled times defined in this protocol as possible.

6.4 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The starting dose of TAK-954 on Day 2 will be 0.5 mg. Subsequent doses will be chosen based on emerging data; the currently proposed doses are 1 mg and 2 mg. Dose escalation to the next dose level (ie, next period) will not take place until the Investigator and the Sponsor have determined that adequate safety/tolerability from the previous period has been demonstrated to permit proceeding to the next dose level. Additional cohorts (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort. For additional details regarding dose escalation and stopping rules see Section 6.2.

6.5 Study Beginning and End/Completion

6.5.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of screening (ie, signing of the ICF) of the first participant.

6.5.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure (ie, Day 16 of Period 3 for participants who complete the study) as outlined in the Schedule of Study Procedures (Section 3.0). For a participant who received at least 1 dose of study drug or placebo and withdraw from the study early, the end of study is defined as the follow-up visit (ie, 10-14 days after the last dose administration).

6.5.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in Day 16 of Period 3 for the last participant in the study.

This time period may change in the event that the study is terminated early or the last participant is lost to follow-up, or if additional cohorts are enrolled to repeat a dose level or to study an interim dose level.

6.5.4 Definition of Study Discontinuation

In consultation with the Sponsor, Celerion reserves the right to terminate the study in the interest of participant welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.5.5 Criteria for Premature Termination or Suspension of the Study

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

- Study stopping rule for termination of the study (Section 6.2) is met.
- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for participants participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

6.5.6 Criteria for Premature Termination or Suspension of a Site

NA

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

7.1 Inclusion Criteria

1. Healthy, adult, male or female, 18--55 years of age, inclusive, at screening.
2. Body mass index (BMI) ≥18 and ≤ 32.0 kg/m^2, weighing ≥50 kg at screening.
3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, orthostatic vital signs, or ECGs, as deemed by the Investigator or designee.
4. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to the first dose and throughout the study, based on participant self-reporting.
5. For a male or female of childbearing potential, use an acceptable birth control method as indicated in Appendix D.
6. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of:
   - risk factors for Torsade de Pointes (eg, heart failure, unexplained syncope, cardiomyopathy, or family history of Long QT Syndrome);
   - family history of sudden death;
   - sick sinus syndrome, second or third degree AV block, myocardial infarction, pulmonary congestion, symptomatic or significant cardiac arrhythmia, prolonged QTcF interval, or conduction abnormalities;
   - cholecystectomy;

- orthostatic hypotension or orthostatic vital sign results at screening with a decrease in systolic >20 mmHg or decrease in diastolic >10 mmHg, and increase in pulse of >20 bpm.

7. Female participants with a positive pregnancy test or who are lactating.
8. Positive urine drug or alcohol results at screening or first check-in.
9. Positive results at screening for HIV, HBsA) or HCV.
10. Seated blood pressure is less than 100/60 mmHg or greater than 140/90 mmHg at screening.
11. QTcF interval is >450 msec (males and females) or has ECG findings deemed abnormal with clinical significance by the Investigator or designee at screening or first check-in including:
    - T wave forms which make accurate QT measurement difficult;
    - Absence of regular atrial or the presence of junctional rhythm;
    - Abnormal sinus rhythm (heart rate <55 bpm or >100 bpm);
    - PR interval >210 msec, or QRS complex >110 msec.
12. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to the first dosing and throughout the study. After randomization, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Acceptable birth control methods as described in Appendix D will be allowed.
    - Any drugs known to be significant inducers of CYP3A4 enzymes and/or P-gp, including St. John's Wort, for 28 days prior to the first dosing and throughout the study.
    - Serotonin antagonists, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, gamma-aminobutyric acid antagonists, and N-methyl-D-aspartate receptor antagonists for 14 days prior to the first dosing and throughout the study.
    - Serotonin agonists for 28 days prior to the first dosing and throughout the study.

    Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/PD interaction with study drug.
13. Participant has infrequent bowel movements (less than approximately once per day) within 30 days prior to first dosing.
14. Recent history of abnormal bowel movements, such as diarrhea, loose stools, or constipation, within 2 weeks of first dosing.
15. Has been on a diet incompatible with the onstudy- diet, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
16. Donation of blood or significant blood loss within 56 days prior to the first dosing.

17. Plasma donation within 7 days prior to the first dosing.
18. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After the randomization, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Acceptable birth control methods as described in Appendix D will be allowed.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case by- -case basis whether the participant may continue participation in the study.

All medications taken by participants during the course of the study will be recorded.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 7.a.

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

Category	Between Screening and Randomization (Days -28 to predose [Day 1])	Post-Randomization (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from 48 hours prior to first dosing in each period and throughout the period of PK sample collection in each Treatment period.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing [a]	Prohibited from 24 hours prior to first dosing in each period and throughout the period of PK sample collection in each Treatment period [a].
Nicotine	Prohibited from 3 month prior to first dosing	Prohibited until end of PK collection in Treatment Period 3.
Medications	See Sections 7.2 and 7.3	See Sections 7.2 and 7.3
Food substance		
Grapefruit/Seville orange	Prohibited from 14 days prior to first dosing	Prohibited until end of PK collection in Treatment Period 3.

