Title: Randomized, Double-Blind, Placebo-Controlled, Three-Part Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects

NCT Number: NCT05567393

Protocol Approve Date: 23 September 2020

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

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

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

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Three-Part Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects

Study Identifier: TAK-951-1001

Compound: TAK-951

Date: 23 September 2020

Amendment Number: 4.0

Amendment History:

Date	Amendment Number	Amendment Type	All Sites
03 January 2019	Initial protocol	Not applicable	United States
11 April 2019	01	Substantial	United States
15 May 2019	02	Substantial	United States
28 June 2019	03	Substantial	United States
23 September 2020	04	Substantial	United States

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1.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc. (Takeda Global Research and Development‑United States)	**Compound:** TAK-951
Study Identifier: TAK-951-1001	**Phase:** 1
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Three-Part Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects.	

Study Design:

This is a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-951 in healthy subjects.

The study will consist of 2 parts:

- Part 1 is a first-in-human (FIH), randomized, double-blind, placebo-controlled, single-rising dose (SRD) study to assess the safety, tolerability, and PK of TAK-951 in healthy volunteers. Up to 13 cohorts may be enrolled. Subjects will be randomized to receive TAK-951 or matching placebo.
- Part 2 of the study has been removed in Protocol Amendment 04 dated 23 September 2020 CCI [redacted]
- Part 3 is a randomized, double-blind, placebo-controlled, multiple-rising dose (MRD) study. CCI [redacted]

Safety and tolerability will be assessed during all parts of the study through physical examination, including vital sign assessment, electrocardiogram (ECG)/telemetry, clinical laboratory assessments, collection of adverse events (AEs) and immunogenicity.

TAK-951 and matching placebo will be administered subcutaneously.

Study Primary Objective:

- Part 1
  - To characterize the safety (including immunogenicity) and tolerability of single subcutaneous (SC) doses of TAK-951 in healthy subjects.
- Part 3
  - To characterize the safety (including immunogenicity) and tolerability of multiple SC doses of TAK-951 in healthy subjects.

Study Secondary Objective

- Part 1
  - To characterize the PK of TAK-951 following single SC doses in healthy subjects.
- Part 3
  - To characterize the PK of TAK-951 following multiple SC doses in healthy subjects.

Study Exploratory Objectives

CCI [redacted]

CCI

Study Subject Population: Healthy volunteers aged 18 to 55 years, inclusive.

Planned Number of Subjects:	**Planned Number of Sites:**
Part 1: up to 104 Part 2: Has been removed from the study in Protocol Amendment 04. Part 3: up to 32	This study is planned on being conducted at one or more sites within the United States.
Dose Levels:	**Route of Administration:**
Part 1: TAK-951 SRD: starting dose 20 µg. Part 2: has been removed from the study in Protocol Amendment 04. Part 3: TAK-951 MRD: dose to be confirmed based on SRD results.	TAK-951
Duration of Treatment:	**Planned Study Duration:**
Part 1: 1 day. Part 2: Has been removed from the study in Protocol Amendment 04. Part 3: 5 days.	Total approximately up to 155 days. Part 1: screening, 28 days; treatment period, 1 day; follow-up, 14-32 days. Part 2: Has been removed from the study in Protocol Amendment 04. Part 3: screening, 28 days; treatment period, 5 days; follow-up, 14-32 days.

Main Criteria for Inclusion:

To be eligible for study participation, subjects must:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be a healthy male or WONCBP (woman of nonchildbearing potential) female subject aged 18 to 55 years, inclusive, at the screening visit.
4. Have a BMI ≥18 and ≤30.0 (kg/m^2) at the screening visit.
5. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug or invasive procedure.

Main Criteria for Exclusion:

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

1. The subject has participated in another investigational study within 4 weeks (or based on local regulations) before the screening visit. The 4-week window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the screening visit of the current study.
2. The subject is an employee of the sponsor or study site or immediate family member (eg, spouse, parent, child, sibling) of the sponsor or study site.
3. The subject has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
4. The subject has a known hypersensitivity or contraindication to any component of TAK-951.
5. The subject has a positive pregnancy test. Women of childbearing potential are not eligible for the study.
6. The subject is a lactating/nursing woman.
7. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody,

or HIV antibody/antigen, at the screening visit. Note: Subjects with positive hepatitis B virus or hepatitis C virus serology may be enrolled if quantitative reverse transcriptase-polymerase chain reaction for hepatitis B virus or hepatitis C virus RNA is negative.

8. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.
9. The subject is unable to refrain from or anticipates using all medications, including herbal medicines, beginning approximately 7 days before administration of the first dose of study drug throughout the study until 2 days after discharge.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is safety and tolerability as assessed through physical examinations, vital signs, ECG/telemetry, laboratory assessments, AEs, and immunogenicity.

The secondary endpoints will be assessed through evaluation of the following PK parameters on Day 1 in Parts 1 and 3, at steady state:

- Part 1: plasma PK parameters for TAK-951
  - Maximum observed plasma concentration (C_{max})
  - Area under the plasma concentration time curve from time 0 to infinity (AUC_{∞})
- Part 3: plasma PK parameters for TAK-951
  - C_{max} on Day 1.
  - Area under the plasma concentration-time curve during a dosing interval where tau (τ) is the length of the dosing interval ($AUC\tau$) on Day 1.

Statistical Considerations:

The primary, secondary, and exploratory endpoints will be analyzed in randomized subjects in Parts 1 and 3 who received at least 1 dose of study drug.

Safety analyses will be based on the safety analysis set. All safety data including AEs, vital signs, and ECG will be summarized using descriptive statistics. No formal statistical tests or inference will be performed for safety analyses. All summaries will be performed by pooled placebo within each part and by TAK-951 dose level.

The PK parameters of TAK-951 will be summarized by dose, cohort, day, and dosing regimen (as appropriate), using descriptive statistics. Dose proportionality will be assessed graphically (dose-normalized C_{max} and AUC versus dose); no formal statistical comparisons will be conducted.

Sample Size Justification:

For Parts 1 and 3, the chosen sample sizes are considered sufficient for evaluation of safety, tolerability, and PK. The study is not statistically powered to perform hypothesis testing in Parts 1 and 3.

1.1 Protocol Amendment 04 Summary of Changes

This document describes the changes in reference to the protocol incorporating amendment 04.

The primary reason for this amendment is to remove all references to Part 2 of the study to CCI [redacted]

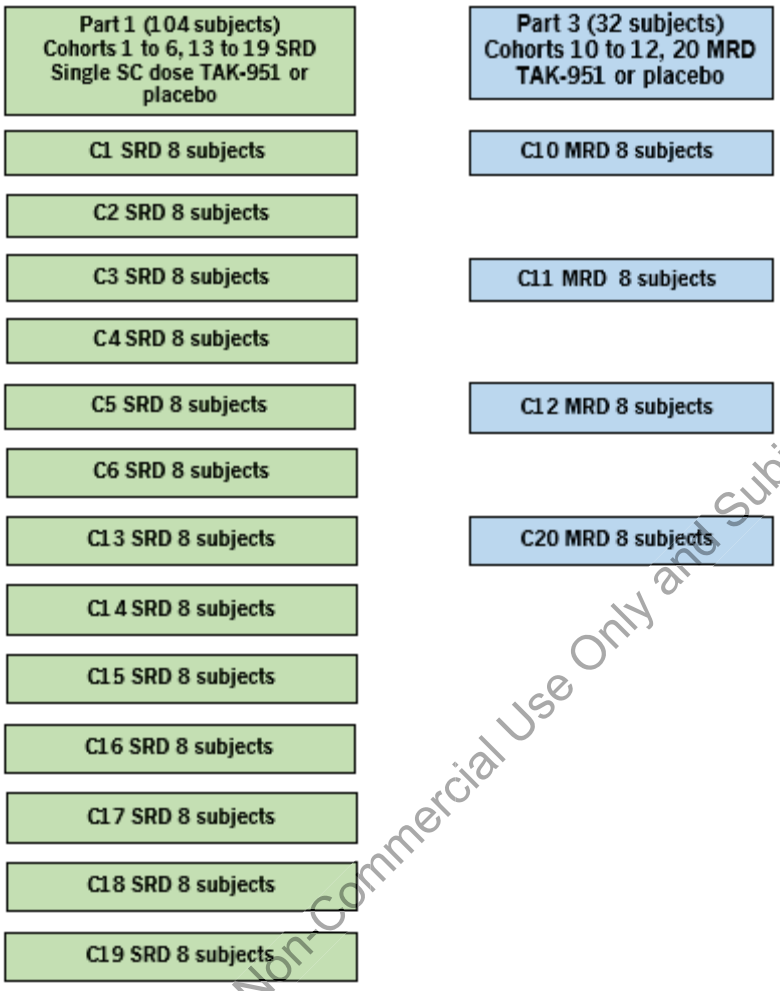
Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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

Changes in Amendment 04

1. Removed all references to Part 2 from the study.

2.0 STUDY SCHEMATIC



CCI intravenous; MRD: multiple-rising dose; SC: subcutaneous; SD: single dose; SRD: single-rising

