Clinical Study Protocol

NCT Number: NCT06610279

Title: A Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, 3-Part Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects

Study Number: TAK-951-1008

Document Version and Date: Amendment 2.0, 16 March 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA DEVELOPMENT CENTER AMERICAS INC

PROTOCOL

A Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, 3-Part Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	TAK-951-1008		
IND Number:	141732	**EudraCT Number:**	Not Applicable
Compound:	TAK-951		
Date:	16 March 2023		
Version/Amendment Number:	2		

Amendment History:

Date	Amendment Number	Amendment Type	Region
16 March 2023	Amendment 2	Substantial	United States
24 January 2023	Amendment 1	Substantial	United States
23 November 2021	Initial protocol	Not applicable	United States

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

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

Contact Type/Role	United States Contact
Serious adverse event and pregnancy reporting	US and Canada email: PVSafetyAmericas@tpna.com Rest of the world email: eupv@tgrd.com Fax: +1-224-554-1052
Responsible Medical Officer	[redacted], MD [redacted], Clinical Science Takeda Development Center Americas, Inc. 10 Green Street Cambridge, MA 02139 Phone: [redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable, can be found on the signature page.

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

[redacted], MD Date
[redacted], Clinical Science
GI Therapeutic Area

[redacted], MD, MA, PhD Date
[redacted], Global Patient Safety
Evaluation

[redacted], PhD Date
[redacted], Statistics and Quantitative
Sciences

[redacted], PhD Date
[redacted], Quantitative
Clinical Pharmacology

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information 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, life, dignity, integrity, confidentiality of personal information, 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 Council for Harmonisation, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.3.1 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the Investigator (Appendix B).

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

1.3 Protocol Amendment 2 Summary of Changes

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reason for this amendment is:

- To provide information about the previously completed cohorts and doses and to specify the starting cohort, starting dose, and proposed dose escalation (single rising dose [SRD]) in Part 1 of the study.

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

See Appendix E for protocol history, including all previous amendments.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Table 6.a Overview of Treatment Cohorts Section 6.1.1 Part 1: SRD Cohorts 1 to 6 Section 6.2 Dose Escalation Table 6.b Injection Volumes, Number of Injections, and Predicted Exposures for Select Doses in Part 1 (SRD) Section 6.4.2 Justification for Dose for SRD, MRD, and Titration	Defined the starting cohort under Protocol Amendment 2 (ie, per the modified study procedures defined by Protocol Amendments 1 and 2) as Cohort 5, which will be dosed at [redacted] single dose. Specified the dose for Cohort 6 at either [redacted] (repeat of Cohort 5) or escalation of [redacted]. Specified that dosing of additional cohorts in Part 1 (ie, beyond Cohort 6) requires an assessment of complete safety and pharmacokinetic (PK) data before dosing and is limited to doses of [redacted] single doses without an updated safety rationale (including safety, tolerability, and PK data from Cohorts 5 and 6).	To specify the starting cohort, starting dose, and proposed dose escalation (single rising dose [SRD]) in Part 1 of the study.
2.	Table 6.a Overview of Treatment Cohorts Section 6.1.1 Part 1: SRD Cohorts 1 to 6 Table 6.b Injection Volumes,	Revised planned maximum dose in Part 1 (SRD) from [redacted]. Dosing of cohorts in Part 1 with doses greater than [redacted] will	To update the planned maximum TAK-951 single dose based on current safety, tolerability, and PK data.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Number of Injections, and Predicted Exposures for Select Doses in Part 1 (SRD) Section 6.4.2 Justification for Dose for SRD, MRD, and Titration	require additional supporting clinical safety, tolerability, and PK data from Cohorts 5 and 6 from Part 1 (SRD).	
3.	Section 4.3 Benefit/Risk Profile Section 6.4.2 Justification for Dose for SRD, MRD, and Titration	Added description of doses and safety results from Cohorts 1 through 4 in Part 1 (SRD).	To provide information about the previously completed cohorts dosed in Part 1 (SRD) of this study under the original protocol (ie, safety data from Cohorts 1, 2, 3, and 4, which were dosed with single doses of [redacted] respectively).
4.	Section 6.1 Study Design Section 6.1.2 Part 2: MRD Cohorts 7 to 10 Section 6.1.3 Part 3: Dose Titration and Redosing Cohorts 11 to 15	Revised text to state that dosing of Parts 2 and 3 will not be initiated before dosing of Cohorts 5 and 6 in Part 1.	To ensure that Parts 2 and 3 are not initiated before additional information is available for single TAK-951 doses in Part 1.
5.	Section 6.3 Study Drug Administration	Added statement to clarify that the maximal doses in Parts 1 and 2 will be limited by the dose cap specified in Protocol Amendment 2 (ie, exposure level with [redacted] dosing) in addition to the maximal dose based on nonclinical data in the original protocol and maximum injection volumes in the original protocol.	To adjust the planned maximal dose for single dose and repeat-dose (BID and TID) administration of TAK-951 based on current understanding of safety, tolerability, and PK of TAK-951.
6.	Section 6.6 Criteria for Premature Suspension of the Study	Specified a planned pause in Part 1 to review safety, tolerability, and PK from the first 2 dose cohorts (ie, Cohorts 5 and 6) in Part 1. Specified that dose levels not previously studied in Part 1 (ie, [redacted] single dose) will require additional supporting clinical safety, tolerability,	To define procedures for re-evaluation of safety, tolerability, and PK data required to exceed a single dose of [redacted] in Part 1.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		and PK data for doses from Cohorts 5 and 6 in Part 1.	
7.	Section 4.3 Benefit/Risk Profile	Added reasoning for the removal of the 0.5-hour postdose time point for orthostatic vital signs assessments in Protocol Amendment 1 (ie, occurrence of orthostatic events in the current study).	To provide rationale for this change previously made in Protocol Amendment 1 to mitigate risk and support benefit-risk assessments.
8.	Section 14.1 Study-Site Monitoring Visits	Revised to remove "to the study site" when referring to monitoring visits.	Clarification.

2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Americas, Inc.</td><td>Compound:
TAK-951</td></tr>
<tr><td>Title of Protocol: A Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, 3-Part Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects</td><td>IND No.: 141732</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td>Study Number: TAK-951-1008</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="3">Study Design:
This is a phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-951 in healthy subjects. Subjects will be randomized to receive TAK-951 or matching placebo.
This is a double-blind study; the investigator and subjects are blinded to treatment assignment. The study will be conducted sponsor-open. Sponsor discussions with investigators and within the study team will be conducted in a blinded manner (ie, no unblinded information will be communicated to blinded investigators, site staff or blinded study monitoring personnel).
The study will consist of 3 parts:
• Part 1 is a randomized, double-blind, sponsor-open, placebo-controlled, single-rising dose (SRD) design to assess the safety, tolerability, PK, and immunogenicity of TAK-951 in healthy subjects. Up to 6 cohorts may be enrolled.
• Part 2 is a randomized, double-blind, sponsor-open, placebo-controlled, multiple-rising dose (MRD) design to assess the safety, tolerability, PK, and immunogenicity of TAK-951 in healthy subjects. Up to 4 cohorts may be enrolled.
• Part 3 is a randomized, double-blind, sponsor-open, placebo-controlled, multiple-dose, dose titration and redosing design to assess the safety, tolerability, PK, and immunogenicity of TAK-951 in healthy subjects. Up to 5 dose regimens will be tested in independent subject cohorts using a dose titration design, followed by redosing with a single dose of study drug after a 2- to 7 day variable washout period.</td></tr>
<tr><td colspan="3">Primary Objectives:
• Part 1: To characterize the safety and tolerability of single subcutaneous (SC) doses of TAK-951 in healthy subjects.
• Part 2: To characterize the safety and tolerability of multiple SC doses of TAK-951 in healthy subjects.
• Part 3: To characterize the safety and tolerability of multiple SC dose regimens of TAK-951 that include titration from lower doses in healthy subjects.</td></tr>
<tr><td colspan="3">Secondary Objectives:
• Part 1:
– To characterize the PK of TAK-951 in plasma following single SC doses in healthy subjects.
– To assess the immunogenicity of TAK-951 following single SC doses in healthy subjects.
• Part 2:
– To characterize the PK of TAK-951 in plasma following multiple SC doses in healthy subjects.
– To assess the immunogenicity of TAK-951 following multiple SC doses in healthy subjects.
• Part 3:
– To characterize the safety and tolerability of single SC rechallenge doses of TAK-951 after a washout from multiple SC dose regimens that include titration from lower doses in healthy subjects.
– To assess the immunogenicity of TAK-951 following multiple SC dose regimens that include titration from lower doses, washout, and redosing in healthy subjects.</td></tr>
</table>

<table>
<tr><td colspan="2">Subject Population: Healthy male and female subjects aged 18 to 55 years, inclusive, at screening. Body mass index (BMI) ≥18 and ≤32.0 (kg/m^2) at screening.</td></tr>
<tr><td>Number of Subjects:
Part 1: Up to approximately 48 subjects.
Part 2: Up to approximately 32 subjects.
Part 3: Up to approximately 40 subjects.
Approximate values do not account for potential replacement of subjects who withdraw for nonsafety reasons.</td><td>Number of Sites:
Up to 3 sites in the United States (US).</td></tr>
<tr><td>Dose Level(s):
Part 1: TAK-951 SRD: starting dose [redacted] (starting dose [redacted] [Cohort 5] under Protocol Amendment 2).
Part 2: TAK-951 MRD: doses to be determined based on Part 1.
Part 3: TAK-951 Dose Titration and Redosing: doses to be determined based on Parts 1 and 2.</td><td>Route of Administration:
SC</td></tr>
<tr><td>Duration of Treatment:
Part 1: 1 day.
Part 2: 5 days.
Part 3: 8 to 13 days (5 days plus 1 day after variable 2 to 7 days of washout).</td><td>Period of Evaluation:
Each part of the study will be approximately 60 days from screening until last follow-up visit.</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:
In order to be eligible for study participation, the subject must:
• Understand the study procedures and agree to participate by providing written informed consent.
• Be willing and able to comply with all study procedures and restrictions.
• Be a healthy man or woman aged 18 to 55 years, inclusive, at the screening visit.
• Continuous nonsmoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to dosing and throughout the study.
• Have a BMI ≥18 and ≤32.0 (kg/m^2) at the screening visit.
• 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, electrocardiogram (ECG), and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug or invasive procedure.</td></tr>
<tr><td colspan="2">Main Criteria for Exclusion:
The subject must be excluded from participating in the study if:
• The subject has participated in another investigational study within 4 weeks (or based on local regulations) or within 5 half-lives, whichever is longest, of the investigational product before the screening visit. The 4-week or 5 half-lives window will be derived from the date of the last study dose in the previous study to the screening visit of the current study.
• 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, as determined by the investigator.
• The subject has a positive pregnancy test or is lactating or breastfeeding.</td></tr>
</table>

- The subject is unable to refrain from or anticipates using any 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.
- The subject has a history or presence of:
  - 3 or more incidences of vasovagal syncope within the last 5 years prior to screening; or
  - A family history of unexplained sudden death or channelopathy; or
  - Brugada syndrome (ie, RBBB pattern with ST-elevation in leads V1-V3); or
  - Cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, stroke, sick sinus syndrome, pulmonary congestion, symptomatic or significant cardiac arrhythmia, second-degree atrioventricular (AV) block type 2, third degree AV block, prolonged QT interval with Fridericia correction method (QTcF) interval, hypokalemia, hypomagnesemia, or conduction abnormalities; or
  - Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome); or
  - Any clinically significant ECG findings or medical history including: long or short QTcF (over 450 msec or less than 360 msec), bifascicular block or QRS ≥120 msec or PR interval >210 msec at screening or Day -1 pre-Hour 0; or
  - The subject has a documented history of sinus bradycardia (<45 beats per minute [bpm]), sinoatrial block or sinus pause ≥3 seconds.
- The subject has an average semirecumbent blood pressure (BP) <90/60 mm Hg or >140/90 mm Hg from screening to predose, inclusive. Any assessments on Day -1 that do not meet this criterion must be discussed with the medical monitor for approval.
- The subject has an average semirecumbent HR (pulse) <55 or >100 bpm at any time point from screening to predose, inclusive. Subjects with an average pulse <55 bpm can be enrolled only with medical monitor approval. Any assessments after admission with an average pulse <55 bpm at any time point, from Day -2 to predose (inclusive), will be left to the judgment of the investigator, unless the pulse rate is <50 bpm, which must be discussed with the medical monitor for approval.
- The subject has orthostatic hypotension defined as a decrease in systolic BP ≥20 mm Hg or a decrease in diastolic BP ≥10 mm Hg at approximately 3 minutes of standing when compared with BP from the semirecumbent position at screening to predose assessments, inclusive. In asymptomatic subjects, any assessments after screening that do not meet this criterion may be repeated after the subject has remained in the semirecumbent or supine position for 15 minutes. If the repeat assessment is exclusionary based on the above criterion, the subject will not be eligible. If the repeat assessment is not exclusionary, the subject will be eligible.
- The subject has postural orthostatic tachycardia, defined as an increase of >30 bpm or a pulse rate >120 bpm at approximately 3 minutes of standing, at screening to predose assessments, inclusive. Any assessments after screening that do not meet this criterion may be repeated with the subject remaining standing for up to a total of 5 minutes, provided that the subject remains asymptomatic. If the repeat assessment occurring within 5 minutes is exclusionary based on the above criterion, the subject will not be eligible. A confirmed orthostatic increase of >30 bpm, but <40 bpm, on 1 or more Day -1 assessments may not be considered exclusionary if not considered clinically significant by the investigator and the medical monitor. Such assessments must be discussed with the medical monitor before determination that the subject is eligible to proceed.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is:

- All parts of the study:
  - The primary safety endpoints of the study are safety and tolerability as assessed through physical examinations, vital signs, ECG, laboratory assessments, and adverse events (AEs).