[a] small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

When confined to the CRU, water will be allowed *ad libitum*. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period. Participants will fast overnight for at least 8 hours prior to each dose and will remain fasted until at least 4 hours postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, participants will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition, and will be taken at approximately the same time in each period.

7.4.2 Activity

Participants will remain seated or semi-reclined for the duration of the infusion and for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures. Participants will then resume normal activity.

However, should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down.

Specific measures will be taken to prevent the participant from missing a urine collection and/or defecation by strictly controlling and providing access to designated restrooms only. Participants will be asked to void prior to entering the shower.

Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Participant

Participants are free to withdraw from the study at any time for any reason.

In addition, participants may be withdrawn from the study by the investigator or designee for the following reasons:

- AEs;
- Positive urine drug or alcohol results;
- Positive pregnancy test;
- Difficulties in blood collection.

A participant may be withdrawn by the investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

7.6 Procedures for Discontinuation or Withdrawal of a Participant

The Investigator may discontinue a participant's study participation at any time during the study when the participant meets the study termination criteria described in Section 7.5. In addition, a participant may discontinue his or her participation without giving a reason at any time during the study. Should a participant'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 end-of-study or early termination as described in Section 3.0.

7.7 Participant Replacement

Discontinued participants may be replaced at the discretion of the Sponsor and the Investigator.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

TAK-954 0.1 mg or placebo will be administered as a single IV lead-in dose on Day 1 followed by a single IV dose of TAK-954, or placebo on Day 2 of each study period (as per randomization sequence). See Table 6.a and Table 9.a for detailed description of treatments and treatment sequences, respectively.

The TAK-954 will be supplied in sealed cartons containing 1 single-use vial. The vial contains solution for infusion. The drug product is prepared in the CRU pharmacy as an IV solution. The solution will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

A saline solution for IV infusion will be used as placebo for the study.

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

The Sponsor will supply sufficient quantities of TAK-954 to allow completion of this study.

Celerion will provide sufficient quantities of saline solutions to allow completion of the study. The same lot number will be used throughout the study.

The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied. All TAK-954 products will be prepared and labeled by licensed pharmacy staff according to the procedures outlined in the pharmacy manual.

8.1.3 Clinical Study Drug Blinding

This is a double-blind, placebo controlled study.

8.1.4 Randomization Code Creation and Storage

A computerized randomization scheme will be created by a Celerion statistician (who will not be involved in the analysis of the study data) and it shall be considered blinded (as per the following).

The randomization is available only to the CRU pharmacy staff that is preparing the drug who will not be involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, participants, or members of the staff responsible for the monitoring and evaluation of safety assessments.

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, case report forms (CRFs) signed by the Investigator, and the database is officially locked.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

One set of sealed envelopes containing the randomization code will be supplied to the Investigator or designee at the start of the study.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the participant or in the event of an interim analysis.

In the event of a medical emergency, it is requested that the Investigator or designee make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the Investigator or designee, for that participant only. In the event that the emergency is one, in which it appears that the other participants may be at imminent risk, the blind may be broken for all participants dosed at that dose level. The unblinding will be properly documented in the study file.

In all cases where the code is broken, the Investigator or designee should record the date and reason for code breaking.

At the end of the study, envelopes will be retained or destroyed according to site procedures unless specified otherwise by the Sponsor.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused TAK-954 study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the participants in non-technical terms. Participants will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Participants will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each participant will be assigned a unique identification number upon screening. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product.

Participants will be randomized to 1 of 3 treatment sequences in a 1:1:1 ratio. The sequences to be used in the randomization are detailed in Table 9.a below. Participants will receive placebo and 2 of the 3 TAK-954 doses.

Table 9.a Sequence Groups

	Period 1		Period 2		Period 3	
Sequence	Day 1 (Lead-in)	Day 2 (Treatment)	Day 1 (Lead-in)	Day 2 (Treatment)	Day 1 (Lead-in)	Day 2 (Treatment)
Sequence 1 (n=2)	Placebo	Placebo	TAK-954	Treatment B	TAK-954	Treatment C
Sequence 2 (n=2)	TAK-954	Treatment A	Placebo	Placebo	TAK-954	Treatment C
Sequence 3 (n=2)	TAK-954	Treatment A	TAK-954	Treatment B	Placebo	Placebo

If replacement participants are used, the replacement participant number will be 100 more than the original (eg, Participant No. 101 will replace Participant No. 1).

9.1.1.2 Study Drug Assignment

This is a 3-period, incomplete block design study. Participants will receive placebo and 2 of the 3 TAK-954 doses as detailed in Section 6.1.

9.1.2 Inclusion and Exclusion

Participants will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.2 and in Section 7.3. All medications taken by participants during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the investigator or designee and/or the Sponsor for reasons related to participant safety.