Refer to Table 6.a for a full overview of treatment cohorts, including planned treatments.
Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

3.0 SCHEDULE OF STUDY PROCEDURES

3.1 Part 1 for SRD Cohorts 1 to 6 and 13 to 19

	Day			Scheduled Time																
	-28 to -2	-1		Day 1 (Hours)																
	Screening		Pre-dose	0	0.5	1	2	3	4	6	8	10	12	14	16	24	30 (discharge)	48 [a]	Follow-up Visit Day 14±2 days	Follow-up Visit Day 29 ±3 days	Early Termination
Administrative Procedures																				
Informed consent	X																			
Inclusion/exclusion criteria	X	X	X																	
Medical history/demographics	X																			
Prior and concomitant medication review	X	X----------Continuous Review----------X																		
Clinic Procedures/Assessments																				
Full physical examination	X	X														X				X
Height	X																			
Weight and BMI	X	X																		
TAK-951/placebo administration [b]				X																
Temperature and respiratory rate	X	X	X				X		X							X				
Blood pressure and pulse [c]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X
Standing blood pressure and pulse [d]		X	X		X		X		X		X					X				
12-lead ECGs	X	X														X				X
Telemetry			X----------Continuous Monitoring----------X																	
Holter monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
AE monitoring	X [e]	X----------Continuous Monitoring----------X																		X
Laboratory Procedures/Assessments																				
Safety laboratory collection (hematology and serum chemistry)	X	X	X						X							X				X
Urinalysis	X	X														X				X
Glucose finger stick			X					X					X							
Urine drug screen	X	X																		
Alcohol breath test		X																		
Cotinine test	X	X																		
Hepatitis screen [f]	X																			
HIV screen	X																			
βhCG (pregnancy) test [g]	X	X															X			X
Serum FSH test [h]	X																			
PK Evaluations																				
Blood sample for PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine sample for PK [i]			X	X					X		X		X		X					

	Day			Scheduled Time																
	-28 to -2	-1		Day 1 (Hours)																
	Screening		Pre-dose	0	0.5	1	2	3	4	6	8	10	12	14	16	24	30 (discharge)	48[i]	Follow-up Visit Day 14±2 days	Follow-up Visit Day 29 ±3 days	Early Termination
Biomarker Evaluations																				
CCI																				
Blood sample for ADA			X																X	X	X
CCI																				
Other																				
Confinement			X----------X																		

ADA: antidrug antibodies; AE: adverse event; anti-HC[redacted]n chorionic gonadotropins; BMI: body mass index; ECG: electrocardiogram; FSH: follicle-stimulating hormone; [redacted] HBsAg: hepatitis B surface antigen; [redacted]; PK: pharmacokinetic.

[a] Additional procedures may be performed at the investigator's discretion.

[b] Subjects will be administered a single dose of TAK-951 or matching placebo. Refer to Section 7.4.1 for further details.

[c] All blood pressure and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency between assessments. On Day -1, vital signs will be assessed at check-in and blood pressure will be assessed again postprandially (approximately ±60 min after lunch, 24 hours before the Day 1 scheduled lunch, based on postdose protocol requirements). At predose, vital signs will be measured within approximately 1 hour before dosing.

[d] Standing blood pressure and pulse will be performed on Day -1 (postprandial), Day 1 predose (approximately 1 hour before), and at 0.5, 2, 4, 8, and 24 hours after dosing to assess orthostatic blood pressure and pulse. For standing blood pressure and pulse assessment, a third blood pressure and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 2 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic blood pressure is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision) (Section 9.2.4).

[e] Collection of AEs will commence at the time the subject signs the informed consent form.

[f] Hepatitis panel, including HBsAg and anti-HCV.

[g] Serum pregnancy test for female subjects only.

[h] An FSH level will be obtained to assess postmenopausal status.

[i] Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-8, 8-12, 12-16, and 16-24 hours.

[j] CCI [redacted]

3.2 Part 2 has been removed from the study in Protocol Amendment 04

3.3 Part 3 for MRD Cohorts 10 to 12 and 20: Days 1 Through 5 and Early Termination

	Day-28 to -2	Day -1	Days									
			Dosing							Follow-up Visit Day 14±2 days	Follow-up Visit Day 29±3 days	Early Termination
	Screening		Predose	1	2	3	4	5	6 (Discharge)			
Administrative Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X	X	X									
Medical history/demographics	X											
Prior and concomitant medications	X----------Continuous review----------X											
Clinic Procedures/Assessments												
Full physical examination	X	X							X			X
Height	X											
Weight and BMI	X	X										
Vital signs [a]	X	X	X	X	X	X	X	X	X		X	X
12-Lead ECGs	X	X										
ECG telemetry/continuous blood pressure monitoring			X	X	X	X	X	X				
TAK-951/placebo administration [b]				X	X	X	X	X				
AE monitoring	X	X	X----------Continuous----------X									
Laboratory Procedures/Assessments												
Safety laboratory collection [c]	X	X	X	X	X	X	X	X	X			X
Glucose finger stick [d]			X	X	X	X	X	X				
Urine drug screen	X	X										
Alcohol breath test		X										
Cotinine test	X	X										
Hepatitis screen [e]	X											
HIV test	X											
βhCG (pregnancy) test [f]	X	X							X			X
Serum FSH test [g]	X											

	Day-28 to -2	Day -1	Days									
			Dosing							Follow-up Visit Day 14±2 days	Follow-up Visit Day 29±3 days	Early Termination
	Screening		Predose	1	2	3	4	5	6 (Discharge)			
PK Evaluations												
Blood sample for PK			X	X	X	X	X	X	X			X
Urine sample for PK			X	X				X				
Biomarkers												
CCI [redacted]												
Blood sample for ADA			X							X	X	X
CCI [redacted]												
Other												
Confinement [k]			X----------X									

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BMI: body mass index; ECG: electrocardiogram; FSH: follicle-stimulating hormone CCI [redacted] BsAg: hepatitis B surface antigen; CCI [redacted]; PK: pharmacokinetic.

[a] Vital signs will include body temperature, blood pressure, respiratory rate, and pulse. On dosing days, vital signs will be collected as described in Section 3.3.1 (Part 3 Day 1 Assessments), Section 3.3.2 (Part 3 Days 2 to 4 Assessments), and Section 3.3.3 (Part 3 Day 5 Assessments).

[b] Dosing regimen for TAK-951/placebo will be determined based on data from Part 1. Refer to Section 7.4.1 for further details.

[c] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters.

[d] Glucose finger stick at ~3 hours postdose on each day.

[e] Hepatitis panel, including HBsAg and anti-HCV.

[f] Serum pregnancy tests for female subjects only.

[g] An FSH level will be obtained to assess postmenopausal status.

[h] CCI [redacted]

[i] CCI [redacted]

	Day-28 to -2	Day -1	Days									
			Dosing							Follow-up Visit Day 14±2 days	Follow-up Visit Day 29±3 days	Early Termination
	Screening		Predose	1	2	3	4	5	6 (Discharge)			
CCI												

[j] CCI

[k] Subjects will be confined (Section 9.5.3).

3.3.1 Part 3 Day 1 Assessments

			Scheduled Time																		
	Day -28 to -2	Day -1	Day 1 (Hours)																		
	Screening		Pre dose	0	0.5	1	2	3	4	6	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24
Administrative Procedures																					
Informed consent	X																				
Inclusion/exclusion criteria	X	X	X																		
Medical history/demographics	X																				
Previous and concomitant medications		X----------Continuous review----------X																			
Clinic Procedures/Assessments																					
Full physical examination	X	X																			
Height	X																				
Weight and BMI	X	X																			
Temperature and respiratory rate	X	X	X				X		X												X
Blood pressure and pulse [a]	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X		X	X	X
Standing blood pressure and pulse [b]		X	X		X		X		X		X		X		X		X				X
12-lead ECGs	X	X					X								X						
ECG telemetry/ continuous blood pressure monitoring				X----------Continuous monitoring----------X																	
TAK-951/placebo administration				X								X									

			Scheduled Time																		
	Day -28 to -2	**Day -1**	**Day 1 (Hours)**																		
	Screening		**Pre dose**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**Pre dose 8**	**8**	**8.5**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**24**
AE monitoring	X----------Continuous review----------X																				
Laboratory Procedures/Assessments																					
Safety laboratory collection [c]	X	X	X														X				
Glucose finger stick			X					X													
Urine drug screen	X	X																			
Alcohol breath test		X																			
Cotinine test	X	X																			
Hepatitis screen [d]	X																				
HIV test	X																				
βhCG (pregnancy) test [e]	X	X																			
Serum FSH test [f]	X																				
PK Evaluations																					
Blood sample for PK [g]			X		X	X	X	X		X	X			X	X	X	X	X	X	X	X
Urine sample for PK			X	X						X			X					X		X	
Biomarkers																					
CCI [redacted]																					
Blood sample for ADA			X																		

			Scheduled Time																	
	Day -28 to -2	Day -1	Day 1 (Hours)																	
	Screening		Pre dose	0	0.5	1	2	3	4	6	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24
CCI [redacted]																					
Other																					
Confinement [j]		X----------																			----------X

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BMI: body mass index; ECG: electrocardiogram; FSH: follicle-stimulating hormone CCI [redacted] HBsAg: hepatitis B surface antigen; CCI [redacted]; PK: pharmacokinetic.