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

- 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 24 hours (AUC_{24}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Terminal disposition phase half-life ($t_{1/2z}$).
  - Apparent clearance after extravascular administration (CL/F).
  - Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Part 2: plasma PK parameters for TAK-951 on Day 1
  - C_{max}, t_{max}, AUC_{24}, and area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval ($AUC\tau$).
- Part 2: plasma PK parameters for TAK-951 at steady state
  - AUC_{τ}, AUC_{24}, $C_{max,ss}$, t_{max}, $t_{1/2z}$, CL/F, V_z/F, observed plasma concentration at the end of a dosing interval (C_{trough}), accumulation ratio based on AUC_{τ} ($R_{ac[AUC]}$), calculated as AUC_{τ} at steady state/AUC_{τ} after a single dose, and accumulation ratio based on C_{max} ($R_{ac[Cmax]}$), calculated as C_{max} at steady state/C_{max} after a single dose.
- Part 3:
  - Safety and tolerability of single SC rechallenge doses after a washout from multiple SC dose regimens of TAK-951 as assessed through vital signs, ECG, laboratory assessments, and AEs.
- All parts of the study:
  - Status of subject's antidrug antibody (ADA) assessment (ie, ADA-negative or ADA-positive, and low or high ADA titer).

Statistical Considerations:

Safety analyses will be based on the safety analysis set (all subjects who are randomized and receive at least 1 dose of study treatment). Subjects will be analyzed according to the study treatment actually received. No formal statistical tests or inference will be performed for safety analyses. All safety data will be summarized descriptively by placebo, TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. In particular, the number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for clinical laboratory evaluations, vital signs, and ECG will be provided. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2)/dose regimen (Part 3) will be pooled across cohorts within each part of the study where appropriate. For Part 3 only, similar safety summary analyses (excluding ADA assessments) will be performed for the single dose after washout from multiple dose regimens of TAK-951 by placebo, TAK-951 single dose level after washout, and TAK-951 single dose overall after washout.

The plasma (all parts of the study) concentrations of TAK-951 will be summarized descriptively by dose level (Parts 1 and 2)/dose regimen (Part 3) at each scheduled sampling day/time within each part of the study separately based on the PK analysis set (all subjects who receive at least 1 dose of TAK-951 and have at least 1 measurable postdose plasma concentration for TAK-951). Subjects will be analyzed according to the study treatment actually received. The PK parameters of TAK-951 determined using a noncompartmental analysis approach will be summarized descriptively by dose level (Parts 1 and 2)/dose regimen (Part 3) of TAK-951, as appropriate, within each part of the study separately, based on the PK analysis set. Dose proportionality may be assessed graphically (log transformed dose normalized C_{max} and AUC versus dose) and by using a power model within each part of the study separately as data allows. No formal statistical comparisons will be conducted. The same dose level (Parts 1 and 2)/dose regimen (Part 3) may be pooled across cohorts within each part of the study

where appropriate.

To support internal decision making regarding further development of [redacted] TAK-951, an interim analysis of safety, tolerability, and PK at a time point dependent on emerging clinical data from TAK-951-1008 may be conducted. If the interim analysis is conducted, the interim analysis will include all available data (including, but not limited to treatment-emergent adverse events [TEAEs], vital signs, ECG, laboratory assessments, physical examinations, and PK). Additional interim analyses may be conducted for sponsor internal decision-making and would be defined in the statistical analysis plan. The details of interim analysis (timing, datasets, and methods), data access management plan, and distribution of results will be described in a separate documents (ie, the statistical analysis plan and data access management plan). A final analysis will be performed at the end of the study after final database lock.

Sample Size Justification: The selected sample sizes in Parts 1, 2, and 3 of the study are considered sufficient for evaluation of safety and tolerability of TAK-951 in healthy subjects. No formal statistical hypothesis testing is planned in Parts 1, 2, or 3. Therefore, no formal power calculations were performed in the determination of sample size for the study.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and sub-investigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and sub-investigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their site.

All institutional affiliations of the investigator(s) and sub-investigator(s) should be declared on their curriculum vitae, which must be provided to the sponsor before the start of the study.

3.2 List of Abbreviations

%CV	percent coefficient of variation
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AV	atrioventricular
BMI	body mass index
bpm	beats per minute
BID	twice daily
BP	blood pressure
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
eCRF	electronic case report form
ECG	electrocardiogram
EDA	electrodermal activity
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
hCG	human chorionic gonadotropin
HR	heart rate
HRV	heart rate variability

ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
IRB	institutional review board
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	UK Medicines and Healthcare products Regulatory Agency
MRD	multiple rising dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
QD	once daily
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
$R_{ac[AUC]}$	accumulation ratio based on AUC_{τ}
$R_{ac[Cmax]}$	accumulation ratio based on C_{max}
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SRD	single rising dose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
TID	3 times daily
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
UK	United Kingdom
US	United States
V_{ss}	volume of distribution at steady state after intravenous administration
V_z/F	apparent volume of distribution during the terminal disposition phase after subcutaneous administration
WBC	white blood cell
[redacted]	[redacted]

4.0 INTRODUCTION

4.1 Background

Nausea and vomiting are among the most common and debilitating symptoms encountered in medicine as either symptoms of disease or side effects of treatments. Because of the complex multifactorial nature of nausea and vomiting, targeted therapies against the 5-HT3 and NK1 receptors do not work effectively as monotherapies, making it a significant unmet medical need.

[redacted]

4.1.1 Clinical Studies

The first-in-human (FIH) study, TAK-951-1001, was a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-951 in healthy subjects with a SRD portion and a multiple rising dose (MRD) portion.

Of a total 96 subjects randomized in the SRD portion of the FIH study, 72 (75%) subjects received a single dose of active study drug (TAK-951) and 24 (25%) subjects received placebo. Of a total 32 subjects randomized in the MRD portion of the study, 24 (75%) subjects received twice daily (BID) dosing for 5 days of active study drug (TAK-951) and 8 (25%) subjects received placebo.

[redacted]

[redacted]

4.1.1.1 Adverse Events in TAK-951-1001 FIH Study

Overall in the SRD part, 33 (34.4%) subjects reported a total of 50 treatment-emergent adverse events (TEAEs): 29 (40.3%) subjects in the TAK-951 group and 4 (16.7%) subjects in the placebo group. Of the 72 total subjects who received TAK-951, 23 (31.9%) subjects reported TEAEs related to TAK-951; 27 (37.5%) subjects reported a Grade 1 event and 2 (2.8%) subjects reported Grade 3 events. There were 4 (16.7%) subjects reporting Grade 1 events in the placebo group.

Overall in the MRD part, 18 (56.3%) subjects reported a total of 61 TEAEs: 15 (62.5%) subjects in TAK-951 group [redacted] and 3 (37.5%) subjects in the pooled placebo group. Of the 18 subjects, 11 subjects reported TEAEs related to TAK-951 and 1 subject reported 1 TEAE related to placebo, as assessed by the investigator. In the TAK-951 group, there were 11 (45.8%) reporting Grade 1 events, 3 (12.5%) subjects reporting Grade 2 events, and 1 (4.2%) subject reporting Grade 3 events, whereas 3 (37.5%) subjects reported Grade 1 events in the placebo group.

There were no deaths, adverse events (AEs) greater than Grade 3 in severity, or AEs leading to discontinuation from the FIH study. One Grade 3 serious adverse event (SAE) of ventricular tachycardia (nonsustained ventricular tachycardia), was reported during the MRD part ([redacted] TAK-951, BID) of the study.

Orthostatic hypotension is considered as an identified risk of TAK-951. In the SRD part of the FIH study, 5 of 72 subjects (6.9%) had TEAEs of dizziness postural (Grade 1 for all 5 subjects); 3 of 72 subjects (4.2%) had TEAEs of postural orthostatic tachycardia syndrome (Grade 1 for all 3 subjects), and 3 of 72 subjects (4.2%) had TEAEs of orthostatic hypotension (Grade 1 for 2 subjects and Grade 3 for 1 subject). In the MRD part, 2 of 24 subjects (8.3%) in the TAK-951 group had TEAEs of orthostatic hypotension (Grade 2). Among these orthostatic hypotension and postural dizziness events, the majority occurred at the 0.5 hours timepoint after dosing.

4.1.1.2 Injection Site Reactions in TAK-951-1001 FIH Study

No injection site reactions were reported in the SRD portion of the FIH study. A total of 3 subjects reported injection site reactions in the MRD part. Two subjects (2 of 32, 6.25%) reported injection site pain [redacted] both were considered related to TAK-951. One subject (1 of 32, 16.7%) reported injection site induration in the [redacted] cohort that was considered not related to the study drug.

4.1.1.3 Vital Sign Changes in TAK-951-1001 FIH Study

Clinical safety results from the FIH study demonstrated a transient decrease in diastolic blood pressure (DBP) and increase in heart rate (HR) in the SRD part of the study. There were more prominent decreases in both systolic blood pressure (SBP) and DBP and increase in HR with postural changes (orthostatic) in some individuals. In the MRD part, the same transient vital sign changes were observed following the first dose of TAK-951. These changes were decreased in magnitude following the second dose, and the change in the vital signs was attenuated following the third and subsequent doses. Given the findings of decreased DBP, increased HR, and orthostatic changes in some individuals following administration of TAK-951, which did not appear to be dose-dependent or related to increased exposure, it is hypothesized that TAK-951 causes vasodilation and orthostatic hypotension is considered to be an identified risk (refer to current version of TAK-951 Investigator's Brochure).

[redacted]

4.1.2 [redacted]

[redacted]

4.2 Rationale for the Proposed Study

The purpose of this study is to evaluate the safety, tolerability, and PK of higher doses of TAK-951 in healthy subjects to support further development of TAK-951. The study will be conducted in 3 parts: single rising doses will be assessed in Part 1; repeat-dose administration will be assessed in Part 2; and dose titration regimens and redosing with a single dose after a washout period will be assessed in Part 3.

The intention of the dose titration portion of Part 3 is to provide an exploratory evaluation to assess the safety and tolerability profile of dose titration at the start of the 5-day treatment period. This comparison will be descriptive (ie, without hypothesis testing) versus tolerability findings in Parts 1 and 2 with comparable exposures to determine whether dose titration results in different tolerability.

4.3 Benefit/Risk Profile

The current study represents an extension study of the FIH study, TAK-951-1001. The main purpose of this study in healthy subjects is to assess the safety and tolerability of TAK-951 at higher doses; 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 [redacted], the potential risks of TAK-951 include increased HR and decreased BP. For peptide-based therapeutics administered SC, immunogenicity, and injection site reactions and more serious hypersensitivity reactions are potential risks.

Based on the safety findings from nonclinical studies conducted with TAK-951, increase in HR, decrease in BP, and synergistic effect when combined with beta blockers are potential risks. Safety results from the FIH study demonstrated a transient increase in HR within the first hour of TAK-951 dosing as well as decreases in SBP and DBP that were more prominent with postural changes (orthostatic) in some individuals within the first 2 hours post dosing. These changes were not clearly dose dependent or related to increased exposure. Postural hypotension (<20 mm Hg in SBP or <10 mm Hg DBP within 3 minutes of standing) is considered an identified risk. After receiving a single-dose of TAK-951, 4 subjects (5%) experienced orthostatic hypotension, including 2 subjects with a Grade 3 event and 5 subjects (7%) reporting postural dizziness. Current preliminary PK and vital sign data reveal that the magnitude of change from baseline in HR and DBP may be saturated at higher doses. Section 6.4.2 summarizes preliminary blinded safety data from Cohorts 1 to 4 [redacted]

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 BP assessments that included orthostatic BP measurements, telemetry, and Holter electrocardiogram (ECG); developing guidance for investigators; and using a clinical study facility where close monitoring could have been performed and rapid institution of appropriate care could have been given when needed in a timely manner.

In addition, by Protocol Amendments 1 and 2, subjects will be required to remain in a supine or semirecumbent position during the 2 hours after dosing without the 0.5 hour postdose orthostatic vital sign assessment. As an additional safety step, a modified orthostatic assessment and physical counterpressure maneuvers will be implemented. In Study TAK-951-1008, reported AEs related to orthostatic vital sign changes (presyncope, syncope, and orthostatic hypotension) had onset by the 2-hour time point. Thus, having subjects remain semirecumbent for up to 2 hours will further mitigate the risks to subjects (ie, with the observed vital sign changes in the first 2 hours of Cohorts 1-4 dosed with [redacted]), while providing additional safety data with respect to orthostatic vital signs at later time points.

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 are evaluated for the development of antidrug antibodies (ADA) as part of the study. The potential risks related to increased HR, decreased BP, and injection site reactions are monitored clinically and/or with laboratory tests and were 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 approximately 600 mL). Overall, the mitigation measures are adequate to monitor safety of the subjects participating in the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective for each part of the study is as follows:

- Part 1: To characterize the safety and tolerability of single SC doses of TAK-951 in healthy subjects.
- Part 2: To characterize the safety and tolerability of multiple SC doses of TAK-951 in healthy subjects.
- Part 3: To characterize the safety and tolerability of multiple SC dose regimens of TAK-951 that include titration from lower doses in healthy subjects.