For this study, safety, tolerability and the collection of blood for plasma concentrations for TAK-954 is a critical parameter and are required to be collected as close to the scheduled times defined in this protocol as possible. During infusion, blood samples should be collected from the contralateral arm opposite the infusion site. -All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

9.2.1 Physical Examination

Physical examinations will be performed as outlined in the Schedule of Study Procedures (Section 3.0).

An abbreviated physical examination will include at the minimum, examination of respiratory, cardiovascular, and GI systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

Symptom-driven physical examinations may be performed at other times, if deemed necessary by the investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, orthostatic blood pressure and heart rate, will be measured as outlined in the Schedule of Study

Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with participants in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the investigator or designee.

For orthostatic vital signs (heart rate and blood pressure), participants should be seated and then stand upright prior to measurement of orthostatic vital signs, as per Celerion standard operating procedures.

Vital signs will be measured prior to Day 1 dosing of each period for the predose time point. At all other predose time points vital signs will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the investigator or designee.

ECGs will be performed with participants in a supine position. All ECG tracings will be reviewed by the investigator or designee.

ECGs will be measured prior to Day 1 dosing of each period for the predose time point. At all other predose time points vital signs will be measured within 2 hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Study Drug Administration

TAK-954 IV solution will be provided as described in Section 8.1.

Lead-in dose and drug treatments are described in Table 6.a.

The IV dose will be administered over approximately 60 minutes. The start and end time of the IV infusion will be recorded.

Hour 0 on Day 1 (Lead-in) will be defined as the start of IV infusion on Day 1. Hour 0 on Day 2 (Treatment) will be defined as the start of IV infusion on Day 2.

The pharmacy at the CRU will provide the IV dose ready for the 60 minute infusion in individual unit dose containers for each participant and for each study period, as per the randomization scheme (Table 9.a).

9.2.7 AE Monitoring

Participants will be monitored throughout the study for adverse reactions to the study formulations and/or procedures as described in Section 10.0.

9.2.8 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the investigator or designee.

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to the serum chemistry sample is taken.

Chemistry evaluations will consist of the following standard chemistry panel

Blood Urea Nitrogen	Sodium
Bilirubin (total and direct)	Potassium
Alkaline phosphatase	Chloride
Aspartate aminotransferase	Glucose
Alanine aminotransferase (ALT)	Creatinine *
Albumin	

* At screening, creatinine clearance will be calculated using the Cockcroft Gault formula.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen – Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone) – Amphetamines – Barbiturates – Benzodiazepines – Cocaine – Cannabinoids
HBsAg	
HCV	
Urine alcohol screen	
Serum pregnancy test (human chorionic gonadotropin [hCG])	

9.3 PK, PD, and Biomarkers Samples

Primary specimen collection parameters are provided in Table 9.b. Instructions for plasma, blood and urine samples processing and handling will be provided in a separate document(s).

Table 9.b Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-954 PK [redacted]	Blood	Plasma	Plasma sample for PK analysis	Mandatory
Blood for DNA analysis	Blood	DNA	Biomarker analysis	Optional
Urine sample for TAK-954 [redacted]	Urine	Urine	Urine sample for PK analysis	Mandatory

9.3.1 PK Measurements

All plasma and urine samples from all participants receiving active drug will be analyzed. Only the Day 2 predose and end of infusion (1 hour postdose) plasma samples will be analyzed from participants when receiving placebo treatment. No urine sample from participants receiving placebo will be analyzed.

The PK parameters of TAK-954 will be derived using non-compartmental analysis methods and will be determined from the concentration-time data for all evaluable participants. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times. A more detailed description will be given in the clinical pharmacology analysis plan (CPAP).

9.3.1.1 Plasma for PK Measurements

CCI

CCI

No PK parameters will be calculated for participants with detectable at 2 or fewer consecutive time points.

Individual and mean plasma concentration-time curves (both linear and log-linear) will be included in the final report.

Other PK parameters may be calculated, if deemed necessary, for the interpretation of the data. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the time windows indicated in Table 9.c will not be captured as a protocol deviation, as long as the exact time of dosing and the sample collection is noted on CRF.

Table 9.c Pharmacokinetics Sample Collection Time Window

Time window (minutes)	Nominal Sample Time
Up to 30 minutes prior to dose	Predose
±2	Immediately post start of infusion to 1.25 hours
±5	>1.25 hours to 6 hours
±10	>6 hours to 36 hours
±30	>36 hours

9.3.1.2 Urine for PK Measurements

CCI CCI

9.3.2 PD Measurements

The time to first stool and number of stools per day will be recorded. Stool samples will be collected and stool form (Bristol Stool Form Scale) will be assessed by the appropriate qualified clinic staff. Stool samples will not be stored and will be discarded following the recording of PD evaluations.

The following parameters derived following dosing on Day 1 until prior to Day 2 dosing and following dosing on Day 2 of each treatment period will be assessed:

- Time to first stool.
- Number of stools per day.
- Stool form (Bristol Stool Form Scale).

9.3.3 Biomarkers Measurements

Blood samples for DNA will be collected to identify biomarkers that are predictive of efficacy, resistance to and or safety of treatment with TAK-954 and for genotyping variations in genes encoding drug metabolizing enzymes (DME) or drug transporters that might be implicated in TAK-954 disposition.