[a] All blood pressure and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency between assessments. On Day -1, vital signs will be assessed at check-in and blood pressure will be assessed again postprandially (approximately ±60 min after lunch, 24 hours before the Day 1 scheduled lunch, based on postdose protocol requirements). At predose, vital signs will be measured within approximately 1 hour before the first dose and 30 minutes before the second dose (ie, 8-hour TAK-951/placebo administration). All blood pressure and pulse assessments must be completed before PK blood sampling.

[b] Standing blood pressure and pulse will be performed on Day -1 (postprandial), Day 1 predose (approximately 1 hour before), and at 0.5, 2, 4, 8 (predose), 8.5, 10, 12, and 24 hours after dosing to assess orthostatic blood pressure and pulse. For standing blood pressure and pulse assessment, a third blood pressure and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 2 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic blood pressure is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision) (Section 9.2.4).

[c] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters.

[d] Hepatitis panel, including HBsAg and anti-HCV.

[e] Serum pregnancy tests for female subjects only.

[f] An FSH level will be obtained for postmenopausal women.

			Scheduled Time																	
	Day -28 to -2	Day -1	Day 1 (Hours)																	
	Screening		Pre dose	0	0.5	1	2	3	4	6	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24

[g] Blood sample for PK may be drawn 10 minutes before the second dose at 8 hours. The 24-hour sample on Day 1 is the same as the predose sample on Day 2. Only one sample will be collected.

[h] CCI [redacted]

[i] CCI [redacted]

[j]

3.3.2 Part 3 Days 2 to 4 Assessments

	Scheduled Time																		
	Days 2-4 (Hours)																		
	Pre dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**Pre dose 8**	**8**	**8.5**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**24**
Administrative Procedures																			
Previous and concomitant medications	X----------Continuous review----------X																		
Clinic Procedures/Assessments																			
Full physical examination																			
Temperature and respiratory rate	X				X		X												X
Blood pressure and pulse [a]	X		X	X	X	X	X	X	X		X	X	X	X	X		X	X	X
Standing blood pressure and pulse [b]	X		X		X		X		X		X		X		X				X
TAK-951/placebo administration [c]		X								X									
ECG telemetry/continuous blood pressure monitoring	X----------Continuous monitoring----------X																		
AE monitoring	X----------Continuous review----------X																		
Laboratory Procedures/Assessments																			
Safety laboratory collection [d]	X														X				
Glucose finger stick	X					X													
Pharmacokinetics Evaluations																			
Blood sample for PK [e]	X								X										
Biomarkers																			
Blood sample for ADA																			
Other																			
Confinement [f]	X----------X																		

AE: adverse event; ECG: electrocardiogram; PK: pharmacokinetic.

[a] All blood pressure and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency between assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose and 30 minutes before the

	Scheduled Time																	
	Days 2-4 (Hours)																	
	Pre dose	0	0.5	1	2	3	4	6	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24

second dose (ie, 8-hour TAK-951/placebo administration). All blood pressure and pulse assessments must be completed before PK blood sampling.

[b] Standing blood pressure and pulse will be performed at 0.5, 2, 4, 8 (predose), 8.5, 10, 12, and 24 hours after dosing to assess orthostatic blood pressure and pulse. For standing blood pressure and pulse assessment, a third blood pressure and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 2 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic blood pressure is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision, etc.) (Section 9.2.4).

[c] Follow-up doses should be given at the same time as on Day 1.

[d] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters.

[e] Trough sample will be collected before the first dose that day. Blood sample for PK may be drawn 10 minutes before dosing. The 24-hour sample on Day 1 is the same as the predose sample on Day 2. Only one sample will be collected.

[f] Subjects will be confined (Section 9.5.3).

3.3.3 Part 3 Day 5 Assessments and Early Termination

	Scheduled Time																					
	Day 5 (Hours)																					
	Predose	0	0.5	1	2	3	4	6	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24	Day 6 (Discharge)	Follow-up Visit Day 14±2 days	Follow-up Visit Day 29 ±3 days	Early Termination
Previous and concomitant medications	X----------Continuous review----------X																					
Clinic Procedures/Assessments																						
Full physical examination																				X			X
Temperature and respiratory rate	X				X		X												X	X			X
Blood pressure and pulse [a]	X		X	X	X	X	X	X	X		X		X		X		X	X	X	X			X
Standing blood pressure and pulse [b]	X		X		X		X		X		X		X		X				X				X
TAK-951/placebo administration [c]		X								X													
ECG telemetry/ continuous blood pressure monitoring	X----------Continuous---------- X																						
AE monitoring	X----------Continuous----------X																						
Laboratory Procedures/Assessments																						
Safety laboratory collection [d]	X														X					X			X
Glucose finger stick	X					X																	
βhCG (pregnancy) test [e]																				X			X
PK Evaluations																							
Blood sample for PK [f]	X		X	X	X	X		X	X			X	X	X	X	X	X	X	X	X			X
Urine sample for PK		X					X				X				X			X					
Biomarkers																							
[redacted]																							
Blood sample for ADA [g]																					X	X	X

	Scheduled Time																			
	Day 5 (Hours)																			
	Predose	0	0.5	1	2	3	4	6	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24	Day 6 (Discharge)	Follow-up Visit Day 14±2 days	Follow-up Visit Day 29 ±3 days	Early Termination
CCI [redacted]																							
Other																							
Confinement [J]	X----------																			X			

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; ECG: electrocardiogram; CCI [redacted] CCI [redacted] PK: pharmacokinetic.

[a] All blood pressure and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency between assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose and 30 minutes before the second dose (ie, 8-hour TAK-951/placebo administration). All blood pressure and pulse assessments must be completed before PK blood sampling.

[b] Standing blood pressure and pulse will be performed at 0.5, 2, 4, 8 (predose), 8.5, 10, 12, and 24 hours after dosing to assess orthostatic blood pressure and pulse. For standing blood pressure and pulse assessment, a third blood pressure and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 2 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic blood pressure is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision, etc.) (Section 9.2.4).

[c] Follow-up doses should be given at the same time as those given on Day 1.

[d] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters.

[e] Serum pregnancy tests for female subjects only.

[f] Blood sample for PK may be drawn 10 minutes before dosing.

[g] Biomarker samples for ADA testing will be taken at predose on Day 1, before discharge on Day 6, Day 14, and at follow-up visit Day 29 ±3 days. If ADAs are present, subjects may be asked to return for additional sample collections.

[h] CCI [redacted].

[i] CCI [redacted].

[j] Subjects will be confined (Section 9.5.3).

4.0 INTRODUCTION

4.1 Background

CCI [redacted]

TAK-951 has the potential to inhibit nausea and vomiting via neural pathways triggered by a variety of chemical agents and physiological signals, including the neurotransmitters dopamine, serotonin, and substance P.

4.2 Rationale for the Proposed Study

The purpose of this first-in-human (FIH) study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-951 in healthy subjects to support further development of TAK-951. The study will be conducted in 2 parts: single-rising doses (SRD) will be assessed in Part 1 and repeat dose administration will be assessed in Part 3. Part 2 has been removed from the study in Protocol Amendment 04, dated 23 September 2020.

4.3 Benefit-Risk Profile

This study represents the first study in humans with TAK-951.

The main purpose of this study in healthy subjects is to assess the safety and tolerability of TAK-951; as such, no clinical benefit is expected for study participants.

The antiemetic properties of TAK-951 have been demonstrated in different preclinical models of emesis in rodents, ferrets, and dogs. Based on the safety findings from nonclinical studies conducted with TAK-951 and human GIP infusion studies, the potential risks of TAK-951 include HR increase and decreased blood pressure. CCI [redacted], immunogenicity, and injection site reactions and more serious hypersensitivity reactions are always possible.

To minimize the risks to the subjects in this study, the sponsor considers the following measures to be appropriate: selecting TAK-951 doses with appropriate safety margins based on nonclinical study data; managing study eligibility criteria; prespecifying safety monitoring procedures, such as frequent blood pressure assessments that include orthostatic blood pressure measurements in Parts 1 and 3, telemetry, and Holter electrocardiogram (ECG); developing guidance for

investigators; and using a clinical study facility where close monitoring can be performed and rapid institution of appropriate care can be given when needed in a timely manner.

Subjects with a history of serious hypersensitivity to any medication or any component of TAK-951 formulation or with a history of significant multiple and/or severe allergies are excluded from this study. Subjects will be evaluated for the development of anti-drug antibodies (ADA) as part of the study. The potential risks related to heart rate (HR) increase, decreased blood pressure, and injection site reactions will be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical study.