5.1.2 Secondary Objectives

The secondary objectives for each part of the study are as follows:

- Part 1:
  - To characterize the PK of TAK-951 in plasma following single SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-951 following single SC doses in healthy subjects.
- Part 2:
  - To characterize the PK of TAK-951 in plasma following multiple SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-951 following multiple SC doses in healthy subjects.

- Part 3:
  - To characterize the safety and tolerability of single SC rechallenge doses of TAK-951 after a washout from multiple SC dose regimens that include titration from lower doses in healthy subjects.
  - To assess the immunogenicity of TAK-951 following multiple SC dose regimens that include titration from lower doses, washout, and redosing in healthy subjects.

5.1.3 Exploratory Objectives

Exploratory endpoints of this study include the following:

[redacted]

- Part 2: To assess the effects of TAK-951 on wearable/digital device biomarkers in healthy subjects.
- Part 3: To characterize the PK of TAK-951 in plasma following multiple SC doses and dosing schedules in healthy subjects.

5.2 Endpoints

5.2.1 Primary Endpoints

- All parts of the study:
  - The primary safety endpoints of the study are safety and tolerability as assessed through physical examinations, vital signs, ECG, laboratory assessments, and AEs.

5.2.2 Secondary Endpoints

Secondary endpoints include:

- 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 24 hours (AUC_{24}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Terminal disposition phase half-life ($t_{1/2z}$).

  - Apparent clearance after extravascular administration (CL/F).
  - Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Part 2: plasma PK parameters for TAK-951 on Day 1.
  - C_{max}, t_{max}, AUC_{24}, and area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_τ).
- Part 2: plasma PK parameters for TAK-951 at steady state.

AUC_τ, AUC_{24}, maximum observed concentration at steady state ($C_{max,ss}$), t_{max}, $t_{1/2z}$, CL/F, V_z/F, observed plasma concentration at the end of a dosing interval (C_{trough}), accumulation ratio based on AUC_τ ($R_{ac[AUC]}$), calculated as AUC_τ at steady state/AUC_τ after a single dose, and accumulation ratio based on C_{max} ($R_{ac[C_{max}]}$), calculated as C_{max} at steady state/C_{max} after a single dose. PK parameters will be calculated as permitted by the data. Additional PK parameters may be computed, as needed.

- Part 3:
  - Safety and tolerability of single SC rechallenge doses after a washout from multiple SC dose regimens of TAK-951 as assessed through vital signs, ECG, laboratory assessments, and AEs.
- All parts of the study:
  - Status of subject's ADA assessment (ie, ADA-negative or ADA-positive, and low or high ADA titer).

5.2.3 Additional/Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

[redacted]

- Part 2: Change from baseline (Day -2 before first dose) in wearable/digital device parameters including: electrodermal activity (EDA), HR, heart rate variability (HRV), actigraphy, and temperature through 48 hours post last dose.
- PK parameters in Part 3 may be computed as permitted by data collected.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability, and PK of TAK-951 in healthy subjects. Subjects will be randomized to receive TAK-951 or matching placebo.

This is a double-blind study; the investigator and subjects are blinded to treatment assignment. The study will be conducted sponsor-open. Sponsor discussions with investigators and within the study team will be conducted in a blinded manner (ie, no unblinded information will be communicated to blinded investigators, site staff, or blinded study monitoring personnel).

The study will consist of 3 parts:

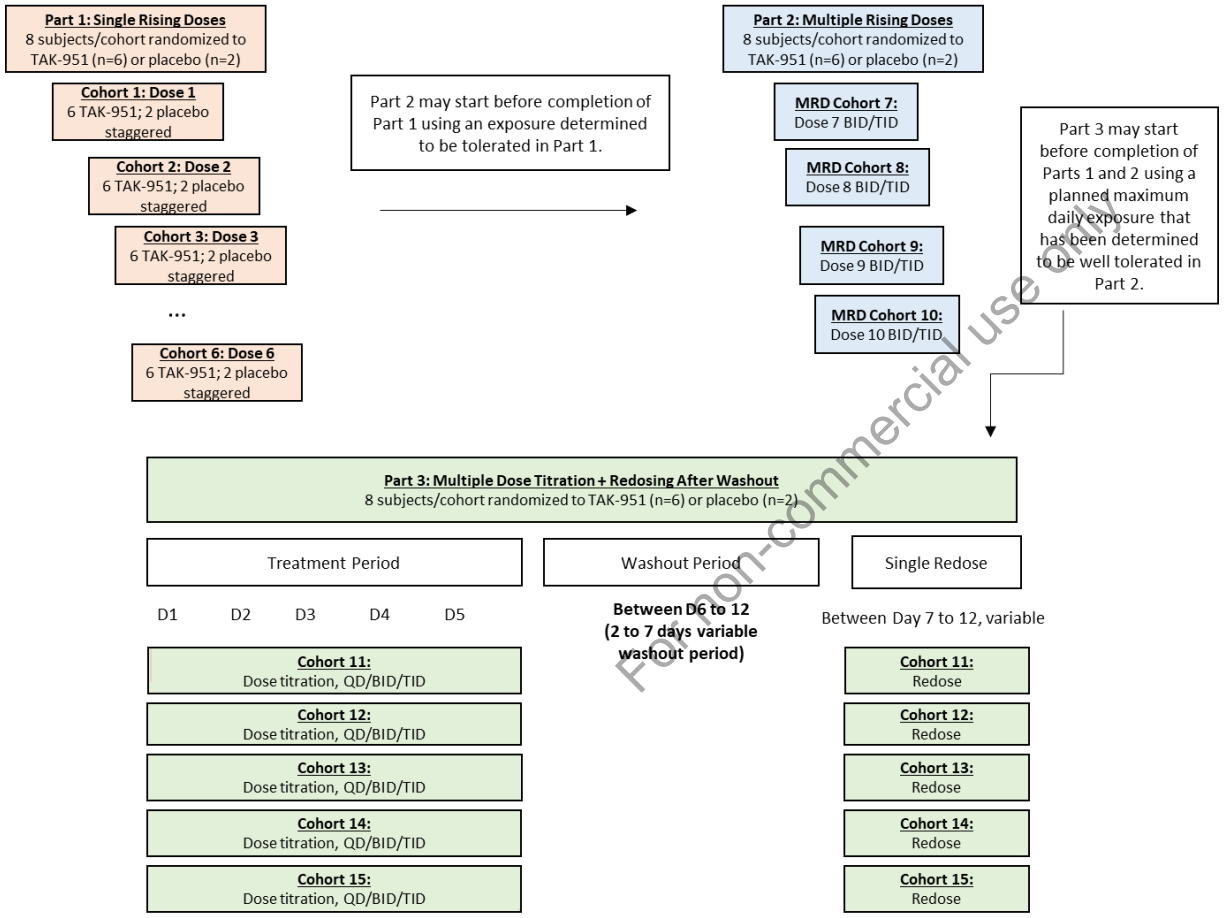
- Part 1 is a randomized, double-blind, sponsor-open, placebo-controlled, SRD design to assess the safety, tolerability, PK, and immunogenicity of TAK-951 in healthy subjects. Up to 6 cohorts may be enrolled.
- Part 2 is a randomized, double-blind, sponsor-open, placebo-controlled, MRD design to assess the safety, tolerability, PK, and immunogenicity of TAK-951 in healthy subjects. Up to 4 cohorts may be enrolled.
- Part 3 is a randomized, double-blind, sponsor-open, placebo-controlled, multiple-dose, dose titration and redosing design to assess the safety, tolerability, PK, and immunogenicity of TAK-951 in healthy subjects. Up to 5 dose regimens will be tested in independent subject cohorts using a dose titration design, followed by redosing with a single dose of study drug after a 2- to 7-day variable washout period.

TAK-951 and matching placebo will be administered SC. Any part of the study may not be conducted based on the sponsor's decision. The daily maximum exposure anticipated at steady state will not exceed an exposure established as tolerated in previous parts of the study. Part 3 will be conducted at the discretion of the sponsor based on a review of the available safety and PK data from Parts 1 and 2. At the discretion of the sponsor, Parts 2 and 3 may be initiated before completion of all cohorts in Parts 1 and 2, respectively, as otherwise permissible in the protocol. Dosing of Parts 2 and 3 will not be initiated before dosing of Cohorts 5 and 6 in Part 1 (see Section 6.1.2 and 6.1.3).

Safety will be assessed by monitoring for AEs, vital signs including orthostatic assessments, 12-lead ECGs, telemetry, safety laboratory assessments after each dose, and immunogenicity. PK sampling times may vary based on emerging safety, tolerability and PK data, but the maximal number of samples will not change.

An overview of treatment cohorts is presented in Table 6.a. A schematic of the study design is included as Figure 6.a. Schedules of assessments for Part 1, Part 2, and Part 3 of the study are presented in Appendix A.

Figure 6.a Schematic of Study Design



BID: twice daily; D: day; MRD: multiple rising dose; QD: once daily; TID: 3 times daily.

Additional cohorts may be included in Part 1 (see Cohorts 6a and 6b in Table 6.a), as determined at the dose escalation meeting based on emerging safety, tolerability, and available PK data during the study.

Table 6.a Overview of Treatment Cohorts

Cohort	Regimen	Treatment	
Part 1			
		TAK-951	**Placebo**
1 (staggered)	SRD	6	2
2 (staggered)		6	2
3 (staggered)		6	2
4 (staggered)		6	2
5 (staggered)		6	2
6 (staggered)		6	2
6a (staggered)		6	2
6b (staggered)		6	2
Part 2			
		TAK-951	**Placebo**
7	MRD	6	2
8		6	2
9		6	2
10		6	2
Part 3			
		TAK-951	**Placebo**
11	Dose Titration, Washout, Redosing	6	2
12		6	2
13		6	2
14		6	2
15		6	2

MRD: multiple rising dose; SRD: single rising dose.

The starting dose in Part 1 (SRD) will be [redacted] (Cohort 1); starting doses of subsequent Parts 1, 2, and 3 cohorts will be determined at the dose escalation meeting based on emerging safety, tolerability, and available PK data as otherwise permitted in the protocol. Dosing will resume with modified procedures as described in Protocol Amendment 1 and 2 at [redacted] (ie, Cohort 5). Cohort 6 may be dosed at [redacted] (repeat of Cohort 5) or at [redacted] as determined at the dose escalation meeting (see Section 6.2). The planned maximum dose in Part 1 (SRD) will be [redacted] (until additional supporting clinical safety, tolerability, and PK data are available from Cohorts 5 and 6 and provided for Food and Drug Administration review before dosing). Additional cohorts may be included in Part 1 (Cohorts 6a and 6b as shown above), as determined at the dose escalation meeting based on emerging safety, tolerability, and available PK data during the study. However, dosing of an additional Part 1 cohort (single dose [redacted]) will not occur until after a pause to review safety and PK data from Cohorts 5 and 6.

6.1.1 Part 1: SRD Cohorts 1 to 6

Part 1 will consist of up to 6 sequential cohorts with 8 healthy subjects per cohort. Subjects in each cohort will be randomly assigned to receive a single dose of TAK-951 or matching placebo

via SC administration in a 3:1 ratio in a double-blind, sponsor-open manner. Up to approximately 48 healthy subjects will be randomized in Part 1 (approximate value does not account for potential replacement of subjects who withdraw for nonsafety reasons).

The schedule of study assessments for Part 1 (SRD) is presented in Table A-1.

Subjects from each cohort will be admitted into the study unit on Day -2. Baseline pulse and BP assessments, including postural measurements, will be taken on Day -1, and will be time-matched to the Day 1 assessments. At least 24-hours of baseline continuous telemetry will be collected within 48 hours before first dose administration. Subjects 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 up to 48 hours after dosing (ie, they can be discharged after the completion of the 48-hour assessments). Blood samples for assessment of TAK-951 plasma concentrations will be collected predose and at the specified time points in the schedule of study procedures. [redacted] Immunogenicity will be assessed predose (baseline), before discharge (postbaseline), and during the specified follow-up visits.

Cohort 1 will use a staggered dosing scheme. After dosing the first 2 subjects (1 receiving TAK-951 and 1 receiving placebo), the investigator will review all available safety and tolerability data up to at least 24 hours postdose and notify the sponsor of key safety findings before dosing the remaining subjects in Cohort 1. A staggered dosing approach will also be used for subsequent cohorts in Part 1. The starting dose will be [redacted] (Cohort 1) as approved by the sponsor safety board (see Table 6.b). Potential subsequent doses for SRD assuming approximately 2-fold dose increase between cohorts will be determined in the dose escalation meeting (composed of representatives from the sponsor and site study teams; see Section 6.2) based on emerging safety, tolerability, and available PK data during the study. The starting dose with implementation of Protocol Amendment 2 will be [redacted] (Cohort 5). The corresponding maximum dose will not exceed the defined exposure limit based on nonclinical safety studies as described in detail in Section 6.4.2, and not exceed [redacted] until safety, tolerability, and PK data from Cohorts 5 and 6 are available. Available safety and PK data obtained from Cohorts 5 and 6 will be provided for review by Food and Drug Administration (FDA) before dosing any additional cohort.