All biomarkers samples collected will be stored by the Sponsor or bioanalytical facility for 15 years following the last dosing. Tubes will be identified with a barcode using an appropriate label. Samples will not be submitted to a public database. The sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses and PK and statistical analyses of the data will have access to the samples and /or the data that resulted from the analysis, if performed. By signing the ICF, participants agree to the possible future analysis of these samples. At any time, the participants can contact the clinical research unit (CRU) staff to requested destruction of the samples. Any additional research on these samples unspecified by this protocol will require approval from the participants.

9.3.4 Confinement

In each treatment period, participants will be housed on Day -1, at the time indicated by the CRU until after the 36-hour blood draw and/or study procedures on Day 3. Participants will return for study procedures as indicated in the Schedule of Study Procedures (Section 3.0).

At all times, a participant may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

As per site preference, participants may be confined throughout the washout period(s). If the washout period is exactly 14 days, Days 15 and 16 of Period 1 and/or Period 2 may occur on Days -1 and 1 of Period 2 and/or Period 3, respectively.

Day 16 of Period 3 will also be considered as the follow-up visit for participants who complete the study. All participants who received at least 1 dose of study drug or placebo and withdraw from the study early will return for a follow-up visit, 10-14 days after the last dose administration.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

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

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

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered 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 captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study participant, at a dose above that which is assigned to that individual participant according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the participant should be treated symptomatically.

10.1.1 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

NA

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the participant died, dosing with study medication had not yet started or dosing with study medication 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.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

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

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

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal liver function tests [LFTs]) will commence at the time the participant signs the informed consent. Routine collection of AEs will continue until the follow-up visit on Day 16 of Period 3 or 10-14 days following the last study drug administration for participants who withdraw from the study early. For participants who discontinue prior to the administration of study medication, AEs will be followed until the participant discontinues study participation.

10.2.8.2 Reporting AEs

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

All participants experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant

changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term;
- Start and end date and time;
- Pattern of AE (frequency);
- Severity/Intensity;
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]);
- Action taken with study drug;
- Outcome of event;
- Seriousness.

10.2.8.3 Reporting SAEs

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

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

A short description of the event and the reason why the event is categorized as serious;

- Participant identification number;
- Investigator's name;
- Name of the study medication(s);
- Causality assessment.

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

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

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

SAE Follow-Up

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

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

10.2.8.4 Reporting Special Interest AEs

NA

10.2.8.5 Reporting of Abnormal LFTs

If a participant is noted to have ALT or AST elevated >3 × upper limit of normal (ULN) on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF 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 participant 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 10.2.8.3. The investigator must contact the Medical Monitor for discussion of the relevant participant details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.8 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

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

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

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

All statistical analysis of the study will be performed using the statistical software, SAS version 9.3 or higher Details concerning the standards for precision, decimals, descriptive statistics will be in the Statistical Analysis Plan (SAP).

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

All participants who received at least one dose of the study drug (active or placebo) will be included in the safety evaluations.

11.1.1.2 PK Set

Samples from all participants will be assayed even if the participants do not complete the study. All participants who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

11.1.1.3 PD Set

All participants who received at least one dose of the study drug (active or placebo) and have at completed at least 1 PD sampling period and/or have at least 1 evaluable parameter will be included in the PD evaluations.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 Safety Analysis

All safety data will be populated in the individual CRFs and listed by participant.

Dosing dates and times (including beginning and end of infusion) will be listed by participant.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.3.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number of participants reporting the TEAE and the number of TEAEs reported. A by-participant AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

11.1.3.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of time of collection and a shift table describing out of normal range shifts will be provided.

11.1.3.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

11.1.3.4 ECGs

ECGs will be summarized by treatment and point of time of collection.

11.1.3.5 Other Safety Parameters

Physical examination findings will be presented in the data listings.

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be listed by participant.

11.1.4 PK Analysis

Descriptive statistics will be provided for the TAK-954 CCI [redacted] concentrations, as applicable, and PK parameters (plasma and urine) using appropriate summary statistics to be fully specified in the CPAP.

PK parameters for plasma concentrations will be calculated as described in Section 9.3.1.1 and for urine, as described in Section 9.3.1.2, respectively.

Dose proportionality will be assessed graphically.

11.1.5 PD Analysis

Descriptive statistics will be provided for time to first stool and number of stools per day using appropriate summary statistics to be fully specified in the SAP.

Stool form (using Bristol Stool Form Scale [Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997 Sep;32(9):920-4.Lewis and Heaton 1997]) will be listed.

11.2 Interim Analysis and Criteria for Early Termination

A blinded safety and tolerability assessment will be conducted by the Investigator and sponsor representative(s) prior to proceeding to the next higher dose level (next period) according to the dose escalation and stopping rules outlined in Section 6.2.

11.3 Determination of Sample Size

The sample size of 6 healthy male and female participants is empirical, was selected without statistical considerations, and is deemed adequate to meet the study objectives. Additional cohorts (approximately 6 participants per cohort) may be enrolled if it is deemed appropriate by the Investigator and the Sponsor to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 CRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be participant to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, participant medical records, informed consent documentation, and review of CRFs 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.