In addition to the potential risks associated with study drug administration, there is minimal risk associated with study procedures, including scheduled periodic phlebotomy (limited to <500 mL). Overall, the potential risks associated with the study are considered reasonable and acceptable.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Study Primary Objective

- Part 1
  - To characterize the safety (including immunogenicity) and tolerability of single subcutaneous (SC) doses of TAK-951 in healthy subjects.
- Part 3
  - To characterize the safety (including immunogenicity) and tolerability of multiple SC doses of TAK-951 in healthy subjects.

5.1.2 Study Secondary Objective

- Part 1
  - To characterize the PK of TAK-951 following single SC doses in healthy subjects.
- Part 3
  - To characterize the PK of TAK-951 following multiple SC doses in healthy subjects.

5.1.3 Study Exploratory Objectives

CCI

[redacted]

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

- Parts 1 and 3
  - The primary safety endpoint of the study is safety and tolerability as assessed through physical examinations, vital signs, ECG/telemetry, laboratory assessments, AEs, and immunogenicity.

5.2.2 Secondary Endpoints

- Part 1: plasma PK parameters for TAK-951
  - Maximum observed plasma concentration (C_{max}).
  - Area under the plasma concentration time curve from time 0 to infinity (AUC_{∞}).
- Part 3: plasma PK parameters for TAK-951
  - C_{max} on Day 1.
  - Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval ($AUC\tau$) on Day 1.

5.2.3 Exploratory Endpoints

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of TAK-951 in healthy subjects.

The study will consist of 2 parts (see Table 6.a):

- Part 1 is a FIH, randomized, double-blind, placebo-controlled, SRD study to assess the safety, tolerability, and PK of TAK-951 in healthy volunteers. Up to 13 cohorts may be enrolled. Subjects will be randomized to receive TAK-951 or matching placebo.
- Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.
- Part 3 is a randomized, double-blind, placebo-controlled, multiple-rising dose (MRD) study. CCI [redacted]

TAK-951 and matching placebo will be administered subcutaneously. Any part of the study may not be conducted at the discretion of the sponsor. Safety will be assessed by monitoring for AEs, vital signs, ECG/telemetry, safety laboratory assessments after each dose and immunogenicity. Sampling times may vary based on emerging PK data, but the maximal number of samples or the maximum time point will not change.

An overview of treatment cohorts is presented in Table 6.a.

Table 6.a Overview of Treatment Cohorts

Cohort	Regimen	Treatment	
Part 1			
		TAK-951	**Placebo**
1	SRD	6	2
2		6	2
3		6	2
4		6	2
5		6	2
6		6	2
13		6	2
14		6	2
15		6	2
16		6	2
17		6	2
18		6	2
19		6	2
Part 3			
		TAK-951	**Placebo**
10	MRD	6	2
11		6	2
12		6	2
20		6	2

MRD: multiple-rising dose; SRD: single-rising dose.
Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

6.1.1 Part 1: SRD Cohorts 1 to 6 and 13 to 19

Part 1 will consist of up to 13 cohorts of 8 healthy subjects. Subjects in each cohort will be randomly assigned to receive a single dose of TAK-951 or placebo in a 3:1 ratio in a double-blind manner. Up to 104 healthy subjects will be randomized in Part 1.

Subjects from each cohort will be admitted into the study unit on Day -1 and will be dosed with TAK-951 or matching placebo on Day 1 after a minimum of 8 hours of fasting. Subjects will be confined for a minimum of 30 hours after dosing (can be discharged after the 30-hour PK sample) and may be confined for up to 48 hours postdose at the discretion of the investigator, if needed to ensure subject safety. After discharge, subjects will return to the study unit for additional assessments as indicated in the schedule of assessments (see Section 3.1). Blood samples for assessment of TAK-951 plasma concentrations will be collected up to 48 hours postdose. Urine will be collected up to 24 hours post TAK-951 dose.

Based on agreement between the investigator and sponsor, a staggered dosing approach may be used for cohorts in Part 1. After dosing the first 2 subjects of each cohort (1 receiving TAK-951

and 1 receiving placebo) the investigator will review all available safety and tolerability data before dosing the remaining subjects in the cohort. The investigator will also consult Takeda as needed at any time.

CCI [redacted] Doses may be subject to change based on emerging PK and safety data. The sponsor may decide to administer lower doses, repeat doses, and cancel or add cohort(s) if deemed necessary. Subjects who drop out of the study for nonsafety reasons may be replaced at the discretion of the sponsor after discussion with the investigator.

After completion of each dosing cohort, and before selecting the next evaluable dose, a fully blinded assessment of the safety and tolerability, laboratory results of at least 24 hours, and available PK data will be performed by the site and select sponsor safety team.

Following each fully blinded dose cohort review, while the site personnel and study subjects will remain blinded to study drug assignment, the sponsor and select sponsor representatives may be unblinded to the completed cohort treatments. Precautions will be taken not to unblind the study staff, including the investigator and the subject, until the study is completed. The blind may be broken before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns.

Study Drug Administration

In Part 1, all attempts should be made to administer the single SC dose of TAK-951 in the abdomen. In all cases, care should be taken to avoid areas of scars or moles. TAK-951 must not be administered into an area where the skin appears to be tender to touch, signs of bruising/bleeding are noted, or the area seems indurated or erythematous. When locating injection sites on the abdomen, avoid giving the injection in the umbilicus, ribs, hip bone. For additional information on study drug administration, please refer to the study pharmacy manual.

6.1.2 Part 2

Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

6.1.3 Part 3: MRD Cohorts 10 to 12 and 20

Part 3 may start before the completion of Part 1. If Part 3 is started before the completion of Part 1, the starting dose in Part 3 will be at a dose level below that currently being studied in Part 1. Similar to Part 1, a staggered dosing approach may be used for cohorts in Part 3. Site personnel and study subjects will be blinded to study drug assignment, but selected sponsor vendors (third-party open) may be unblinded (Section 6.1.1). Part 3 consists of up to 4 sequential ascending cohorts of healthy subjects. In each cohort, 8 healthy subjects will be randomly assigned to receive TAK-951 or matching placebo in a 3:1 ratio in a double-blind manner. Up to 32 healthy subjects may be randomized in Part 3.

Subjects will be admitted to the study unit on Day -1 and will be dosed on Day 1 in each cohort/period after a minimum of 8 hours of fasting. Subjects will be confined until Day 6,

30 hours after last dose on Day 5 to assess safety, tolerability, and PK. Subjects will return after discharge for additional assessments as indicated in the study flow chart.

In Part 3, CCI safe and tolerable doses from Part 1 CCI [redacted] will be studied in an ascending manner. Based on emerging PK data from Part 1, adjustments to dose and to repeat dosing duration may be implemented. CCI [redacted] The schedule of assessments for Part 3 can be found in Section 3.3.

After completion of each dosing cohort, and before selecting the next evaluable dose, a fully blinded assessment of the safety and tolerability, laboratory results of at least 24 hours, and available PK data will be performed by the site and select sponsor safety team.

Following each fully blinded dose cohort review, while the site personnel and study subjects will remain blinded to study drug assignment, the sponsor and select sponsor vendors (third-party open) may be unblinded to the completed cohort treatments. Precautions will be taken not to unblind the study staff, including the investigator and the subject, until the study is completed. The blind may be broken before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns.

Subjects who drop out may be replaced at the discretion of the sponsor after discussion with the investigator.

Study Drug Administration

In Part 3, when administering TAK-951, injection sites must be rotated. All attempts should be made to administer the single SC dose of TAK-951 in the abdomen first, followed by upper arms, then thigh as alternative sites, avoiding areas of scars or moles. If repeat injections of TAK-951 are given in the same spot, this may cause scarring and hardening of fatty tissue, which may interfere with the absorption of the drug; if feasible, injections should not be given at the same location repeatedly. Each TAK-951 injection must be administered approximately 2 inches (5 centimeters) apart and must not be administered into an area where the skin appears to be tender to touch, signs of bruising/bleeding are noted, or the area seems indurated or erythematous. If locating injection sites on the abdomen, avoid giving the injection in the umbilicus, ribs, hip bone. If injecting in the thighs, use the outer areas, below the groin and above the knee. For additional information on study drug administration, please refer to the study pharmacy manual.

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale of Study Design

A randomized, double-blind, placebo-controlled design for Part 1 is considered adequate to characterize the safety, tolerability, and PK of single doses of TAK-951.

Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

Part 3 of the study is a randomized, double-blind, placebo-controlled, sequential panel MRD study CCI [redacted] studied under repeat dose conditions.

6.2.2 Rationale for Dose

6.2.2.1 TAK-951

The starting dose for this FIH study is 20 µg and is based on the rationale detailed below.

FIH Starting Dose Consideration Based on Nonclinical Safety Study Results

The principle of the Food and Drug Administration (FDA) Guidance "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" is to use a 10-fold safety factor on the no-observed-adverse-effect-level (NOAEL) from nonclinical data to identify a starting clinical dose.