The sponsor may decide to administer lower doses, repeat doses, shift/omit time points, and add or cancel cohort(s) if deemed appropriate. Subjects who withdraw from the study for nonsafety reasons may be replaced at the discretion of the sponsor after discussion with the investigator.

6.1.2 Part 2: MRD Cohorts 7 to 10

Dosing of Part 2 will not be initiated before dosing of Cohorts 5 and 6 in Part 1. If Part 2 is started before the completion of Part 1, the daily doses in Part 2 will be based on exposures predicted to be below the observed daily tolerated exposures in Part 1. Doses in Part 2 are planned to be administered SC BID or 3 times daily (TID) for 5 days. A staggered dosing

approach may be used for cohorts in Part 2. Part 2 will consist of sequential dosing in up to 4 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, sponsor-open manner. Up to approximately 32 healthy subjects may be randomized in Part 2 (approximate value does not account for potential replacement of subjects who withdraw due to non-safety reasons).

The schedule of study assessments for Part 2 (MRD) are presented in the following tables:

Table A-2 Part 2 for MRD: Screening Through Day 1; BID

Table A-3 Part 2 for MRD: Days 2 Through 4; BID

Table A-4 Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET; BID

Table A-5 Part 2 for MRD: Screening Through Day 1; TID

Table A-6 Part 2 for MRD: Days 2 Through 4; TID

Table A-7 Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET; TID.

Subjects will be admitted to the study unit on Day -2. Baseline pulse and BP assessments will be taken on Day -1, and will be time-matched to the Day 1 assessments, include postural measurements. At least 24 hours of baseline continuous telemetry will be collected within 48 hours before first dose administration. Subjects in each cohort will be dosed with TAK-951 or matching placebo on Day 1 after a minimum of 8 hours of fasting for a total of 5 days of dosing. Subjects will be confined up to 48 hours after the Day 5 dose to assess safety, tolerability, and PK (ie, they can be discharged after the completion of the 48-hour assessments). Blood samples for assessment of TAK-951 concentrations will be collected predose and at the specified time points postdose as described in schedule of study procedures. Blood samples [redacted] metabolite profiling/metabolite identification will also be collected. Optional DNA samples will also be collected from subjects that provide consent for collection through a separate procedure. Immunogenicity will be assessed predose and during the specified follow-up visits.

In Part 2, up to 4 doses will be studied in an ascending manner. The daily maximum exposure in Part 2 will not exceed highest exposure determined to be tolerated in Part 1. Doses in Part 2 are planned to be administered SC either BID or TID. Doses and frequency will be determined in the dose escalation meeting (See Section 6.2) based on emerging safety, tolerability, and available PK data. The sponsor may decide to administer lower doses, repeat doses, and add or cancel cohort(s) if deemed appropriate.

Subjects who withdraw from the study for nonsafety reasons may be replaced at the discretion of the sponsor after discussion with the investigator.

6.1.3 Part 3: Dose Titration and Redosing Cohorts 11 to 15

Dosing of Part 3 will not be initiated before dosing of Cohorts 5 and 6 in Part 1. The overall purpose of Part 3 is to characterize the safety and tolerability of multiple SC dose regimens of

TAK-951 involving dose titration over 5 days of treatment. The intent of this study part is to enable a descriptive analysis (ie, without hypothesis testing) of safety and tolerability findings with dose titration. The redosing component of Part 3 is intended to provide an evaluation to assess the effects of a single rechallenge dose (after 2 to 7 days [48 to 168 hours] of washout following the 5-day treatment period) on the safety and tolerability profile (vital signs, AEs, and other safety parameters) of TAK-951.

The schedule of study assessments for Part 3 (dose titration and redosing) are presented in the following tables:

Table A-8 Part 3: Screening Through Day 1 Assessments; QD

Table A-9 Part 3: Days 2 Through 4 Assessments; QD

Table A-10 Part 3: Day 5 Through Washout Assessments; QD

Table A-11 Part 3: Redosing Through Discharge, Follow-Up, and ET;

Table A-12 Part 3: Screening Through Day 1; BID

Table A-13 Part 3: Days 2 Through 4 Assessments; BID

Table A-14 Part 3: Day 5 Through Washout Assessments; BID

Table A-15 Part 3: Screening Through Day 1; TID

Table A-16 Part 3: Days 2 Through 4; TID

Table A-17 Part 3: Day 5 Through Washout Assessments; TID

Part 3 may start before the completion of Parts 1 and 2. If Part 3 is started before the completion of Part 2, the starting dose will be decided in the dose escalation meeting (see Section 6.2); the doses for each cohort and dose frequencies will also be determined. The maximum daily exposure in Part 3 will be at a total daily exposure level at or below the highest completed cohort in Part 1 or Part 2 that has been determined to be tolerated. A staggered dosing approach may be used for cohorts in Part 3. Part 3 consists of up to 5 cohorts of healthy subjects, which may be dosed in parallel. 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, sponsor-open manner. Up to approximately 40 healthy subjects may be randomized in Part 3 (approximate value does not account for potential replacement of subjects who withdraw due to non-safety reasons).

Subjects will be admitted to the study unit on Day -2. Baseline pulse and BP assessments will be taken on Day -1, and will be time-matched to the Day 1 assessments. At least 24 hours of baseline continuous telemetry will be collected within 48 hours before the first dose. Subjects will be dosed with TAK-951 or matching placebo on Day 1 in each cohort/period after a minimum of 8 hours of fasting. Subjects will be confined up to 24 hours after the Day 5 dose to assess safety, tolerability, and PK. Blood samples for assessment of TAK-951 concentrations will be collected predose and at the specified time points postdose as described in the corresponding schedule of study procedures. [redacted]. Subjects will be discharged on Day 6 and after a 2-

to 7-day washout (48 to 168 hours after the last dose of the 5-day treatment period), they will be readmitted the evening before redosing. Subjects will be dosed with a single dose of study drug (ie, at the same dose and double-blind, sponsor-open treatment assignment as their highest daily dose during the 5-day treatment period). The duration of washout before redosing may be subject to change based on emerging safety, tolerability, and available PK data. Subjects will be confined the evening before redosing and for at least 24 hours after their redosing, while not being confined for the entire washout period. Subjects will return for additional immunogenicity and other assessments at the follow-up visit 14 ± 3 days after the redose. Based on emerging safety, tolerability, and available PK data, subjects may be confined during washout at the discretion of the investigator in consultation with the sponsor and medical monitor.

Doses in Part 3 are planned to be administered SC once daily (QD), BID, or TID depending upon emerging safety, tolerability, and available PK data. The daily exposure will not exceed an exposure established as tolerated in Part 2. Based on emerging PK data from Parts 1 and 2, or PK data from prior cohorts in Part 3, adjustments to dose and to repeat dosing duration may be implemented. The PK data from the TAK-951-1001 FIH study will also be utilized to evaluate various titration schemes.

The members of the dose escalation meeting will determine the doses and dose schedule of Part 3 cohorts based on safety, tolerability and available PK data. After completion of each cohort, and before selecting the next dose schedule, a blinded assessment of the safety and tolerability, laboratory results of at least 24 hours after the last dose (Day 5 dose) in the cohort, and available PK data will be analyzed at the dose escalation meeting. The dose will not exceed the dose studied in the highest completed dose cohort in Parts 1 and 2.

Subjects who completed the entire Part 1 or 2, including the follow-up visits, may enroll in Part 3 provided it is at least 4 weeks after the last follow-up visit in the previously enrolled part. Subjects who withdraw may be replaced at the discretion of the sponsor after discussion with the investigator.

6.2 Dose Escalation

The dose escalation meeting will occur with representatives from the sponsor (Clinical Science, Clinical Pharmacology, Global Patient Safety Evaluations, and Clinical Operations) and site investigators, who are responsible for assessing the safety and tolerability, laboratory results of at least 24 hours after the last dose in the cohort, and available PK data for each dosing cohort after completion and before selecting the next dose. See Section 6.1 for specified doses in Cohorts 5 and 6 of Part 1, and requirement for review of safety, tolerability, and PK data from Cohorts 5 and 6 before dosing an additional cohort[redacted].

The sponsor will be open and the investigator and site study team will remain blinded. Discussions within the dose escalation meeting will be conducted in a blinded manner (ie, no unblinded information will be communicated at the dose escalation meeting).

6.3 Study Drug Administration

[redacted]

Table 6.b [redacted]

In Part 1, the first SC dose(s) of study drug (TAK-951 or placebo) should be administered in the abdomen (at least 2 cm away from the umbilicus) followed by upper arms, then thigh as alternative sites. In all cases, care should be taken to avoid areas of scars, moles, tattoos, or other irritated skin (eg, vitiligo, eczema, etc). Study drug 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, or hip bone. Subjects will be semirecumbent during dosing with subsequent observation and monitoring in that position following administration to mitigate the risk of orthostatic hypotension for 2 hours. Subjects will be requested to stand for orthostatic BP and pulse measurements 2 hours post dose.

In Parts 2 and 3, when administering study drug, injection sites must be rotated. The first dose of study drug should be administered in the abdomen first (at least 2 cm away from the umbilicus), followed by upper arms, then thigh as alternative sites, avoiding areas of scars, moles, tattoos, or

other irritated skin (eg, vitiligo, eczema, etc). If repeat injections of study drug are given in the same spot, this may cause scarring and hardening of fatty tissue, which may interfere with the absorption of the drug, and therefore injections should not be given at the same location repeatedly. Each study drug 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, or hip bone. If injecting in the thighs, use the outer areas, below the groin and above the knee. Subjects will be semirecumbent during dosing with subsequent observation and monitoring in that position following administration to mitigate the risk of orthostatic hypotension and other cardiovascular AEs for 2 hours. Subjects will be requested to stand for orthostatic BP and pulse measurements 2 hours post dose.

For additional information on study drug administration, please refer to the study pharmacy manual.

6.4 Justification for Study Design, Dose, and Endpoints

6.4.1 Justification for Study Design

A randomized, double-blind, sponsor-open, 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 the study is a randomized, double-blind, sponsor-open, placebo-controlled, sequential panel MRD study where up to 6 doses/dose regimens will be studied under repeat dose conditions.

The intention with the dose titration part of Part 3 is to provide an exploratory evaluation to assess the safety and tolerability profile of dose titration at the start of the 5-day treatment period. Tolerability findings will be reviewed in Parts 1 and 2 with comparable exposures to determine whether dose titration results in different tolerability. The redosing part of Part 3 is intended to provide an exploratory evaluation to assess the effects of a single dose (after 2 to 7 days of washout following the 5-day treatment period) on vital signs, AEs, and other safety parameters.

6.4.2 Justification for Dose for SRD, MRD, and Titration

The starting dose for Part 1 of this study will be [redacted] (Cohort 1) and the maximum dose will not exceed exposures as defined below. The starting dose with implementation of Protocol Amendment 2 will be [redacted] (Cohort 5). Cohort 6 may be dosed at [redacted] (repeat of Cohort 5) or at [redacted] as determined at the dose escalation meeting (see Section 6.2).

The safety, tolerability, and PK of TAK-951 in healthy subjects has been evaluated in the FIH TAK-951-1001 study. However, the maximum tolerated dose was not identified in this FIH study. The highest evaluated dose was [redacted] in the SRD and [redacted] BID for 5 days in the MRD. Based on the overall safety data of Study TAK-951-1001, TAK-951 was well tolerated at the highest doses evaluated in SRD and MRD. Postural hypotension was confirmed as an identified

risk related to TAK-951. No other safety concerns were identified. Refer to the Investigator's Brochure (Edition 5.0) for details of the AEs reported.

A total of 32 subjects received TAK-951/placebo in this study. There have been 4 cohorts, 8 subjects in each cohort (6 assigned to active drug and 2 to placebo), that were dosed with [redacted] of TAK-951/placebo, in Cohorts 1 to 4, respectively, as of this protocol amendment (Protocol Amendment 2). A total of 24 subjects (75%) reported TEAEs, of which 22 subjects (68.8%) experienced TEAEs that were considered related to TAK-951/placebo. The majority of subjects experienced TEAEs that were Grade 1 in severity (20 of 32, 62.5%), followed by Grade 2 (10 of 32, 31.3%), and Grade 3 (1 of 32, 3.1%).

The most frequently (≥5% of subjects) reported TEAEs that were related to TAK-951/placebo included tachycardia (12 of 32, 37.5%); orthostatic hypotension (6 of 32, 18.8%); presyncope and injection site reactions (4 of 32, 12.5% each); and muscle spasms, myalgia, and pain in extremity (2 of 32, 6.3% each). One subject had a TEAE with Grade 3 severity (syncope; 1 of 32, 3.1%); presyncope and orthostatic hypotension were Grade 2 in severity for 4 of 32 subjects (12.5%) each; and tachycardia was Grade 2 in severity for 2 of 32 subjects (6.3%).

One subject reported an SAE of syncope (as summarized in the narrative below for this suspected unexpected serious adverse reactions [SUSAR]), and there were no discontinuations due to TEAEs.