12.2 Protocol Deviations

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

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

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be participant 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 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 12.1.

13.0 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 International Conference on Harminsation (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 A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this 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 or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and participant informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

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

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRB or IEC and Sponsor.

13.2 Participant Information, Informed Consent, and Participant 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 ICF, participant authorization form (if applicable), and participant information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study. The ICF and the participant 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 ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the participant authorization form. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

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

The participant, or the participant'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 participant, or the participant's legally acceptable representative, determines he or she will participate in the study, then the ICF and participant authorization form (if applicable) must be signed and dated by the participant, or the participant's legally acceptable representative, at the time of consent and prior to the participant entering into the study. The participant or the participant'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 ICF and participant authorization (if applicable) at the time of consent and prior to participant 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 ICF, participant authorization form (if applicable), and participant information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed ICF, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

All revised ICFs must be reviewed and signed by relevant participants or the relevant participant'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 participant's medical record, and the participant should receive a copy of the revised ICF.

Participants who consented and provided a 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.

13.3 Participant Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the participant'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 participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process (see Section 13.2).

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

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the 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 clinical 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.

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with

this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study 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 Americas 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 study information. Once participants receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established participant screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the Sponsor.

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

13.4.3 Clinical Study Results Disclosure

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

13.5 Insurance and Compensation for Injury

Each participant in the study must be insured in accordance with the regulations applicable to the site where the participant 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 participants. Refer to the study site agreement regarding the Sponsor's policy on participant compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	PPD

14.1.2 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 participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 (R2) 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 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 Protocol Amendment 01 Summary of Changes

Rationale for Amendment No. 01

The purpose of this amendment is to update the protocol to update the period of PD assessments (time to onset of defecation, number of stool per day, and stool form) on Day 1 from predose only to following dosing on Day 1 until prior to dosing on Day 2, to allow assessment of the effect of the lead-in dose on GI transit. A clarification was also made to indicate that stool will be collected and stool form will be assessed by the appropriate qualified clinic staff.

In addition, the following changes were also applied:

- Addition of postdose ECG and orthostatic vital signs measurements.
- Removal of indication for infusion site assessments.
- Correction of discrepancy in the indication in inclusion criteria #3 between Section 1.0 Study Summary (under Criteria for Inclusion) and Section 7.1 – Inclusion Criteria.
- Correction of discrepancy in the primary endpoints between Section 1.0 – Study Summary (under Main Criteria for Evaluation and Analysis) and Section 5.3.1 – Primary Endpoints.
- Clarification of the restriction period for alcohol and xanthine and/or caffeine in Section 7.3 - Excluded Medications, Supplements, Dietary Products.
- Clarification of the arm from which blood sampling should be conducted during drug infusion.
- Update the PK sample collection deviation window to include specific deviation windows to different postdose sampling times.

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

14.1.5 List of Abbreviations

AE	Adverse event
Ae	Amount of drug excreted in urine
ALT	Alanine aminotransferase
AUC	Area under the concentration-time curve
AUClast	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration
AUC_{0-24}	Area under the concentration-time curve, from time 0 to the 24-hour time point
AUC_{0-inf}	Area under the concentration-time curve, from time 0 extrapolated to infinity
AV	Atrioventricular

BMI	Body mass index
bpm	Beats per minute
Ceoi	Concentration at end of infusion
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CLR	Renal clearance
cm	Centimeter
C_{max}	Maximum observed concentration
CPAP	Clinical pharmacology analysis plan
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome P450
ECG	Electrocardiogram
fe	Fraction of IV dose excreted in urine
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LFT	Liver function test
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
MTD	Maximum tolerated dose
NA	Not applicable
ng	Nanogram
P-gp	P-glycoprotein
PD	Pharmacodynamic(s)

pg	Picogram
PK	Pharmacokinetic(s)
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSARs	Suspected unexpected serious adverse reactions
t½	Apparent first-order terminal elimination half-life
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
USA	United States of America
Vz	Volume of distribution
WHO	World Health Organization

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA®. Drugs will be coded using the WHO drug dictionary.

15.1 CRFs (Electronic and/or Paper)

Completed CRFs are required for each participant who signs an informed consent.

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor on CD.

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

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

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

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the investigator with use of change and modification records of the CRFs. The Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the participant's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs 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.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, participant authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of CRFs, 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 participant's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor.

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

16.0 REFERENCES

1. TAK-954. Millennium Pharmaceuticals, Inc. Global Investigator Brochure. Edition 2.0, March 2018.
2. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997 Sep;32(9):920-4.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are participant 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 that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential participants, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each participant who participates in the study, and document the date of consent in the participant's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a participant authorization, then the investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, 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.