For TAK-951, NOAELs were identified in the 2-week Good Laboratory Practice (GLP)-compliant, repeat-dose toxicity studies, and no-observed-effect-levels (NOELs) were identified in the respiratory and central nervous system safety pharmacology studies. [redacted]

However, cardiovascular effects in dogs were the principal finding in the safety pharmacology studies. In this study, the lowest dose [redacted] TAK-951 produced a transient increase in HR and a transient decrease in blood pressure, and a NOEL was not identified. By comparison, there were no effects on cardiovascular parameters in cynomolgus monkeys [redacted]

Given the reversible nature of the cardiovascular changes, variable effects between species, and the lack of other significant safety findings, the [redacted] TAK-951 dose is not anticipated to result in adverse effects. [redacted]

[redacted]

CCI

[redacted]

Summary of FIH Starting Dose Consideration

In summary, given the totality of these findings from nonclinical safety, published literature and preclinical pharmacology, the proposed starting dose is CCI

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

Rationale for Dosing Interval

CCI [redacted]

The dosing regimens selected for Part 3 will have a projected AUC CCI [redacted] above for Part 1.

6.2.3 Starting Dose for This Study

Refer to Section 6.2.2.

6.2.4 Rationale for Endpoints

The PK and safety endpoints are standard for this type of study and are used widely and are recognized as reliable, accurate, and relevant. Additional PK parameters may be calculated if deemed necessary for the interpretation of the data.

6.2.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the following procedures are critical:

Parts 1 and 3:

- Timing of PK, blood pressure, and Holter assessments (Holter assessments in Part 1 only).

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

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

This is a phase 1 study of TAK-951 in humans, and the PK and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures, as outlined below, may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study subjects.

As such, the following alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily exposure, may not exceed that currently outlined in Section 6.2.2:

- The duration of study drug administration (eg, number of days) in the study may be decreased.
- In Parts 1 and 3, the dose of study drug administered may be repeated or decreased in subsequent cohorts.
- In Part 3, the dosing interval may be adjusted in subsequent cohorts CCI [redacted] based on available PK data. The total exposure, however, will not exceed 2590 h*ng/mL (Table 6.a).
- Instructions to take study drug with or without food or drink may be modified based on newly available data.
- The PK sampling scheme may be modified during the study based on newly available PK data (eg, to obtain data closer to the time of first occurrence of C_{max}). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional markers.
- Up to an additional 49 mL (never more than 50 mL) of blood may be drawn for PK analyses. This blood volume may include repeat samples or modified PK time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire study.
- The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECGs, safety laboratory tests) may be modified during the study based on newly available safety, tolerability, and PK (eg, to obtain data closer to the time of first occurrence of C_{max}). These

changes will not increase the number of study procedures for a given subject during his/her participation in the entire study.

- Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information.

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the sponsor in a letter to the study file and forwarded to the investigator for retention.

6.4 Study Beginning and End/Completion

6.4.1 Definition of Beginning of the Study

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

6.4.2 Definition of End of the Study

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

6.4.3 Definition of Study Discontinuation

Study discontinuation because of nonsafety reasons, such as the following:

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

Study discontinuation because of safety reasons:

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

6.4.3.1 Criteria for Premature Termination or Suspension of Study

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

6.4.3.2 Procedures for Premature Termination or Suspension of the Study

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

6.4.4 Criteria for Premature Termination or Suspension of a Site

6.4.4.1 Criteria for Premature Termination or Suspension of a Site

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

6.4.4.2 Procedures for Premature Termination or Suspension of a Site

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

6.4.5 Stopping Rules

The safety assessments will provide measures of safety and tolerability of TAK-951 following each single and/or multiple dose regimen.

If notable AEs or safety concerns are found at one of the planned TAK-951 dose levels, the principal investigator and/or the sponsor may pause the dosing for safety review and consider potential changes in the next planned dose level. Possible changes in dose administration include, but are not limited to:

- Administration of an intermediate dose between the current and next planned dose.
- Repeated administration of the current dose.
- Administration of a lower dose than the existing dose levels.
- Study termination.

Notable AEs include:

- Any SAE.
- Any TAK-951 related Grade 3 or higher AE (CTCAE version 5.0).

Furthermore, the principal investigator and the sponsor may also consider the number and/or severity of AEs as consideration to pause dosing or to discontinue the study.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including laboratory test results, need to be confirmed before the first dose of study drug as outlined in the Schedule of Study Procedures in Section 3.0.

7.1 Inclusion Criteria

The subject must understand the study procedures and agree to participate by providing written informed consent. The subject must be willing and able to comply with all study procedures and restrictions.

To be eligible for participation in this study, the subject must:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be a healthy male or WONCBP (woman of nonchildbearing potential) female subject aged 18 to 55 years, inclusive, at the screening visit.
4. Have a BMI ≥18 and ≤30.0 (kg/m^2) at the screening visit.
5. Be judged to be in good health (eg, no evidence of psychiatric, hepatic, renal, pulmonary, or cardiovascular disease) by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug or invasive procedure.
6. Meet the following birth control requirements:
   - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from the first dose of study drug until 5 half-lives after the last dose of study drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1 year after bilateral vasectomy procedure before the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year before the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
   - Is a male subject who agrees to not donate sperm from the first dose of study drug until 5 half-lives after the last dose of study drug.
   - Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
     - Postmenopausal (defined as 12 -months of spontaneous amenorrhea in females aged >45 years or 6 months of spontaneous amenorrhea in females aged >45 years with serum follicle-stimulating hormone (FSH) levels >40 mIU/mL). Appropriate documentation of FSH levels is required.

- Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
- Had a tubal ligation with appropriate documentation of surgical procedure.
- Has a congenital condition resulting in no uterus.

7.2 Exclusion Criteria

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

1. The subject has participated in another investigational study within 4 weeks (or based on local regulations) before the screening visit. The 4-week window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the screening visit of the current study.
2. The subject is an employee of the sponsor or study site or immediate family member (eg, spouse, parent, child, sibling) of the sponsor or study site.
3. The subject has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
4. The subject has a known hypersensitivity or contraindication to any component of TAK-951.
5. The subject has a positive pregnancy test. Women of childbearing potential are not eligible for the study.
6. The subject is a lactating/nursing female.
7. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody/antigen, at the screening visit. Note: Subjects with positive hepatitis B virus or hepatitis C virus serology may be enrolled if quantitative polymerase chain reaction for hepatitis B virus or hepatitis C virus ribonucleic acid is negative.
8. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.
9. The subject is unable to refrain from or anticipates using all medications including herbal medicines beginning approximately 7 days before administration of the first dose of study drug, throughout the study until 2 days after discharge.
10. Heavy consumption of alcohol within 3 months before screening (>7 drinks/week for women, >14 drinks/week for men, where 1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) or use of soft drugs (such as marijuana) within 3 months before screening, or hard drugs (such as cocaine and phencyclidine) within 1 year before screening.

11. The subject has used nicotine-containing products (including, but not limited to, cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 28 days before check-in (Day -1) or cotinine test is positive at screening or Day -1.
12. The subject has a substance abuse disorder or has a positive urine drug results for drugs of abuse at screening or Day -1.
13. The subject has had 3 incidences of vasovagal syncope within the last 5 years.
14. Subject with previous major psychotic disorder.
15. The subject has had family history of unexplained sudden death or channelopathy.
16. The subject has any clinically significant ECG findings including: long or short QT interval with Fridericia correction method (QTcF) (over 450 msec or less than 360 msec), second-degree atrioventricular (AV) block type 2, third-degree AV block, bifascicular block or QRS ≥0.12 at screening or admission.
17. The subject has Brugada syndrome (RBBB pattern with ST-elevation in leads V1-V3).
18. The subject has a documented history of sinus bradycardia (<45 bpm), sinoatrial block or sinus pause ≥3 seconds.
19. The subject has a documented history of any clinically significant disorders, including psychiatric, cardiovascular, nephrological, neurological, metabolic, and gastrointestinal disease including prior cholecystectomy.
20. The subject has an average semirecumbent systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg at screening or admission.
21. The subject has an average HR <60 or >100 bpm (at screening, at Day -1, or at predose); athletic subjects with an average HR <60 bpm can be enrolled only with medical monitor approval.
22. The subject has orthostatic hypotension defined as a decrease in systolic blood pressure ≥20 mm Hg or a decrease in diastolic blood pressure ≥10 mm Hg after 2 minutes of standing when compared with blood pressure from the sitting position at screening, and at Day -1. Subjects with postural orthostatic tachycardia, defined as HR >120 bpm standing, will also be excluded.

7.3 Excluded/Allowed Concomitant Medications, Supplements, Dietary Products

7.3.1 Concomitant Medications

The use of concomitant medications approximately 7 days before administration of the first dose of study drug, throughout the study until 2 days after discharge is not permitted. Subjects must be instructed not to take any medications without first consulting with the investigator. Any concomitant medication use must first be discussed with the sponsor, unless the investigator or designee considers immediate administration is necessitated.

The occasional use of acetaminophen (approximately <1 g/day) is allowed.

7.3.2 Fruit Juice

Subjects will refrain from consuming grapefruit juice, grapefruits, and products containing grapefruit beginning approximately 2 weeks before administration of the first dose of study drug, throughout the study, and until the last PK sample has been collected.

7.3.3 Alcohol

Subjects will refrain from consuming alcohol, 24 hours before admission until the final PK sample has been collected. Subjects may undergo an alcohol breath test at the discretion of the investigator.