Narrative of event of syncope: A [redacted] subject ([redacted], Patient ID: [redacted]), after receiving [redacted] TAK-951/placebo, had an event of syncope during the protocol-defined procedure for orthostatic vital signs at the 0.5-hour postdose time point that met the protocol-defined stopping criteria and was reported as an SAE. The event was Grade 3 in severity and considered to be related to the study drug TAK-951/placebo. The subject regained consciousness after 10 seconds and reported no neurological or cardiovascular changes after recovery. No ectopy or other vital sign changes were reported. At 2 hours after dosing, the orthostatic vital signs (systolic blood pressure/diastolic blood pressure: 0/+5 mm Hg; HR: +14 bpm changes from semirecumbent values) were noted to be stable and were not associated with recurrence of the event. At the time of the event, the standing measurements were not taken.

[redacted]

[redacted]

6.4.3 Justification for Dosing Interval

Based on Study TAK-951-1001 MRD portion where BID dosing (8 hours apart) was administered for 5 days, TAK-951 exposure [redacted] Transient vital sign changes were observed following the first dose of TAK-951. These changes were decreased in magnitude following the second dose, and the change in the vital signs was attenuated following the third and subsequent doses.

[redacted]

Therefore, BID or TID regimens will be explored in the current study to evaluate the safety, tolerability, and PK after multiple-day dosing. The exposures in BID or TID regimens will not exceed exposure determined to be safe and tolerable in Part 1 (SRD).

6.4.4 Justification for Dose Titration and Redosing After Washout

Part 3 of the study is intended to evaluate whether dose titration can result in a different tolerability, particularly with regard to CV effects, and whether redosing after a 2- to 7-day washout results in CV effects (ie, loss of potential attenuation of CV effects with dose titration and multiple dosing). For evaluating titration, dosing frequency (ie, QD, BID, or TID) may vary on different dosing days within the same cohort. [redacted] Thus, Part 3 of this study is designed to test these concepts clinically to identify the appropriate tolerizing doses, escalation, and length of time of exposure that can potentially minimize CV effects at therapeutic doses.

6.5 Premature Termination or Suspension of Study or Study Site

6.5.1 Criteria for Premature Termination of the Study

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

- Any subject experiences a Hy's Law reaction (defined as alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 × the upper limit of normal [ULN] in conjunction with elevated total bilirubin >2 × ULN without findings of cholestasis or other alternate etiology).
- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk profile for TAK-951, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises patient safety or compromises the ability to achieve the primary study objectives.
- The sponsor may elect to terminate or suspend the study for administrative reasons including plans to modify, suspend, or discontinue development of the study drug.

6.6 Criteria for Premature Suspension of the Study

In addition, dosing in the study (across all parts) will be paused to review safety data if any one of the stopping criteria is met within an individual dose cohort:

- Two or more subjects experience a sinus tachycardia with HR (pulse) >120 bpm at rest while semirecumbent with symptoms of palpitation or lightheadedness requiring medical intervention and considered related to TAK-951/placebo, or

- Two or more subjects experience a CTCAE v5.0 Grade ≥3 hypotension (ie, requiring medical intervention) and considered related to TAK-951/placebo, or
- One subject experiences a CTCAE v5.0 Grade ≥3 vasovagal syncope (fainting or orthostatic collapse), considered related to TAK-951/placebo, or
- Two or more subjects experience a CTCAE v5.0 Grade ≥3 event considered related to TAK- 951/placebo, or
- One subject experiences a CTCAE v5.0 Grade 4 event considered related to TAK-951/placebo, or
- One subject with ALT or AST >5 × ULN after TAK-951 administration, or
- One subject with ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), or
- One subject with increases in creatinine >1.5 × ULN after TAK-951 administration, or
- One subject with an SAE considered related to TAK-951/placebo, or
- Two or more subjects experience a CTCAE v5.0 Grade ≥2 injection site reaction (defined as pain combined with lipodystrophy and/or edema).

The totality of the safety data from the study will be reviewed by representatives of the sponsor and site investigators at the dose escalation meeting once the dosing is paused. If notable AEs or safety concerns are identified after review of the data, the investigator and/or the sponsor may 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.

Study drug dosing may resume if no safety concern is identified by the investigator and sponsor.

In addition, there is planned suspension of the study to review safety, tolerability, and PK data from Cohort 5 ([redacted]) and Cohort 6 ([redacted]) single doses before dosing additional cohorts in Part 1. Dosing of cohorts in Part 1 with doses greater than [redacted] will require additional supporting clinical safety, tolerability, and PK data from Cohorts 5 and 6 from Part 1 (SRD).

During Study Drug Dosing in Part 2 (MRD)

If the criteria for pausing occur in SRD Part 1 at a higher level than is being dosed in MRD Part 2, dosing in Part 2 may continue provided it is at a lower daily dose than in Part 1 than that at which the event was observed, and the sponsor and investigator agree after careful review of the totality of the available data.

During Study Drug Dosing in Part 3 (Titration and Redosing)

If the criteria for pausing occur in MRD Part 2 or SRD Part 1 at a higher level than is being dosed in Part 3 (ie, higher level than the maximal dose during titration or Day 12), dosing in Part 3 may continue provided it is at a lower daily dose than in Parts 1 or 2 than that at which the event was observed, and after careful review of the totality of the available data at the dose escalation meeting.

6.6.1 Criteria for Premature Termination or Suspension of Study Sites

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

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

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

6.6.3 Definition of End-of-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, withdraws consent from overall study participation, is lost to follow-up (ie, the investigator is unable to contact the subject), or the sponsor ends the study, whichever occurs first.

6.6.4 Total Study Duration

- Part 1 will consist of a 28-day screening period, a 1-day treatment period, and a follow-up period of 28 days.
- Part 2 will consist of a 28-day screening period, a 5-day treatment period, and a follow-up period of 28 days.
- Part 3 will consist of a 28-day screening period, a 5-day treatment period, a 2- to 7-day washout period, a 1-day retreatment period, and a follow-up period of 14 days.

The duration of follow up in any part of the study may be altered by the sponsor based on evolving data. The investigator may extend the duration of follow up for individual subjects as needed to evaluate subject safety.

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 (Appendix A).

7.1 Inclusion Criteria

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 man or woman aged 18 to 55 years, inclusive, at the screening visit.
4. Be a continuous nonsmoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to dosing and throughout the study.
5. Have a body mass index (BMI) ≥18 and ≤32 (kg/m^2) at the screening visit.
6. Be judged to be in good health (eg, no evidence of psychiatric, hepatic, renal, pulmonary, or CV 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.
7. Meet the following birth control requirements (see Section 9.6):
   - 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 30 days 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 not to donate sperm from the first dose of study drug until 30 days after the last dose of study drug.
   - Women of childbearing potential are eligible for the study provided they have a negative pregnancy test, are not lactating or breastfeeding, and are willing and agreeable to use highly effective contraception during the study and up to 30 days after the last dose of study drug.

– Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:

a) 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.

b) Surgically sterile by hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

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

d) 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) or within 5 half-lives, whichever is longest, of the investigational product before the screening visit. The 4-week or 5 half-lives window will be derived from the date of the last dose 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, as determined by the investigator.
4. The subject has a known hypersensitivity or contraindication to any component of TAK-951.
5. The subject has a positive pregnancy test or is lactating or breastfeeding.
6. 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.
7. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.
8. The subject is unable to refrain from or anticipates using any 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.
9. The subject is unable to refrain from or anticipates using marijuana or cannabis-containing products beginning approximately 7 days before administration of the first dose of study drug, throughout the study until after the last PK dose.

10. The subject has a history or presence of alcoholism or drug abuse within the past 2 years prior to dosing, or frequent or heavy use (ie, near-daily) of medical or recreational cannabis in the past 3 months before screening, as determined by the investigator.
11. The subject drinks alcohol in excess of 7 drinks/week for women or 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 [45% alcohol]) within 3 months before screening.
12. The subject has a positive alcohol test or urine drug screen results at screening or check-in.
13. The subject has had a previous major psychiatric disorder.
14. The subject has a history or presence of:
    - 3 or more incidences of vasovagal syncope within the last 5 years prior to screening; or
    - A family history of unexplained sudden death or channelopathy; or
    - Brugada syndrome (ie, RBBB pattern with ST-elevation in leads V1-V3); or
    - Cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, stroke, sick sinus syndrome, pulmonary congestion, symptomatic or significant cardiac arrhythmia, second-degree atrioventricular (AV) block type 2, third-degree AV block, prolonged QT interval with Fridericia correction method (QTcF) interval, hypokalemia, hypomagnesemia, or conduction abnormalities; or
    - Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome); or
    - Any clinically significant ECG findings or medical history including: long or short QTcF (over 450 msec or less than 360 msec), bifascicular block or QRS ≥120 msec or PR interval >210 msec at screening or Day 1 pre-Hour 0; or
    - The subject has a documented history of sinus bradycardia (<45 bpm), sinoatrial block or sinus pause ≥3 seconds.
15. The subject has an average semirecumbent BP <90/60 mm Hg or >140/90 mm Hg from screening to predose, inclusive. Any assessments on Day -1 that do not meet this criterion must be discussed with the medical monitor for approval.
16. The subject has an average semirecumbent HR (pulse) <55 or >100 bpm at any time point from screening to predose, inclusive. Subjects with an average HR (pulse) <55 bpm can be enrolled only with medical monitor approval. Any assessments after admission with an average HR (pulse) <55 bpm at any time point, from Day -2 to predose (inclusive), will be left to the judgment of the investigator, unless HR (pulse) is <50 bpm, which must be discussed with the medical monitor for approval.
17. The subject has orthostatic hypotension defined as a decrease in SBP ≥20 mm Hg or a decrease in DBP ≥10 mm Hg at approximately 3 minutes of standing when compared with BP from the semirecumbent position at screening to predose assessments, inclusive. In

asymptomatic subjects, any assessments after screening that do not meet this criterion may be repeated after the subject has remained in the semirecumbent or supine position for 15 minutes. If the repeat assessment is exclusionary based on the above criterion, the subject will not be eligible. If the repeat assessment is not exclusionary, the subject will be eligible.

18. The subject has postural orthostatic tachycardia, defined as an increase of >30 bpm or pulse >120 bpm at approximately 3 minutes of standing, at screening to predose assessments, inclusive. Any assessments after screening that do not meet this criterion may be repeated with the subject remaining standing for up to a total of 5 minutes, provided that the subject remains asymptomatic. If the repeat assessment occurring within 5 minutes is exclusionary based on the above criterion, the subject will not be eligible. A confirmed orthostatic increase of >30 bpm, but <40 bpm, on 1 or more Day -1 assessments may not be considered exclusionary if not considered clinically significant by the investigator and the medical monitor. Such assessments must be discussed with the medical monitor before determination that the subject is eligible to proceed.
19. The subject has a known or suspected current coronavirus disease 2019 (COVID-19) infection or is at risk of COVID-19 infection as assessed by the investigator.

7.3 Excluded and Allowed Concomitant Medications, Supplements, and 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 test at the discretion of the investigator.

7.3.4 Caffeine

In Part 1, subjects will refrain from consuming caffeinated beverages from the evening of Day -3 until the PK blood sample at 48 hours after dosing in each cohort. At all other times in Part 1 and in Parts 2 and 3, 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 from screening until discharge after the last scheduled dose.

7.4 Diet, Fluid, and Activity

7.4.1 Diet and Fluid

7.4.1.1 Part 1

On Day -1 of each cohort, subjects will fast overnight (at least 8 hours) and will continue to fast for 4 hours after Hour 0 for the collection of baseline time-matched pulse and BP assessments. On Day 1 of each cohort, subjects will fast overnight (at least 8 hours) before study drug dosing and will continue to fast for an additional 4 hours (after Hour 0) postdose.

On Day 1 of each cohort, meals and snacks must be completed at least 1 hour before any telemetry recording extractions and/or safety ECG.

Normal fluid intake of water is permitted and encouraged, and decaffeinated coffee or tea with nothing added are also 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 and 3

On Day -1 of each cohort, subjects will fast overnight (at least 8 hours) and will continue to fast for 4 hours after Hour 0 for the collection of baseline time-matched pulse and BP assessments. On Days 1 and 5 in Part 2, and Days 1, 5, and the day before redosing in Part 3, subjects will fast overnight (at least 8 hours) before the dose and will continue to fast for an additional 4 hours (after Hour 0) postdose.

Normal fluid intake of water is permitted and encouraged, and decaffeinated coffee or tea with nothing added are also 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 strenuous physical activity (eg, weight-lifting, running, bicycling) from 72 hours before admission to the study site, throughout the study (including the washout interval in Part 3), and until after discharge after the last scheduled dose.

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. For screen failure subjects, refer to Section 9.6.5.

1. 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.
2. Liver function test (LFT) abnormalities.
   - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN without findings of cholestasis or other alternate etiology. See Appendix D.
3. Significant protocol deviation. The discovery that the participant did not meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not attend visits and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.
6. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.6.4.
8. AE of potential injection site reaction. An AE of potential injection site reaction may require discontinuation of study drug if in the judgment of the investigator continued participation imposes risk or discomfort to the subject's continuing on study drug (eg, in receiving multiple injections/day in Part 2 of the study).

9. Other.

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

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.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

8.1.1 Study Drugs

In this protocol, the term study drug refers to all or any of the drugs defined below. TAK-951 SC 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

[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.

8.1.1.2 Comparator

Blinded matching placebo will be prepared by the pharmacy at the study site using syringes identical to those used for TAK-951 and saline.

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.

TAK-951 must be stored at -25°C to -15°C with protection from light.

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 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 unblinded 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, the designated site pharmacist should acknowledge the receipt of the shipment by signing the 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.

8.3 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.