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

Appendix B Elements of the Participant Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the participant'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 participants involved in the study.
7. A description of the participant'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 participant may receive.
11. A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the participant or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the participant will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the participant or the participant'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 participant for participating in the study.
17. The anticipated expenses, if any, to the participant for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), participant's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the participant.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant otherwise is entitled, and that the participant or the

participant's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

20. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
21. A statement that the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.
22. A statement that results of DNA 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 participant's participation in the study may be terminated.
24. A written participant authorization (either contained within the ICF or provided as a separate document) describing to the participant the contemplated and permissible uses and disclosures of the participant's personal information (including personal health information) for purposes of conducting the study. The participant authorization must contain the following statements regarding the uses and disclosures of the participant's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer participants 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 medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that participants 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 participant's identity will remain confidential in the event that study results are published.

25. Female participants of childbearing potential (eg, nonsterilized, premenopausal female participants) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female participants of childbearing potential. If a participant is found to be pregnant during study, study drug will be discontinued and the investigator will offer the participant the choice to receive unblinded treatment information.
26. Male participants must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 90 days after the last dose of study drug. If the partner of the participant is found to be pregnant during the study, the investigator will offer the participant the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

- Assessment of the suitability of investigator for the 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 medication.
- 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 D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Animal studies for TAK-954 have demonstrated embryotoxicity and there is a lack of adequate reproductive toxicity data in humans. Given that TAK-954 did not exhibit genotoxic potential in the standard battery of genotoxicity assays and the terminal disposition phase half-life of TAK-954, the duration of contraception for 30 days is considered acceptable. This is in line with the Clinical Trials Facilitation Group "Recommendations related to contraception and pregnancy testing in clinical trials" [CTFG, 2014].

Females of reproductive potential, as well as fertile men and their partners who are female of reproductive potential, must agree to abstain from sexual intercourse or to use 2 highly effective forms of contraception from the time of giving informed consent, during the study, and for 30 days (females and males) following the last dose of study drug. An effective form of contraception is defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, double-barrier method (eg, synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel) or male partner sterilization.

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 postmenopausal 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.

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.

Pregnancy

If any subject is confirmed 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 30 days after the last dose should also be recorded following authorization from the subject's partner. A pregnancy notification form should be submitted within 24 hours of learning of the pregnancy.

If the female subject and/or female partner of a male subject agree 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.

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. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after the birth of the child will also be conducted.

The following procedures apply for contraception and pregnancy avoidance.

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:

- Non-Hormonal Methods:
  - Intrauterine device (IUD).
  - Bilateral tubal occlusion.
  - Vasectomised partner (provided that partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical assessment of the surgical success).
  - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the participant. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 30 days after last dose.
- Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, 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 ovulation1 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 shorter till she has been on contraceptive for 3 months;
    - oral.
    - Injectable.
    - Implantable.

28. Effective methods of contraception (there may be a higher than 1% failure rate) are:

- Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
- Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.

29. 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.

Reference:

Clinical Trials Facilitation Group, Recommendations related to contraception and pregnancy testing in clinical trials. Sep 2014.

Appendix E Detailed Description of Amendments to Text

Change 1. Update collection period of PD measurements on Day 1 from predose on Day 1 to following dosing on Day 1 through prior to dosing on Day 2.

The primary change occurs in Section 1.0 – Study Summary, under Study Design (last sentence in the fourth paragraph) and in Section 6.1 – Study Design (last sentence in the fourth paragraph).

Initial wording:	The time to first stool will be recorded postdose on Day 2 and number of stools per day and stool form (Bristol Stool Form Scale) will be recorded for 36 hours postdose on Day 2.
Amended or new wording:	The time to first stool will be recorded following dosing on Day 1 until prior to dosing on Day 2 and following dosing on Day 2. The number of stools per day and stool form (Bristol Stool Form Scale) will be recorded following dosing on Day 1 until prior to dosing on Day 2 and for 36 hours following Day 2 dosing.

Rationale for Change:

Extend the collection time for PD measurements on Day 1 to allow the assessment of the effect of the lead-in dose on GI transit time.

Other Sections Affected:

Section 3.1 – Screening and Period 1 and Section 3.2 – Periods 2 and 3 (under Section 3.0 - Schedule of Study Procedures).

Initial wording:

	(…)	**Study Period**								(…)
		Day 1							**Day 2**	
		Hours relative to start of infusion on Day 1							**Hours relative to start of infusion on Day 2**	
		Predose	**0**	**1**	**1.083**	**1.25**	**3**	**9**	**Predose**	
Pharmacodynamic Evaluations										
Time to Onset of Defecation		X								
Number of Stools per Day		X								
Stool Form (Bristol Stool Form Scale)		X								

Amended or new wording:

	(…)	**Study Period**							(…)
		Day 1						**Day 2**	
		Hours relative to start of infusion on Day 1						**Hours relative to start of infusion on Day 2**	
		Predose	**0**	**1**	**1.083**	**1.25**	**3**	**9**	**Predose**
Pharmacodynamic Evaluations									
Time to Onset of Defecation			X ---------- Continuous ----------X						
Number of Stools per Day			X ---------- Continuous ----------X						
Stool Form (Bristol Stool Form Scale)			X ---------- Continuous ----------X						

Section 9.3.2– PD measurements

Initial wording:	The following parameters derived after TAK-954 administration on Day 2 of each treatment period will be assessed:
Amended or new wording:	The following parameters derived following dosing on Day 1 until prior to Day 2 dosing and following dosing on Day 2 of each treatment period will be assessed:

Change 2. Addition of text to indicate that stool samples will be collected and stool form will be assessed by the appropriate qualified clinic staff, and that stool samples will not be stored and will be discarded following the recording of PD evaluations.