7.3.4 Caffeine

In Part 1, subjects will refrain from consuming caffeinated beverages, 24 hours before the screening visit and follow-up visit and from 24 hours before admission and until the last PK blood sample has been collected in each cohort. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit = 120 mg of caffeine).

7.3.5 Smoking

Subjects will abstain from the use of tobacco- or nicotine-containing products before dosing and during confinement in the clinic.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

7.4.1.1 Part 1

In Part 1 of the study, subjects will fast for at least 8 hours before study drug dosing and will continue to fast for an additional 4 hours postdose. Water is permitted. Standard meals will be administered at approximately 4 (lunch), 7 (snack), 10 (dinner), and 13 (snack) hours postdose on Day 1. Standardized meals will be served on all other confinement days.

7.4.1.2 Part 2

Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

7.4.1.3 Part 3

In Part 3 of the study on Days 1 and 5, subjects will fast for at least 8 hours before the first dose and will continue to fast for an additional 4 hours postdose. Water is permitted. Standard meals will be administered at approximately 4 (lunch), 7 (snack), 10 (dinner) and 13 (snack) hours postdose on dosing days. All meals should be served at approximately the same time each day.

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (eg, weight lifting, running, bicycling) from the screening visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), and until the follow-up visit.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories.

- The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form using the following categories.
- Pretreatment event or AE. The subject has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pretreatment event or AE.
- Liver function test (LFT) abnormalities.
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) in conjunction with elevated total bilirubin >2 times the ULN.
- Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
- Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category.

- Study termination. The sponsor, IRB, or regulatory agency terminates the study.
- Pregnancy. The subject is found to be pregnant. Note: If the subject is found to be pregnant, the subject must be withdrawn immediately.

Note: The specific reasons should be recorded in the "specify" field of the electronic case report form.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

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

7.7 Subject Replacement

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

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

8.1.1 Study Drugs

In this protocol, the term study medication refers to all or any of the drugs defined below. TAK-951 SC injection and matching placebo injection will be provided to the investigator by the sponsor.

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation, of the active drug and placebo can be found in the pharmacy manual or in the referenced compounding manual when applicable. Study drug will be packaged to support enrollment and replacement of subjects as required.

8.1.1.1 TAK-951

The study site will be supplied by the sponsor with the following medication in an open-label manner:

CCI [redacted] The study medication will be provided in a labeled glass vial and packaged in an appropriately labeled carton with a single-panel label that will contain, but will not be limited to, the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, caution statement and storage conditions.

Additional reference information and administration instructions can be found in the pharmacy manual.

8.1.2 Clinical Study Drug Labeling

A clinical label will be affixed to study drug containers in accordance with local regulatory requirements.

8.1.3 Clinical Study Drug Inventory and Storage

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained.

CCI [redacted]

The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

8.1.4 Clinical Study Drug Blinding

This is a double-blind study; the investigator and subjects are blinded to treatment assignment. An unblinded study drug supply will be provided to an unblinded pharmacist or other qualified personnel at the study site who will blind the study supplies. Treatment identity (name and strength or potency) will be included on the study drug container label. Randomization code/disclosure envelopes or lists will be provided per the standard operating procedures of the study site.

After completion of each dosing cohort, and before selecting the next evaluable dose, a fully blinded assessment of the safety and tolerability, laboratory results of at least 24 hours, and available PK data will be performed by the site and select sponsor safety team.

Following each fully blinded dose cohort review, while the site personnel and study subjects will remain blinded to study drug assignment, the sponsor and select sponsor vendors (third-party open) may be unblinded to the completed cohort treatments. Precautions will be taken not to unblind the study staff, including the investigator and the subject, until the study is completed. The blind may be broken before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns.

8.1.5 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.6 Clinical Study Blind Maintenance/Unblinding Procedure

The study drug blind will be maintained through a randomization schedule held by the unblinded pharmacist at the study site or by the sponsor. The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the medical monitor should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

8.1.7 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator and investigator's designated site pharmacy must ensure that the sponsor or contract research organization (CRO) supplied drug is used in accordance with the protocol and

pharmacy manual and is dispensed only to subjects enrolled in the study. To document appropriate use of the sponsor supplied drugs (TAK-951 vials), the investigator pharmacy/site must maintain records of drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the designated blinded pharmacist must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, designated site pharmacist should acknowledge the receipt of the shipment by signing bottom half of the packing list. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator's designated blinded pharmacist must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the drug accountability log is completed for each prepared dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

8.2 Ancillary Supplies

All ancillary supplies will be provided by either the study site or the sponsor or designee, depending upon availability. The list of ancillary supplies and source information can be found in the pharmacy manual or in the referenced compounding manual when applicable. If provided by the sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the sponsor or designee.

9.0 STUDY PROCEDURES

The following sections describe the study procedures to be performed and data to be collected as indicated in the schedule of study procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.1.1 Assignment of Screening and Randomization Numbers

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

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than one randomization number.

9.1.1.2 Study Drug Assignment

On Day 1, subjects will be assigned a randomization number in ascending numerical order at the clinical site. The randomization number encodes the subject assignment to either TAK-951 or placebo, according to the randomization schedule generated before the study. Each subject will be dispensed blinded study drug, labeled with his/her unique randomization number, throughout the study.

9.1.2 Inclusion and Exclusion

Each subject will be assessed through randomization, according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Qualified site personnel will collect subject significant medical history (past and concurrent medical conditions), per the clinical site's standard of care and appropriate clinical judgment, and subject demographics.

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

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Examination

Qualified site personnel will conduct full physical examinations.

9.2.2 Height and Weight

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

9.2.3 Body Mass Index

Body mass index (BMI) equals a subject's weight in kilograms divided by height in meters squared (BMI = kg/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4, round down, and 0.5 to 0.9, round up.

9.2.4 Vital Signs

Body temperature will be measured with either an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (ie, oral or tympanic) must be used for all measurements for each individual subject and should be the same for all subjects. At predose, vital signs will be measured within approximately 1 hour predose.

Subjects should rest in a semirecumbent position for at least 3 minutes before vital signs are measured. Vital signs will include pulse rate (beats per minute [bpm]), respiratory rate, and systolic and diastolic blood pressure in all parts of the study. Blood pressure and pulse assessments should be made in duplicate with an interval of approximately 2 minutes between the 2 assessments. The PI can take a third BP assessment if results are inconsistent. The final BP read out should be the average of these assessments.

For orthostatic blood pressure and pulse assessment, a third blood pressure and pulse assessment with the subject standing will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 2 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic blood pressure is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision, etc).

The same method (eg, same size cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

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

When vital signs are scheduled at the same time as blood draws, they will be obtained before the scheduled blood draw.

9.2.5 Glucose

Blood glucose will be monitored using finger-stick blood samples in Parts 1 and 3 and will also be monitored using safety laboratory testing.

9.2.6 ECG Procedure

9.2.6.1 Screening and Safety ECGs

A 12-lead ECG will be collected at the time points specified in the Schedule of Study Procedures (see Section 3.0).

The investigator will interpret the safety ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded.

The following parameters will be recorded on the eCRF from the subject's ECG trace: HR, RR interval, QRS interval, PR interval, QT interval, and QTcF.

The investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the investigator for subject safety and will be provided in an appropriate format with the clinical study report.

Ad hoc 12-lead ECGs will also be required, if a subject complains of palpitations, dizziness, breathlessness, chest tightness or any other symptoms suggestive of arrhythmia, between Day 1 (postdose) and discharge. Pulse will be checked immediately, and if it is greater than 120 bpm, a 12-lead ECG, blood pressure and pulse will be measured and recorded. The ECG, blood pressure and pulse measurements will be reviewed by the investigator, who will use clinical judgment regarding further monitoring and management.

9.2.6.2 Telemetry

In Parts 1 (SRD) and 3 (MRD), cardiac monitoring (pulse and ECG) will be assessed via telemetry and will be performed for approximately 2 hours before dosing through to approximately 24 hours postdose.

Subjects should remain sitting or supine for at least 5 minutes before each telemetry reading. At the 0-hr timepoint, telemetry may be assessed in the semirecumbent position to allow for the most efficient capture of the other multiple assessments.

9.2.6.3 Holter

The 12-lead Holter ECG monitoring will be captured on Day 1 of Part 1 (SRD) with a minimum of 23.5 hours of continuous cardiac monitoring. Continuous 12-lead Holter ECG monitoring will be performed from 1 hour predose until 24 hours postdose. For all postdose ECG collections, three 10-second ECGs will be extracted at each extraction window time point.

ECG extraction time points will occur before PK blood draws. Accordingly, subjects will be supervised and quietly resting supine beginning a minimum of 10 minutes before each actual ECG extraction window of 10 minutes. Subjects will be supervised while remaining at rest, quiet, and awake and in a supine position from at least 10 minutes before the beginning of each ECG extraction time point and will remain quiet, awake, motionless, and supine for at least 10 minutes after the beginning of each ECG extraction time point.

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[redacted]

9.2.7 Study Drug Administration

Study Drug (TAK-951) will be administered as shown in the Schedule of Study Procedures in Section 3.0.