Subjects in each cohort will be randomly assigned to receive TAK-951 or matching placebo in a 3:1 ratio in a double-blind, sponsor-open manner. Subject randomization will not be stratified.

In Part 1, all cohorts will use a staggered dosing scheme. After dosing the first 2 subjects (1 receiving TAK-951 and 1 receiving placebo), the investigator will review all available safety and CV tolerability profile data up to at least 48 hours postdose and discuss with the sponsor before dosing the remaining subjects in the cohort. A staggered dosing approach may be used for subsequent cohorts in Parts 2 or 3 (if decided during the dose escalation meeting). Except for the starting dose, doses may be modified based on emerging safety and available PK data during the study, but will have a corresponding dose that does not exceed the maximal defined exposure.

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

8.4 Blinding

This is a double-blind study; the investigator and subjects are blinded to treatment assignment. The study will be conducted sponsor-open. 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.

After completion of each dosing cohort, and before selecting the next dose, a blinded assessment of the safety and tolerability, laboratory results of at least 24 hours, and available PK data will be reviewed during the dose escalation meeting.

Discussions with the dose escalation meeting members will be conducted in a blinded manner (ie, such that no unblinded information is communicated to other members of the meeting).

The operational plan for blinding will describe study procedures for maintaining the blind of investigators and site personnel including procedures related to investigator participation in the dose escalation meetings, medical monitoring, site monitoring, and querying of data before the database lock.

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. Where appropriate, the medical monitor should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

9.0 STUDY PLAN

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 C.

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 1 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. Rescreening of subjects will be considered on a case-by-case basis by the sponsor. This case-by-case consideration by the sponsor includes screening of subjects in Part 3 who have completed the entire Part 1 or 2 and are potentially eligible for Part 3, as described in Section 6.1.

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 1 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 Demographics and Medical History

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.

9.1.3 Concomitant Medications

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 or symptom-driven physical examinations as indicated in the Schedule of Study Procedures (Appendix A).

9.2.2 Weight and Height

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

9.2.3 BMI

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 Sign Procedure

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. The same size cuff must be used for all BP measurements for each individual subject.

At screening, and from admission to the clinical research unit through predose (inclusive of Day -1 and predose on Day 1) vital signs including orthostatic BP and pulse will be used to assess for eligibility for randomization and dosing (see exclusion criteria #15 to #18 in Section 7.2).

After randomization, results of BP, pulse, orthostatic BP, and orthostatic pulse assessments immediately before dosing (the single dose in Part 1, first dose in Part 2, and first dose in Part 3) should be consistent with the vital sign criteria as defined in Section 7.2 (exclusion criteria). If vital sign criteria are outside of the specified range defined in Section 7.2 for any dose after the first dose in Parts 2 and 3, the investigator may exercise discretion related to appropriateness of the subject's ongoing study participation on the basis of assessment of clinical significance of vital signs and any ongoing AEs. The investigator will regularly update the Takeda medical monitor of vital sign findings outside of the ranges described in Section 7.2 and ongoing AEs. No protocol deviation will be issued for dosing that may be delayed for up to 1 hour due to an ongoing AE (Part 2 and Part 3) or vital sign criteria defined in Section 7.2. Should dosing be delayed in Parts 2 or 3 of the study, adjustment should be made on subsequent days to administer

the dose as close as possible to the originally planned TAK-951 dosing time based on Day 1 dosing.

Subjects should rest in a semirecumbent position for at least 5 minutes before vital signs are measured. Vital signs will include pulse (bpm), respiratory rate, and SBP and DBP in all parts of the study. BP and pulse assessments should be made in duplicate with an interval of approximately 2 minutes between the 2 assessments. The investigator can take a third BP and pulse rate assessment if results are inconsistent (ie, a difference >10 bpm in pulse or a difference >10 mmHg in SBP or DBP between assessments). If 3 measurements are obtained, the final BP and pulse readout should be the average of the 2 more consistent assessments.

Subjects in each study part will have baseline pulse and BP assessments performed on Day -1 which are time-matched (±5 minutes) to the Day 1 assessments (ie, time matched baseline).

At the predose or before Hour 0 time points, BP and pulse will be measured within 1 hour ± 10 minutes before dosing at Hour 0. When scheduled after the dose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

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

Subjects will remain semirecumbent for the first 4 hours with vital signs obtained at the timepoints indicated in Appendix A, except at the time that orthostatic vital signs are obtained or for other study-related procedures if needed. Subjects will then be permitted to ambulate provided that their vital signs remain stable and there are no significant orthostatic changes observed.

Prior to discharge, vital signs will be assessed and must meet the following criteria: semirecumbent pulse <100 bpm and BP >90/60 mmHg and no symptoms or signs of postural hypotension and tachycardia. The investigator may repeat these assessments before determining whether a subject can be discharged. If 3 measurements are obtained, the final BP and pulse readout should be the average of the 2 more consistent assessments**.**

9.2.4.1 Orthostatic Measurements

Orthostatic BP and pulse rate assessments will be performed in the outlined sequence as follows:

1. After resting for 5 minutes in a semirecumbent position, BP and pulse will be measured.
2. Subjects will then sit at bedside with crossed legs for 3 minutes.
3. Subjects will then stand for 2 minutes before collecting vital signs.

- If the pulse increases by more than 30 bpm on standing and the subject is asymptomatic, the subject may remain standing for up to a total of 5 minutes and the investigator may repeat standing measurements within 5 minutes as appropriate. Individual pulse values and the average should be reported.

- If there is a decrease in SBP ≥20 mm Hg or a decrease in DBP ≥10 mm Hg at approximately 2 minutes of standing when compared with BP from the semirecumbent position and the subject is asymptomatic, semirecumbent and standing measurements may be repeated after the subject has remained in the semirecumbent or supine position for 15 minutes. Individual BP values and the average should be reported.
- Standing assessments **must not** be performed if semirecumbent SBP 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). See Section 10.2.8.4.2 for management of symptomatic hypotension.

9.2.4.2 Wearable Device

For Part 2 (MRD), subjects will be provided with a wearable device (embracePlus) at check-in and will be asked to wear the device on their dominant wrist daily until discharge, except when the device is being charged.

The device will measure:

1. EDA, also known as the electrodermal response (and in older terminology as "galvanic skin response") is the phenomenon during which skin momentarily becomes a better conductor of electricity when either external or internal stimuli occur that are physiologically arousing.
2. HR is the speed of the heartbeat measured by the number of contractions of the heart per minute. The HR can vary according to the body's physical needs, including the need to absorb oxygen and excrete carbon dioxide, and is also modulated by other factors including genetics, physical fitness, stress and psychological status, diet, drugs, hormonal status, environment and disease/illness as well as the interaction between and among these factors.
3. HRV is a measure of the variation in time between each heartbeat. This variation is controlled by the autonomic nervous system, which subconsciously regulates, among other things, HR, BP, breathing, and digestion.

Raw data will be collected on embracePlus and transferred to a cell phone and will consequently be uploaded to a cloud storage location for further analysis. Details on the analysis of data from the wearable device will be provided in a separate document (Biomarker Analysis Plan).

9.2.4.3 Follow-up Safety Monitoring

All subjects who terminate Part 2 or 3 of the study early will be provided with the telemetry patch and BP cuff for safety monitoring for the duration of the protocol-specified observation period. Any additional AE data will be collected in the database. Follow-up telemetry and BP cuff data will not be entered into the database, but the telemetry patch and BP report will be stored in the site source documents. If the subject does not agree to allow the use of monitoring and would like to withdraw from the study, an Against Medical Advice (AMA) form will be provided to the subject prior to discharge from the CRU.

Any subject who terminates the study early for any reason, eg, if a subject tests positive for COVID-19 (Point of Care or Polymerase Chain) and is required to discharge from CRU per policy or if a subject should leave the CRU due to unforeseen circumstances, the sponsor will be consulted immediately to discuss the following:

- If the subject is asymptomatic in relation to CV symptoms but **without** telemetry observations during the postdose period, the subject could be discharged home after discussion with the sponsor, and with potential real-time monitoring (eg, Holter monitor, remote continuous telemetry monitoring and ambulatory blood pressure) for the protocol-specified telemetry observation period.
- If the subject is asymptomatic in relation to CV symptoms but **with** telemetry observations during the postdose period, the subject could be discharged to home after discussion with the sponsor. Adequate real-time monitoring (eg, Holter monitor, remote continuous telemetry monitoring and ambulatory blood pressure) for the protocol-specified telemetry observation period will be implemented and potential transfer to emergency department will be considered in consultation with the sponsor.
- If the subject has CV symptoms **with or without** telemetry observations during the postdose period, the recommendation is to discuss disposition with the sponsor and potentially discharge to the emergency department.

Based on assessment, a decision will be made to either remove the monitor because of sufficient data/safety assessment, continue remote monitoring under the supervision of an external physician, or refer the subject to the emergency department or outpatient cardiology.

9.2.5 Glucose

Blood glucose will be monitored using finger-stick blood samples in Parts 1, 2, 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 Appendix A). 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, develops tachycardia with HR >120 bpm at rest for at least 5 minutes with no physical exertion, or experiences hypotension with SBP <85 mm Hg between Day 1 (postdose) and discharge. If the subject experiences symptoms suggestive of hypotension, the subject should be instructed to lie flat, BP and HR should be re-assessed, and a 12-lead ECG should be performed to assess arrhythmia. The BP, HR, and ECG, measurements will be reviewed by the investigator, who will use clinical judgment regarding further monitoring and management. See Section 10.2.8.4 for management of symptomatic tachycardia or hypotension.

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. If the 12-lead ECG tracing is incomplete, or has motion or other artefact, the ECG will be repeated.

The following parameters will be recorded on the eCRF from the subject's ECG trace: HR, RR interval, QRS duration, PR interval, QT interval, and QTcF (using the formula $QTcF = QT/RR^{1/3}$).

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 (CSR).

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

9.2.6.2 Telemetry

In Parts 1, 2, and 3, cardiac monitoring (HR and ECG) will be assessed via telemetry and will be performed for at least 24 hours before dosing and at least 24 hours postdose.

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

Telemetry data (12-lead) will be used for real-time safety monitoring to alert site staff and will not be recorded in the eCRF. Data will be stored for review. If an AE occurs, a 12-lead ECG should be collected and interpreted by the investigator as specified in Section 9.2.6.1. Real-time actively monitored telemetry may be limited to less than 12 leads (ie, 2 leads for real time alerts).

Extractions of the 12-lead telemetry will be captured in Parts 1, 2, and 3 with a minimum of 48 hours of cardiac monitoring (24 hours predose and 24 hours postdose) (see Appendix A). The purpose of the telemetry extraction data is to support future detailed thorough QT (TQT) analysis as described below. 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 semirecumbent beginning a minimum of 5 minutes before each actual ECG extraction window of 5 minutes if possible. The rest period before the early PK draws (<1 hour postdose) may need to be shortened to accommodate the events schedule. At all other time points, subjects will be supervised while remaining at rest, quiet, and awake and in a semirecumbent position from at least 5 minutes before the beginning of each ECG extraction time point and will remain quiet, awake, motionless, and semirecumbent for at least 5 minutes after the beginning of each ECG extraction time point.

ECG extraction data from 12-lead telemetry will be archived. The continuous telemetry data are not intended to be analyzed as a predefined safety endpoint for all subjects for this study. However, these data will be available for real-time safety monitoring and to further evaluate

individual subjects who present with symptoms or signs that could be suggestive of an arrhythmia. Data will be archived for potential concentration-QT analysis unless a safety signal is detected and additional information is required for proper interpretation of the findings. eCRF data for telemetry extractions will only include date and start and stop time and whether assessment was performed.

If further review of data is requested by the sponsor for safety assessment, the site investigator should review results and interpretation of results and determine clinical significance. Results, including interpretation and associated documentation should be filed in the source documents. The sponsor should be informed of the investigator's review of the content filed in the source documents.

Collected ECG data from 12-lead telemetry may also be used to explore the relationship with TAK-951 exposure. If conducted, the results from these analyses will not be included in the CSR but will be reported separately.

9.2.7 Study Drug Administration

Study drug (TAK-951 or matching placebo) will be administered as shown in the Schedule of Study Procedures in Appendix A.

9.2.8 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 (Appendix A).

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 standard 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)	Creatine kinase

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

If subjects experience ALT or AST >3 × 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. In Parts 2 and 3, if subjects experience ALT or AST >3 × ULN or total bilirubin >2 × ULN, laboratory tests for ALT and AST should be repeated before the next scheduled dose.

If ALT or AST remains elevated >3 × 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 see 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	Nitrite
Specific gravity	

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

Hepatitis B surface antigen	Hepatitis C virus antibody
HIV	FSH (for females only)
Serum pregnancy test (βhCG) (for females only)	Urine cotinine

βhCG: beta human chorionic gonadotropin; FSH: follicle-stimulating hormone.

Alcohol Screen

Subjects will undergo an alcohol test. A breath or 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	Methamphetamines

9.4 PK, Immunogenicity, Biomarker, and DNA Samples

Samples for PK, ADA, and other biomarker analysis will be collected as specified in the Schedule of Study Procedures (Appendix A). Please refer to the laboratory manual for information on the collection 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. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional biomarkers.