The primary change occurs in Section 9.3.2 – PD Measurements.

Amended or new wording:	The time to first stool and number of stools per day will be recorded. Stool samples will be collected and stool form (Bristol Stool Form Scale) will be assessed by the appropriate qualified clinic staff. Stool samples will not be stored and will be discarded following the recording of PD evaluations.

Rationale for Change:

Clarifies the stool collection, form assessment, and sample handling processes.

Change 3. Update of the PD analysis language to clarify that stool form assessments results will be listed, and no summary statistics will be conducted.

The primary change occurs in Section 11.1.5 - PD Analysis.

Initial wording:	Descriptive statistics will be provided for time to first stool, number of stools per day, and stool form using appropriate summary statistics to be fully specified in the SAP. Stool form (using Bristol Stool Form Scale [Lewis SJ, Heaton KW, 1997]) will be summarized by treatment and point of time of collection.
Amended or new wording:	Descriptive statistics will be provided for time to first stool and number of stools per day using appropriate summary statistics to be fully specified in the SAP. Stool form (using Bristol Stool Form Scale [Lewis SJ, Heaton KW, 1997]) will be listed.

Rationale for Change:

Due to the qualitative nature of the stool form assessment, summary statistics will not provide an added value for data interpretation.

Change 4. Addition of postdose ECG and orthostatic vital signs measurements.

The primary change occurs in Sections 3.1- Screening and Period 1 and Section 3.2– Periods 2 and 3.

Initial wording:

		Study Period															
		Day 1							**Day 2**								**Day 3**
		Hours relative to start of infusion on Day 1							**Hours relative to start of infusion on Day 2**								
		Pre dose	**0**	**1**	**1.083**	**1.25**	**3**	**9**	**Pre dose**	**0**	**0.5**	**1**	**2**	**4**	**6**	**12**	**24**	**36**
12-Lead ECG		X							X									
Orthostatic Vital Signs (HR, BP)	(…)								X			X	X		X		X	

	Study Period				
	Day 8	**Day 10**	**Day 12**	**Day 14**	**Day 16**
	Hours relative to start of infusion on Day 2				
	144	**192**	**240**	**288**	**336**
Orthostatic Vital Signs (HR, BP)	X	X	X	X	

Amended or new wording:

		Study Period 1 [b]																
		Day 1							Day 2									Day 3
		Hours relative to start of infusion on Day 1							Hours relative to start of infusion on Day 2									
		Pre dose	0	1	1.083	1.25	3	9	Pre dose	0	0.5	1	2	4	6	12	24	36
12-Lead ECG		X		X			X		X			X	X		X		X	
Orthostatic Vital Signs (HR, BP)	(…)			X			X		X			X	X		X		X	

	Study Period				
	Day 8	Day 10	Day 12	Day 14	Day 16
	Hours relative to start of infusion on Day 2				
	144	192	240	288	336
12-Lead ECG	X	X	X	X	
Orthostatic Vital Signs (HR, BP)	X	X	X	X	

Rationale for Change:
ECG and orthostatic vital signs measurements were added to improve the subjects' safety.

Other Sections Affected:
Section 9.2.5 - 12-Lead ECG (sentence added to the last paragraph).

Initial wording:	ECGs will be measured prior to Day 1 dosing of each period for the predose time point. At all other predose time points vital signs will be measured within 2 hours prior to dosing.
Amended or new wording:	ECGs will be measured prior to Day 1 dosing of each period for the predose time point. At all other predose time points vital signs will be measured within 2 hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

Change 5. Removal of indication for infusion site assessments.	
The primary change occurs in Section 9.2.6 – Infusion Site Evaluation.	
Initial wording:	9.2.6 – Infusion Site Reaction In monitoring AEs, special attention will be paid to potential infusion site reactions (ie, local tolerability). Infusion site reactions will be evaluated as outlined in the Schedule of Study Procedures (Section 3.0) and any abnormal findings will be reported as AEs.
Amended or new wording:	(section removed)
Rationale for Change: Infusion site reaction will be assessed as part of AE monitoring and not at schedule time points. As such, the section was removed.	
Other Sections Affected: Section 1.0– Study Summary, under Study Design (first sentence in the fourth paragraph) and Section 6.1 – Study Design (first sentence in the fourth paragraph).	
Initial wording:	Safety will be assessed by monitoring for adverse events (AEs), vital signs, orthostatic vital signs, electrocardiograms (ECGs), infusion site assessment, safety laboratory assessments, and physical examinations throughout each dosing period.
Amended or new wording:	Safety will be assessed by monitoring for adverse events (AEs), vital signs, orthostatic vital signs, electrocardiograms (ECGs), safety laboratory assessments, and physical examinations throughout each dosing period.