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[redacted]

9.2.9 AE Monitoring

AE monitoring begins after signing of the informed consent form. Changes in subject health status from the baseline assessment until study drug administration should be captured in the subject's medical history. A complete description of AE collections and procedures is provided in Section 10.0.

9.3 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be collected following a minimum 8-hour overnight fast at the time points stipulated in the schedule of study procedures (Section 3.0).

9.3.1 Hematology

Hematology will consist of the following tests:

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

9.3.2 Chemistry

Chemistry evaluations will consist of the following chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride and lipase
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total) if above the upper limit of normal, total bilirubin will be fractionated
Protein (total)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase

If subjects experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and international normalized ratio) should be performed 24 hours after the abnormality was noted, and the medical monitor should be contacted.

If ALT or AST remains elevated >3 times the ULN, the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE.

Please refer to Section 7.5 for subject discontinuation criteria regarding abnormal liver test results and Section 10.2.8.5 for guidance on reporting abnormal liver test results.

9.3.3 Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrate

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

9.3.4 Diagnostic Screening

Other

HIV	Hepatitis screen (hepatitis B surface antigen, hepatitis C virus antibody)
FSH	βhCG (pregnancy) test

Alcohol Screen

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

Urine

The urine drug screening assessment will include the following tests:

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

9.4 PK, CCI [redacted], and Immunogenicity Samples

Samples for PK, ADA CCI [redacted] analysis will be collected as specified in the Schedule of Study Procedures (Section 3.0). Please refer to the laboratory manual for information on the collection, processing, and shipment of samples to the central laboratory.

The decision as to which plasma and/or serum samples collected will be assayed for evaluation of PK will be determined by the sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). CCI [redacted]

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

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Plasma	Plasma	PK measurement	Mandatory
Urine sample for PK	Urine	Urine	PK measurement	Mandatory
Blood sample for ADA	Blood	Blood	ADA analysis	Mandatory
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ADA: anti-drug antibody; CCI CCI

[a] A single follow-up optional sample will be collected.

9.4.1 PK Measurements

The PK parameters of TAK-951 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be involved in all computations involving sampling times.

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The following plasma PK parameters will be determined after single dose and at steady state:

Symbol/Term	Definition
Plasma/Blood/Serum	
AUC_{24}	Area under the plasma/blood/serum concentration-time curve from the time 0 to time 24 hours.
AUC_{τ}	Area under the plasma/blood/serum concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval.
AUC_{last}	Area under the plasma/blood/serum concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the plasma/blood/serum concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty} = AUC_t + C_{last}/\lambda_z$
R	Accumulation ratio (index) calculated as AUCτ at steady state/AUC_{∞} after a single dose.
$R_{ac(AUC)}$	Accumulation ratio (based on AUC), calculated as AUC_{τ} at steady state/AUC_{τ} after a single dose.
C_{max}	Maximum observed plasma/blood/serum concentration.
$C_{max,ss}$	Maximum observed steady-state plasma/blood/serum concentration during a dosing interval.
CL/F	Apparent clearance after extravascular administration, calculated as = Dose/AUC_{∞} after a single dose and as Dose/AUC_{τ} after multiple dosing (at steady state).
λ_z	Terminal elimination rate constant calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal disposition phase half-life calculated as $\ln(2)/\lambda_z$.
t_{lag}	Lag time to first quantifiable concentration.
t_{max}	Time of first occurrence of C_{max}.
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.

The following urine PK parameters of TAK-951 will be determined after SD administration in Part 1:

Urine	
$Ae_{t1\text{-}t2}$	Amount of drug excreted in urine from time 1 to time 2, calculated as $C_{ur} \times V_{ur}$, where C_{ur} is the concentration of drug excreted in urine and V_{ur} is the volume of urine excreted.
Ae_t	Total amount of drug excreted in urine from time 0 to time t.
Ae_{τ}	Amount of drug excreted in urine during a dosing interval (τ) at steady state.
f_e	Fraction of drug excreted in urine, calculated as $(Ae_t/dose) \times 100$. Molecular weight adjustment needed for metabolites.
CL_R	Renal clearance calculated as $Ae_{0\text{-}24}/AUC_{24}$.

Additional PK parameters may be calculated as appropriate. Further details will be provided in the clinical pharmacology analysis plan.

9.4.1.1 Plasma or Serum for PK Measurements

Blood samples for PK analysis of TAK-951 will be collected into chilled blood collection tubes (vacutainer) containing the anticoagulant K2EDTA. The collected blood samples may be archived for additional analysis of potential metabolites.

The actual time of sample collection will be recorded on the source document and eCRF. Sampling time points may be adjusted based on the preliminary emerging concentration data collected from prior subject(s), but the total number of samples collected per subject should not exceed the planned number.

9.4.1.2 PK Sample Analysis

Plasma and urine concentrations of TAK-951 will be measured by a validated high-performance liquid chromatography with tandem mass spectrometry assay.

9.4.2 Immunogenicity (ADA) Measurements

Protein products have the potential to induce anti-drug immune response which may affect the safety and efficacy of the compound under study. Detection and analysis of ADA formation is a helpful tool in understanding drug immunogenicity, efficacy, and safety. To understand drug immu[CCI]mples will be collected on Day 1, predose, and at the follow-up visit. Othe[CCI]have reported the formation of ADAs, however, an ADA assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, the incidences of ADA formation cannot be directly compared with the other products. ADA samples will be taken in all parts of the study across all cohorts.

9.4.3 Biomarker Measurements

[CCI]

CCI

[redacted]

CCI

[redacted]

9.5 Confinement

9.5.1 Part 1 (SRD)

Subjects will report to the clinical site the evening before the scheduled day of study drug administration (Day -1). Subjects will remain in the clinic for 30 hours postdose (Day 2) or until 48 hours postdose if requested by the investigator and deemed necessary to ensure subject safety. At the discretion of the investigator, subjects may be requested to remain in the clinical site longer.

9.5.2 Part 2 (SD Apo Challenge)

Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

9.5.3 Part 3 (MRD)

Subjects will report to the clinical site the evening before the scheduled day of study drug administration (Day -1). Subjects will remain in the clinic from Day-1 until discharge on Day 6. Subjects will be discharged 30 hours after last dose of TAK-951/placebo. At the discretion of the investigator, subjects may be requested to remain in the study site longer.

9.6 Childbearing Status and Methods of Contraception

9.6.1 Women of Childbearing Potential

Women of childbearing potential will be excluded from this study.

9.6.1.1 Definition of Women of Childbearing Potential

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile.

9.6.2 Women of Nonchildbearing Potential

A female subject of nonchildbearing potential is defined as satisfying at least 1 of the following criteria:

- Postmenopausal: At least 12 months of spontaneous amenorrhea and a FSH concentration >40 mIU/mL.
- Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
- Has no uterus as a result of a congenital condition.

9.6.2.1 Contraception for WONCBP

No contraception is required for WONCBP.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a 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) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of 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 subject 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 before 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 subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject 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 eCRF, 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 subject should be treated symptomatically.

10.1.1 SAEs

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

1. Results in DEATH.

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

Table 10.a Takeda Medically Significant AE List

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

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

10.1.2 Special Interest AEs

AEs of special interest for TAK-951 include injection site reactions, hypotension, and tachycardia. These AEs will be monitored by the investigator and sponsor.

10.2 AE Procedures

10.2.1 Assigning Severity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to NCI CTCAE v5.0. AEs not listed by the NCI CTCAE will be graded as displayed in Table 10.b.

Table 10.b NCI CTCAE

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the subject.

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication 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 subject and/or investigator.

10.2.4 End Date

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

10.2.5 Pattern of AE (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 subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE).
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject'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 LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until approximately 30 days after the last dose of investigational product. For subjects who discontinue

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

All subjects 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 eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and 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 drugs).
- 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.
- Subject 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 Appendix 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 Management of Specific AEs

Sinus Tachycardia

CTCAE Grade	Management
CTCAE Grade 2 sinus tachycardia (ie, Symptomatic [a]; nonurgent medical intervention indicated) with HR 120 and above at rest for at least 5 minutes with no physical exertion.	Evaluate ECG for abnormalities, manage as per local guidelines and call the medical monitor immediately. In MRD, the subject may be rechallenged with the agreement of the sponsor and investigator. In MRD, if a subject develops a second episode of symptomatic tachycardia, discontinue treatment with study drug.
Any CTCAE Grade 3 sinus tachycardia (ie, urgent medical intervention indicated) or Grade 4 (life-threatening)	Evaluate ECG for abnormalities, manage as per local guidelines and call the medical monitor immediately. In all subjects, discontinue further treatment with study drug.

CTCAE: Common Terminology Criteria for Adverse Events; ECG: electrocardiogram; MRD: multiple-rising dose.
[a] Symptoms may include dizziness, light headedness, chest pain, chest heaviness, palpitations, and shortness of breath.

Low Blood Pressure

If a subject develops symptoms suggestive of hypotension or postural hypotension, blood pressure should be assessed for evidence of hypotension, which should be managed as per local guidelines, and the medical monitor should be contacted.