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

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-951 PK	Blood	Plasma	PK analysis	Mandatory
Plasma sample for metID	Blood	Plasma	metID analysis	Mandatory
Serum sample for immunogenicity	Blood	Serum	ADA analysis	Mandatory
Blood sample for DNA	Blood	DNA	DNA analysis	Optional
[redacted]				

ADA: antidrug antibody; [redacted]; metID: metabolite identification; PK: pharmacokinetic.

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.

Exploratory metabolite profiling may be conducted on blood samples to determine the metabolites of TAK-951. If conducted, these data will be reported separately and not be reported in the CSR.

PK parameters that will be determined after single dose and at steady state include, but are not limited to, the following:

Symbol/Term	Definition
Plasma/Blood/Serum	
AUC_{24}	Area under the plasma concentration-time curve from the time 0 to time 24 hours.
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval.
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty} = AUC_t + C_{last}/\lambda_z$
$R_{ac(AUC)}$	Accumulation ratio (based on AUC), calculated as AUC_{τ} at steady state/AUC_{τ} after a single dose.
$R_{ac(Cmax)}$	Accumulation ratio (based on C_{max}), calculated as C_{max} at steady state/C_{max} 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).
C_{trough}	Observed plasma concentration at the end of a dosing interval.
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 $(CL/F)/\lambda_z$.

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

9.4.1.1 Plasma for PK Measurements and Metabolite Identification

Plasma samples for PK analysis of TAK-951 will be measured by a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay and samples will be collected into chilled blood collection tubes (vacutainer) containing the anticoagulant K2EDTA. The collected blood or resultant plasma samples may be archived for exploratory characterization of potential circulating metabolites. If conducted, these data will be reported separately and not be reported in the CSR. A full description of PK sample collection, handling, storage, and shipping can be found in the laboratory manual.

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.

Peptide drugs are often catabolized by numerous peptidases and proteases ubiquitously distributed throughout the body. An evaluation of the coverage and relative abundance of human catabolites will be conducted for cross-comparison to nonclinical species. Therefore, subject plasma samples will be collected for catabolite profiling analysis to provide an assessment of catabolite coverage in nonclinical safety testing (FDA 2020). Samples will be collected as specified in the Schedule of Study Procedures (Appendix A). These data will be reported as a separate FIH metabolite profiling and metID report and will not be reported in the CSR.

Immunogenicity (ADA) Measurements

Protein products have the potential to induce antidrug immune response that 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 immunogenicity, blood samples will be collected in all study parts according to the Schedule of Study Procedures (Appendix A). [redacted] 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.

A 3-tiered ADA testing strategy will be applied to this study. A sample will initially be screened for ADA by the ADA screening assay. Any positive sample in the screening assay is considered a potential positive, which will be confirmed for true positivity by the confirmatory assay. If a sample is confirmed as an ADA true positive, ADA titer will be assessed.

The extra immunogenicity samples will be stored for potential future use in additional ADA characterization, which will be dependent on the initial assessment of the effect of ADA status on the observed PK, pharmacodynamic, safety, and efficacy profile of TAK-951 in this study as well as the regulatory request if it is applied.

9.4.2 Biomarker Measurements

9.4.2.1 [redacted]

9.4.2.2 [redacted]

[redacted]

9.4.3 DNA Measurements

9.4.3.1 Blood Sample for DNA Analysis

Sampling of blood for DNA analysis is optional in this study and will be obtained for all subjects who consent to providing a sample for DNA. Collection of DNA will be performed for each consented subject as indicated in the Schedule of Study Procedures (Appendix A).

[redacted]

As DNA research is an evolving science, further assessments may be performed based on newly available data. DNA analysis will not be reported in the CSR.

Detailed instructions for collection, storing, handling, and shipping samples will be provided in the laboratory manual.

9.4.3.2 Biological Sample Retention and Destruction

In this study, samples of blood for DNA analysis will be collected as described in Section 9.4.3.1. Any leftover samples, if not used, will be preserved and retained at the sponsor-selected long-term storage facility for up to 5 years from the end of the study. Genetic material will be initially stored at a vendor or comparable laboratory, under contract to the sponsor, with validated procedures in place, and then preserved and retained at a long-term storage vendor, or a comparable laboratory, with validated procedures in place, for up to but not longer than 15 years from the end of the study when the CSR is signed, or if less, the maximum period permitted under applicable law or until consent is withdrawn.

The sponsor and vendors working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited

access, and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

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

Subjects who consented and provided a sample for DNA analysis can withdraw their consent at any time and request disposal of a stored sample. Any remaining sample that can be identified as coming from the subject will be destroyed. The investigator and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

9.5 Confinement

9.5.1 Part 1 SRD

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic for 48 hours postdose (Day 3). At the discretion of the investigator, subjects may be requested to remain in the clinical site longer.

9.5.2 Part 2 MRD

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until discharge on Day 7 (48 hours after last dose of study drug). At the discretion of the investigator, subjects may be requested to remain in the study site longer.

9.5.3 Part 3 Dose Titration and Redosing

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until first discharge on Day 6, 24 hours after the fifth dose of study drug. Subjects will report to the clinical site for readmission on the evening before the scheduled day of study drug redosing. Subjects will remain in the clinic until final discharge, 24 hours after the single redose of study drug. Based on emerging safety, tolerability, and available PK data, subjects may be confined during the variable washout period at the discretion of the investigator in consultation with the sponsor and medical monitor. At the discretion of the investigator, subjects may be requested to remain in the study site longer.

9.6 Contraception and Pregnancy Avoidance Procedure

9.6.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without

spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.6.2 Female Subjects and Their Male Partners

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

For studies in which teratogenicity/genotoxicity/embryotoxicity has been demonstrated (IP or comparator or background medication), or there is a lack of adequate reproductive toxicity data, female subjects should be instructed to use 2 highly effective methods of contraception/one highly effective and 1 effective method (from the list below).

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

9.6.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, 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 post-menopausal 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, the only acceptable methods of contraception are:

    - Non-Hormonal Methods:
        - Intrauterine device (IUD).
        - Bilateral tubal occlusion.

  - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success.
  - Same-sex partners not utilizing assisted reproductive technology.

- 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 ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter until she has been on contraceptive for 3 months;
    - Oral.
    - Injectable.
    - Implantable.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign an

consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   - 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?
5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have a negative urine hCG pregnancy test before receiving any dose of study medication (as close as possible and prior to first dose of study medication, preferably on the same day).

9.6.4 Pregnancy

If any subject is found to be pregnant during the study, she must be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, eg, after admission or within 30 days after the last dose of active study drug, the pregnancy must be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

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

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

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

9.6.5 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent and receive study treatment. Screen failures will be captured outside of the clinical database as part of the study source documentation.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

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

10.1.2 Definition and Elements of AEs

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

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An untoward finding generally may:

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

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 findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding 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:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

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

Changes in intensity of AEs:

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

Preplanned procedures (surgeries or interventions):

- 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 recorded 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.

Insufficient clinical response (lack of efficacy):

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

Overdose:

- 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.
- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.9.
- In the event of drug overdose, the subject should be treated symptomatically.
- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 SAEs

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

1. Results in DEATH.

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

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 10.1.2 and 10.1.3).

10.1.4 AEs of Special Interest

AEs of special interest for TAK-951 include injection site reactions, hypotension, orthostatic tachycardia, and tachycardia. In addition, orthostatic hypotension is considered an identified risk based on previous clinical experience.

10.2 Procedures

10.2.1 Assigning Severity/Intensity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 (ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50, NIH Cancer Therapy Evaluation Program, Accessed 20 November 2021). AEs not listed by the NCI CTCAE will be graded as displayed in Table 10.a.

Table 10.a NCI CTCAE Grading Guidelines Version 5.0

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.

AE: adverse event; 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 CV 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

10.2.8.1 AE 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 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a SAE 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 drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All 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:

1. Event term.
2. Start and stop date and time.
3. Pattern of AE (frequency).
4. Severity/intensity.
5. Causality (investigator's opinion of the causal relationship between the event and administration of study drugs) (related or not related).
6. Action concerning study drug.
7. Outcome of event.
8. 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 Section 3.0.

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

10.2.8.4.1 Sinus Tachycardia

CTCAE Grade	**Management**
CTCAE v5.0 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.
Any CTCAE v5.0 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; HR: heart rate; MRD: multiple rising dose. [a] Symptoms may include dizziness, light headedness, chest pain, chest heaviness, palpitations, and shortness of breath.	

If a subject complains of palpitations, dizziness, breathlessness, chest tightness, or any other symptoms suggestive of arrhythmia, the subject should be advised to lie flat, and pulse and BP should be measured and recorded, followed by a 12-lead ECG (urgently if hypotension is detected; otherwise as soon as is feasible). The BP, pulse, and ECG measurements will be reviewed by the investigator, who will use their clinical judgment regarding further monitoring and management.

10.2.8.4.2 Low BP

If a subject develops symptoms suggestive of hypotension or postural hypotension, BP should be assessed for evidence of hypotension, which should be managed as per local guidelines, and the medical monitor should be contacted. TAK-951 administration will be discontinued on occurrence of an event of CTCAE v5.0 Grade ≥3 hypotension (ie, requiring medical intervention).

If SBP is <85 mm Hg or if the subject is experiencing symptoms suggestive of postural hypotension after standing, the subject should be advised to lie flat, and BP and pulse should be rechecked in that position. If SBP remains <85 mm Hg, a 12-lead ECG should be performed and the investigator will use their clinical judgment regarding further monitoring and management.

10.2.8.4.3 Injection Site Reaction

If a subject develops a CTCAE v5.0 Grade ≥2 injection site reaction (defined as pain combined with lipodystrophy and/or edema) discontinue administration of TAK-951, provide immediate treatment and contact medical monitor.

10.2.8.4.4 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).

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

10.2.8.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × 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 Collection and Reporting of SAEs

All AEs spontaneously reported by the subject or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.2.8 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.2.8 for the period of observation) by the investigator to the Takeda Global Patient Safety Evaluation department or designee within

24 hours of becoming aware of the event. A sample of the paper-based SAE form and processing directions are in the Study Manual.

SAE Reporting Contact Information	
Fax numbers:	**United States and Canada** +1-224-554-1052
Email address:	PVSafetyAmericas@tpna.com

In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Email submission of SAE forms with a PDF attachment should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event. In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information. Information in the SAE report or form must be consistent with the data provided on the eCRF.

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

10.2.10 Reporting of Abnormal Liver-Associated Test Results

For any subject with ALT >3 × ULN **AND** total bilirubin >2 × ULN **OR** international normalized ratio (INR) >1.5 × ULN for which an alternative etiology has not been found, report the event as an SAE, contact the Medical Monitor and Takeda Trial Clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Appendix D.

10.3 Follow-up of SAEs

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

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

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all 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 to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

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

A dose escalation meeting will be held to review the emerging data as described in Section 6.2.

An external safety adjudication committee (ESAC) will perform a blinded review of ongoing cardiovascular AEs of interest throughout the conduct of the study. Details will be provided in the adjudication committee charter.

12.0 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 medical conditions will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms (including consent to use digital tools and applications, if applicable), subject authorization forms regarding the use of personal health information (if separate from the informed (e)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(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (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(R2) Section 5.5.11 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before interim analysis and 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.

Depending on the prevalence of COVID-19 infections in regions where the study is conducted, analysis may be performed to evaluate the impact of COVID-19 on the safety of all randomized subjects, where appropriate.

13.1.1 Analysis Sets

13.1.1.1 Safety Analysis Set

The safety analysis set consists of all subjects who are randomized and receive at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment actually received. The safety analysis set will be used for the analyses of demographics and baseline characteristics, all safety endpoints, and biomarkers.

13.1.1.2 PK Analysis Set

The PK analysis set consists of all subjects who receive at least 1 dose of TAK-951 and have at least 1 measurable postdose plasma concentration for TAK-951. Subjects will be analyzed according to the study treatment actually received. The PK analysis set will be used for the analyses of plasma concentrations and PK parameters of TAK-951.

13.1.1.3 Immunogenicity Analysis Set

The immunogenicity analysis set consists of all subjects who receive at least 1 dose of study treatment and have the baseline sample and at least 1 postbaseline sample ADA assessment. Subjects will be analyzed according to the study treatment actually received. The immunogenicity analysis set will be used for the analyses of immunogenicity (status of subject's ADA assessments).

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for continuous demographic variables and baseline characteristics variables (eg, age, height, weight, and BMI) for placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall in Parts 1, 2, and 3 separately. 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 placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall in Parts 1, 2, and 3 separately. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2)/dose regimen (Part 3) will be pooled across cohorts within each part of the study where appropriate. The safety analysis set will be used to summarize the demographics and baseline characteristics. All data will be provided in by-subject listings.

13.1.3 PK Analysis

The plasma concentrations of TAK-951 will be summarized by dose level (Parts 1 and 2 (BID and TID, separately))/dose regimen (Part 3) at each scheduled sampling day/time within each part of the study separately, using descriptive statistics (n, mean, standard deviation, geometric mean, percent coefficient of variation [%CV], median, minimum, and maximum) based on the PK analysis set. The PK parameters of TAK-951 determined using a noncompartmental analysis approach will be summarized by dose level (Parts 1 and 2 (BID and TID, separately))/dose regimen (Part 3) of TAK-951, as appropriate, within each part of the study separately, using descriptive statistics (n, mean, standard deviation, geometric mean, %CV, median, minimum, and maximum) based on the PK analysis set. Dose proportionality may be assessed graphically (log-transformed dose-normalized C_{max} and AUC versus dose) and by using a power model within each part of the study separately as data allow; no formal statistical comparisons will be conducted. The same dose level (Parts 1 and 2)/dose regimen (Part 3) may be pooled across cohorts within each part of the study where appropriate. All data will be provided in by-subject listings.