Change 6. Correction of discrepancy in Inclusion criteria #3 between Section 1.0 – Study Summary (under Criteria for Inclusion) and Section 7.1 – Inclusion Criteria.	
The primary change occurs in Section 7.1 – Inclusion criteria.	
Initial wording:	Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
Amended or new wording:	Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, orthostatic vital signs, or ECGs, as deemed by the Investigator or designee.

Rationale for Change:

Orthostatic vital signs are assessed as part eligibility assessments at screening and as such, the indication for orthostatic vital signs was added to Inclusion criteria #3 in Section 7.1 – Inclusion criteria to correct the discrepancy with the correct indication in Section 1.0 – Study Summary (under Criteria for Inclusion).

Change 7. Removal of physical examination from the primary endpoints in Section 1.0 – Study Summary (under Main Criteria for Evaluation and Analysis) to correct a discrepancy with Section 5.3.1 – Primary Endpoints.

The primary change occurs in Section 7.1 – Inclusion criteria.

Initial wording:	The following safety parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period: • Treatment emergent AE (TEAE) assessments. • Vital signs. • 12-lead ECG. • Clinical laboratory testing (hematology, serum chemistry and urinalysis). • Physical Examinations
Amended or new wording:	The following safety parameters of TAK-954 derived after a single dose of TAK-954 on Day 2 of each treatment period: • Treatment emergent AE (TEAE) assessments. • Vital signs. • 12-lead ECG. • Clinical laboratory testing (hematology, serum chemistry and urinalysis).

Rationale for Change:

Physical examinations are assessed as during the study but are not considered a primary endpoint and as such, was removed from the primary endpoints in Section 1.0 – Study Summary (under Main Criteria for Evaluation and Analysis) to correct the discrepancy with the correct indication in Section 5.3.1 – Primary Endpoints.

Change 8. Clarification of restriction period for alcohol and xanthine and/or caffeine post-randomization (Day 1) to Follow-up.

The primary change occurs in Section 7.3 - Excluded Medications, Supplements, Dietary Products (under Table 7.a).

Initial wording:

Category		Post-Randomization (Day 1) to Follow-Up
Alcohol	(…)	Prohibited in each period and throughout the period of PK sample collection in each Treatment period.
Xanthine and/or caffeine		Prohibited in each period and throughout the period of PK sample collection in each Treatment period.

Amended or new wording:

Category		Post-Randomization (Day 1) to Follow-Up
Alcohol	(…)	Prohibited from 48 hours prior to first dosing in each period and throughout the period of PK sample collection in each Treatment period.
Xanthine and/or caffeine		Prohibited from 24 hours prior to first dosing in each period and throughout the period of PK sample collection in each Treatment period.

Rationale for Change:

Clarify that the restriction period prior to first dose (i.e. 48 hours for alcohol and 24 hours for xanthine and/or caffeine) is applicable to each study period.

Change 9. Addition of language to clarify that during infusion, blood samples should be collected from the contralateral arm opposite the infusion site.

The primary change occurs in Section 9.2 - Clinical Procedures and Assessments (second paragraph).

Initial wording:	For this study, safety, tolerability and the collection of blood for plasma concentrations for TAK-954 is a critical parameter and are required to be collected as close to the scheduled times defined in this protocol as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.
Amended or new wording:	For this study, safety, tolerability and the collection of blood for plasma concentrations for TAK-954 is a critical parameter and are required to be collected as close to the scheduled times defined in this protocol as possible. During infusion, blood samples should be collected from the contralateral arm opposite the infusion site. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Rationale for Change:

For consistency in blood sample collection, it is clarified that during infusion, blood samples should be collected from the contralateral arm opposite the infusion site.

Change 10. Removal of the general deviation window (10%) for PK sampling with a table that includes different and more strict deviation windows based on the nominal sampling time.

The primary change occurs in Section 9.3.1.1 - Plasma for PK Measurements (last paragraph).

Initial wording: Other PK parameters may be calculated, if deemed necessary, for the interpretation of the data. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time from dosing will not be captured as a protocol deviation, as long as the exact time of dosing and the sample collection is noted on CRF.

Amended or new wording: Other PK parameters may be calculated, if deemed necessary, for the interpretation of the data. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the time windows indicated in Table 9.c will not be captured as a protocol deviation, as long as the exact time of dosing and the sample collection is noted on CRF.

Table 9.c Pharmacokinetics Sample Collection Time Window

Time window (minutes)	Nominal Sample Time
Up to 30 minutes prior to dose	Predose
±2	Immediately post start of infusion to 1.25 hours
±5	>1.25 hours to 6 hours
±10	>6 hours to 36 hours
±30	>36 hours

Rationale for Change:

Clarify and tighten the allowed deviation window for sample collection to guaranty a closer association between the nominal and actual sampling time.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	13-Mar-2019 20:20 UTC
	Clinical Science Approval	13-Mar-2019 20:21 UTC
	Clinical Pharmacology Approval	13-Mar-2019 23:07 UTC