Injection Site Reaction

If a subject develops a CTCAE Grade 3 (ulceration or necrosis; severe tissue damage, operative intervention need) or 4 (life-threatening consequences; urgent intervention indicated) discontinue administration of TAK-951, provide immediate treatment and contact medical monitor.

Hypersensitivity

If anaphylaxis or other serious allergic reactions occur, TAK-951 administration will be discontinued immediately and appropriate management initiated (eg, epinephrine, and antihistamines, and further immediate care as necessary).

10.2.8.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST >3 times the ULN and total bilirubin >2 times the ULN, 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 subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.3 must also be performed.

10.2.9 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs, 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 in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

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

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

11.1.1 Analysis Sets

11.1.1.1 Safety Set

The safety analysis set will consist of all subjects who are enrolled and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

11.1.1.2 PK Set

The PK analysis set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration of TAK-951.

CCI [redacted]

11.1.1.4 Immunogenicity Set

The immunogenicity set consists of patients who receive at least 1 dose of TAK-951 and have an ADA status assessment at baseline, and at least 1 postbaseline sample.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (eg, age, height, weight, and BMI) for pooled placebo group, each TAK-951 dose level, TAK-951 overall in Part 1 and Part 3. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (eg, gender, ethnicity, race) will be tabulated for pooled placebo group, each TAK-951 dose level, and overall. Placebo data will be pooled across cohorts within each part of the study. Individual subject demographic and baseline characteristics data will be listed.

CCI [redacted]

11.1.4 PK Analysis

The plasma and urine concentrations of TAK-951 will be summarized by dose, cohort, day, and dosing condition (as appropriate) over each scheduled sampling time, using descriptive statistics. The PK parameters of TAK-951 will be determined from the concentration-time profiles for all evaluable subjects using noncompartmental analysis approach. Actual sampling times, rather than scheduled sampling times, will be involved in the derivation of PK parameters. Dose

proportionality will be assessed graphically (dose-normalized C_{max} and AUC versus dose) as data allows; no formal statistical comparisons will be conducted.

Additional PK parameters may be calculated as appropriate. Further details will be specified in the SAP.

11.1.5 Safety Analysis

Safety analyses will be based on the safety analysis set. No formal statistical tests or inference will be performed for safety analyses. All summaries will be performed by pooled placebo within each part, and TAK-951 dose level.

11.1.5.1 AEs

Treatment-emergent adverse events (TEAEs) will be summarized by placebo, each TAK-951 dose level and TAK-951 overall for each part of the study.

11.1.5.2 Clinical Laboratory Evaluations

Baseline, postdose, and change from baseline to postdose laboratory data will be summarized by treatment. Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be summarized. All clinical laboratory data will be provided in the data listings.

11.1.5.3 Vital Signs

Vital signs data will be summarized using descriptive statistics for each cohort. Individual vital sign results meeting the sponsor's markedly abnormal criteria will also be summarized.

11.1.5.4 ECG

ECG data captured through telemetry and Holter will be listed by subject and treatment group for each part.

11.1.5.5 Other Safety Parameters

Physical examination findings will be presented in the data listings.

CCI [redacted]

11.1.7 Immunogenicity Analysis

Immunogenicity will be summarized using the Immunogenicity set. Descriptive statistics will be used to summarize subjects in the following categories: ADA negative, ADA positive, low or high ADA titer.

The relationship between immunogenicity status (ADA and ADA titer) and PK, CCI and safety may be explored. Further details will be provided in the SAP.

11.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned. Section 6.0 describes the safety, tolerability and PK review that will take place after completion of each cohort and before next dose escalation stage in the study.

11.3 Determination of Sample Size

For Parts 1 and 3, the selected sample sizes are considered sufficient for evaluation of safety, tolerability, PK, and PD. The study is not statistically powered to perform hypothesis testing in Parts 1 and 3.

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 eCRFs. 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.

All aspects of the study and its documentation will be subject 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, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

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

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

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected,

where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the 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 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 Approval

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

The sponsor or designee will supply relevant documents for submission to the IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will 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. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the IRB,

and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

13.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The

investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

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

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

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject'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 subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

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

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

13.4 Publication, Disclosure, and Clinical 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 Trial Registration

To ensure that information on clinical studies 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 studies 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 subjects 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 subject 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 studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Study contact numbers can be found in the study manual, the communication plan, or other similar documents provided to the site.

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 subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.9 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/Province)

_____

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 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
CCI	[redacted]
AST	aspartate aminotransferase
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{τ}	area under the concentration-time curve during a dosing interval
AV	atrioventricular
BMI	body mass index
BPM	beats per minute
CCI	[redacted]
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CRO	contract research organization
CTX	carboxy-terminal collagen crosslinks
CCI	[redacted]
EC_{50}	half-maximal effective concentration
eCRF	electronic case report form
ECG	electrocardiogram
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
CCI	[redacted]
GLP	Good Laboratory Practice
GLP-1	glucagon like peptide-1
hCG	human chorionic gonadotropin
HED	human equivalent dose
HR	heart rate
ICH	International Conference on Harmonisation
IRB	institutional review board
IV	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple-rising dose
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRS	Numeric Rating System

[redacted]

PK	pharmacokinetic
[redacted]	
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	single dose
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reactions
TAG	triacylglyceride
TEAE	treatment-emergent adverse event
$T_{1/2z}$	terminal disposition phase half-life
ULN	upper limit of normal
Vz/F	apparent volume of distribution during the terminal phase after extravascular administration
WBC	white blood cell

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 Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

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

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

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

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

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

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

eCRFs 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 subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

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 subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to

enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the 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

CCI

[redacted]

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this 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 subjects, 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 that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

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

Appendix B Elements of the Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

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

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

25. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 5 half-lives after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical study 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.

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

Male Subjects and Their Female Partners

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

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, 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. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included/excluded, the only acceptable methods of contraception are:

- Non-Hormonal Methods:
  - IUD (Intrauterine device).
  - 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 subject. 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 5 half-lives.

- 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 for shorter duration until she has been on contraceptive for 3 months;
    - oral †.
    - Injectable.
    - Implantable.

2. If genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drug, comparator, background therapy or standard of care medications 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.

3. Unacceptable methods of contraception are:

- Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
- Spermicides only.
- Withdrawal.
- No method at all.
- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.
- Sexual abstinence is NOT an acceptable method of contraception.

4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
5. During the study, regular serum/urine human chorionic gonadotropin (hCG) pregnancy tests will be performed for female subjects and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:

- contraceptive requirements of the study
- reasons for use of barrier methods (ie, condom) in males with pregnant partners
- assessment of subject compliance through questions such as
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late? (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

Pregnancy

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

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

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

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

Appendix E Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 04.

CCI

[redacted]

Rationale for Change: All references to Part 2 of the study have been removed CCI [redacted]

The following sections contain these changes:

- Section 1.0 STUDY SUMMARY
- Section 2.0 STUDY SCHEMATIC
- Section 3.2 Part 2 for SD Apo Cohorts 7 to 9 (section content has been deleted)
- Section 4.2 Rationale for the Proposed Study
- Section 4.3 Benefit-Risk Profile
- Section 5.1 Study Objectives
- Section 5.2 Endpoints
- Section 6.1 Study Design, including references to Part 2 in Table 6.a
- Section 6.1.2 CCI [redacted]
- Section 6.2.1 Rationale of Study Design
- Section 6.2.2. CCI [redacted]
- Section 6.2.2.3 CCI [redacted]
- Section 6.2.4 Rationale for Endpoints

- Section 6.2.5 Critical Procedures Based on Study Objectives: Timing of Procedures
- Section 6.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters
- Section 6.4.5 Stopping Rules
- Section 7.2 Exclusion Criteria and Section 1.0 STUDY SUMMARY Main Criteria for Exclusion
- Section 7.4.1.2 Part 2 (under Diet and Fluid)
- Section 8.1.1.2 CCI [redacted]
- Section 8.1.1.3 CCI [redacted]
- Section 8.1.2 Use of Rescue Medication (section has been deleted)
- Section 8.1.3 Clinical Study Drug Inventory and Storage
- Section 8.1.7 Accountability and Destruction of Sponsor-Supplied Drugs
- Section 8.3 Companion Medication (section has been deleted)
- Section 8.4 Rescue Medication (section has been deleted)
- Section 9.2.4 Vital Signs
- Section 9.2.5 Glucose
- Section 9.2.6.2 Telemetry
- Section 9.2.7 Study Drug Administration
- CCI [redacted]
- CCI [redacted]
- Section 9.5.2 Part 2 (SD Apo Challenge)
- Section 11.1.1.3 PD Set
- Section 11.1.2 Analysis of Demography and Other Baseline Characteristics
- CCI [redacted]
- CCI [redacted]
- Section 11.3 Determination of Sample Size

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Pharmacovigilance Approval	24-Sep-2020 12:22 UTC
	Biostatistics Approval	24-Sep-2020 12:26 UTC
	Clinical Pharmacology Approval	24-Sep-2020 12:39 UTC
	Clinical Approval	24-Sep-2020 13:54 UTC