A population PK analysis may be conducted and a more detailed description of these analyses will be given in a separate analysis plan. The results from these analyses will not be included in the CSR and may be a standalone report.

13.1.4 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 safety data will be summarized descriptively by placebo, TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. In particular, the number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for clinical laboratory evaluations, vital signs, and ECG will be provided. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2)/dose regimen (Part 3) will be pooled across cohorts within each part of the study where appropriate. For Part 3 only, similar safety summary analyses (excluding ADA assessments) will be performed for the single dose after washout from multiple dose regimens of TAK-951 by placebo, TAK-951 single dose level after washout, and TAK-951 single dose overall after washout. All data will be provided in by subject listings.

13.1.4.1 AEs

The summary of TEAEs will include the number and percentage of subjects with at least 1 TEAE by MedDRA System Organ Class and Preferred Term and by placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. Similar summary analyses will be provided for treatment-related TEAEs, SAEs, AEs of special interest, and AEs leading to permanent treatment discontinuation as well. For Part 3 only, similar summary analyses of TEAEs will be performed for the single dose after washout from multiple dose regimens of TAK-951 by placebo, TAK-951 single dose level after washout, and TAK-951 single dose overall after washout.

13.1.4.2 Clinical Laboratory Evaluations

Clinical laboratory parameters will be summarized using descriptive statistics for baseline, postdose, and change from baseline to postdose by placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for clinical laboratory parameters will be presented by placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. For Part 3 only, similar summary analyses of clinical laboratory data will be performed for the single dose after washout from multiple dose regimens of TAK-951 by placebo, TAK-951 single dose level after washout, and TAK-951 single dose overall after washout.

13.1.4.3 Vital Signs

Vital signs (including but not limited to BP) data will be summarized using descriptive statistics for baseline, postdose, and change from baseline to postdose by placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for vital signs (including but not limited to BP) will be presented by placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. For Part 3 only, similar summary analyses of vital signs data will be performed for the single dose after washout from multiple dose regimens of TAK-951 by placebo, TAK-951 single dose level after washout, and TAK-951 single dose overall after washout.

13.1.4.4 ECG

ECG parameters (including but not limited to HR, QT/QTc, PR) will be summarized using descriptive statistics for baseline, postdose, and change from baseline to postdose by placebo, each TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall within each part of the study separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for ECG parameters (including but not limited to HR, QT/QTc, and increase from baseline in QT/QTc) will be presented by placebo,

each TAK-951 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-951 overall within each part of the study separately. For Part 3 only, similar summary analyses of ECG data will be performed for the single dose after washout from multiple dose regimens of TAK-951 by placebo, TAK-951 single dose level after washout, and TAK-951 single dose overall after washout.

ECG data will be listed by subject and treatment group for each part of the study.

13.1.4.5 Other Safety Parameters

Physical examination findings will only be presented in the data listings.

13.1.5 Immunogenicity Analysis

Immunogenicity will be summarized using the immunogenicity analysis set. The number and percentage of subjects in each category of the immunogenicity status (ADA-negative or ADA-positive, and low or high ADA titer) will be tabulated by placebo, TAK-951 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-951 overall at scheduled time points within each part of the study separately. The relationship between immunogenicity status (ADA-negative or ADA-positive, and low or high ADA titer) and PK, and safety may be explored. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2)/dose regimen (Part 3) will be pooled across cohorts within each part of the study where appropriate. All data will be provided in by-subject listings.

13.1.6 Biomarker Analysis

Biomarker measurements will be summarized using the safety analysis set. [redacted]

13.2 Interim Analysis

To support internal decision making regarding further development of [redacted] TAK-951, an interim analysis of safety, tolerability, and PK at a time point dependent

on emerging clinical data from TAK-951-1008 may be conducted. If the interim analysis is conducted, the interim analysis will include all available data (including, but not limited to TEAEs, vital signs, ECG, laboratory assessments, physical examinations, and PK). Additional interim analyses may be conducted for sponsor internal decision-making and would be defined in the SAP. The details of interim analysis (timing, datasets, and methods), data access management plan, and distribution of results will be described in a separate documents (ie, SAP and data access management plan).

13.3 Determination of Sample Size

The selected sample sizes in Parts 1, 2, and 3 of the study are considered sufficient for evaluation of safety and tolerability of TAK-951 in healthy subjects. No formal statistical hypothesis testing is planned in Parts 1, 2, or 3. Therefore, no formal power calculations were performed in the determination of the sample size for this study.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits 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. In the event a monitor cannot visit the site in a timely manner, alternative monitoring approaches, such as remote source verification or telephone contact, may be used to ensure data quality and integrity and maintain patient safety.

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.

14.2 Protocol Deviations

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

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.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] FDA, the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed (e)consent and investigator responsibilities.

15.1 IRB

IRBs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the 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.

15.2 Subject Information, Informed (e)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, including the use of electronic devices and associated technologies (if applicable). 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, and the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. 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 a ballpoint pen with either blue or black ink in the case of written informed consent. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent or after receipt of subject signature (in the case of eConsent) and before the subject enters 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, or certified copy (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) will be maintained by the study site. 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 provided to the subject.

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

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

15.3 Subject Confidentiality

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

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventative actions in response. These actions will be documented and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, UK MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study

participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

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

15.4 Clinical Trial Disclosures and Publication

15.4.1 Clinical Trial Registration and Results Disclosure

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials before study start and disclose the results of those trials in a manner and timeframe compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on ClinicalTrials.gov, other clinical trial registries/databases as required by law, and on Takeda's corporate website(s).

15.4.2 Publication

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.

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 venue (eg, congress, journal) will appropriately reflect contributions to the production, review, and approval of the document.

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

FDA 2020. Guidance for Industry: Safety Testing of Drug Metabolites. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).

[redacted]

APPENDICES

Appendix A Schedules of Study Procedures

Part 1 SRD: Cohorts 1 to 6

Table A-1 Part 1 for SRD: Screening Through Day 3, Follow-Up, and ET

	Day -2 8 to -3	Day -2 [a]	Day -1 (Hours)													Day 1 (Hours)														Day 2	Day 3	Follow-Up		
	Screening		0	0.5	1	2	3	4	6	8	10	12	14	16	24 [b]	P	0	0.5	1	2	3	4	6	8	10	12	14	16	24	30	48 Discharge [c]	Day 14 ±2	Day 29 ±3	ET
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 [d]		X [d]			X
Height	X																																	
Weight and BMI	X	X																																X
TAK-951/placebo administration [e]																	X																	
Vital Signs	X	X														X				X		X							X					X
Semirecumbent BP and pulse [f]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Standing BP and pulse [g]	X					X		X		X					X	X				X		X		X					X			X		X
12-lead ECGs	X	X													X	X													X					X
ECG telemetry (12-lead)				X——Continuous Monitoring [h]——X														X——Continuous Monitoring——X																
Telemetry extraction [i]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X					X
AE monitoring	X [j]		X——Continuous Review——X																													X	X	X

Table A-1 Part 1 for SRD: Screening Through Day 3, Follow-Up, and ET

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)													Day 1 (Hours)														Day 2	Day 3	Follow-Up		
	Screening		0	0.5	1	2	3	4	6	8	10	12	14	16	24 [b]	P	0	0.5	1	2	3	4	6	8	10	12	14	16	24	30	48 Discharge [c]	Day 14 ±2	Day 29 ±3	ET
Laboratory Procedures/Assessments																																		
Safety laboratory collection (hematology and serum chemistry)	X	X														X						X [k]							X		X	X	X	X
LFTs [l]	X															X															X	X	X	X
Urinalysis	X	X																											X					X
Serum sample for CK [m]																X													X		X			X
Glucose finger stick																X					X					X								X
Urine drug screen	X	X																																
Alcohol test		X																																
Cotinine test	X	X																																
Hepatitis screen [n]	X																																	
HIV screen	X																																	
βhCG (pregnancy) test [o]	X	X																													X			X
Serum FSH test [p]	X																																	
PK Evaluations																																		
Plasma sample for TAK-951 PK																X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Immunogenicity and Biomarker Evaluations																																		
Serum sample for immunogenicity [q]																X																X	X	X
Blood sample for DNA (optional) [r]																															X			X

[redacted]

Table A-1 Part 1 for SRD: Screening Through Day 3, Follow-Up, and ET

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)													Day 1 (Hours)														Day 2	Day 3	Follow-Up		
	Screening		0	0.5	1	2	3	4	6	8	10	12	14	16	24 [b]	P	0	0.5	1	2	3	4	6	8	10	12	14	16	24	30	48 Discharge [c]	Day 14 ±2	Day 29 ±3	ET
[redacted]																																		
Other																																		
Confinement		X														Continuous															X			

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; d: days; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; LFT: liver function tests; P: predose; PK: pharmacokinetic; SRD: single rising dose.

[a] Subjects will be admitted to the site on Day -2.

[b] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[c] Subjects will be confined for 48 hours after dosing (can be discharged after the 48-hour PK sample). At the 48-hour visit, additional procedures may be performed at the investigator's discretion.

[d] Physical examination at the indicated visit will be symptom-driven.

[e] Subjects will be administered a single dose of TAK-951 or matching placebo.

[f] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[g] Standing BP and pulse, assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[h] At least 24 hours of continuous telemetry monitoring will be conducted between check-in on Day -2 and predose on Day 1.

[i] Predose time-matched telemetry extractions may take place on either Day -2 or Day -1 at the corresponding time.

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

[k] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.

[l] LFTs may be collected at additional time points based on investigator discretion.

[m] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

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

[o] Serum or urine pregnancy test for female subjects only.

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

[q] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, at ET (if applicable), and at follow-up visits on Day 14 and Day 29. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

Table A-1 Part 1 for SRD: Screening Through Day 3, Follow-Up, and ET

																															Follow-Up		
	Day -2 8 to -3	Day -2 [a]	Day -1 (Hours)													Day 1 (Hours)														Day 2	Day 3			
	Screening		0	0.5	1	2	3	4	6	8	10	12	14	16	24 [b]	P	0	0.5	1	2	3	4	6	8	10	12	14	16	24	30	48 Discharge [c]	Day 14 ±2	Day 29 ±3	ET

[r] If subjects have provided consent for the optional DNA collection, blood samples may be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

Part 2 MRD: Cohorts 7 to 10

Part 2 BID Dosing Schema

Part 2 for MRD: Screening Through Day 1, BID

Table A-2 Part 2 for MRD: Screening Through Day 1; BID

	Day		Scheduled Time																																				
	-28 to -3	-2 [a]	Day -1 (Hours)																		Day 1 (Hours)																			
	Screening		0	0.5	1	2	3	4	6	7	8	8.5	9	10	11	12	13	14	16	24 [b]	P	0	0.5	1	2	3	4	6	7	P 8	8	8.5	9	10	11	12	13	14	16	24 [b]
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																																						
Height	X																																							
Weight and BMI	X	X																																						
Vital signs	X	X																			X				X		X													X
Semirecumbent BP and pulse [c]	X			X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X
Standing BP and pulse[d]	X					X		X				X		X		X				X	X				X		X			X		X		X		X				X
12-lead ECGs	X	X																			X																			X
ECG telemetry (12-lead)			X------Continuous Monitoring [e]------X																		X------Continuous Monitoring------X																			
Telemetry extraction [f]			X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X		X	X	X	X		X		X			X	X	X	X	X	X	X	X
Wearable device [g]			X------Continuous wear until discharge------X																																					
TAK-951/ placebo administration [h]																						X									X									

Table A-2 Part 2 for MRD: Screening Through Day 1; BID

	Day		Scheduled Time																																					
	-28 to -3	-2 [a]	Day -1 (Hours)																		Day 1 (Hours)																			
	Screening		0	0.5	1	2	3	4	6	7	8	8.5	9	10	11	12	13	14	16	24 [b]	P	0	0.5	1	2	3	4	6	7	P 8	8	8.5	9	10	11	12	13	14	16	24 [b]
AE monitoring	X [i]		X ---------- Continuous Monitoring ---------- X																																					
Laboratory Procedures/Assessments																																								
Safety laboratory collection (hematology and serum chemistry)	X	X						X [j]													X						X [j]									X				
LFTs [k]	X																				X																			
Serum sample for CK [l]																					X																			X
Urinalysis	X	X	X																		X															X				
Glucose finger stick			X																		X					X														
Urine drug screen	X	X																																						
Alcohol test		X																																						
Cotinine test	X	X																																						
Hepatitis screen [m]	X																																							
HIV screen	X																																							
βhCG (pregnancy) test [n]	X	X																																						
Serum FSH test [o]	X																																							
PK Evaluations																																								
Plasma sample for TAK-951 PK																					X		X	X	X	X		X		X [p]			X	X	X	X	X	X	X	X
Plasma sample for metID																					X		X		X			X		X [p]				X						X
Immunogenicity and Biomarker Evaluations																																								
Serum sample for immunogenicity [q]																					X																			

Table A-2 Part 2 for MRD: Screening Through Day 1; BID

	Day		Scheduled Time																																				
	-28 to -3	-2 [a]	Day -1 (Hours)																		Day 1 (Hours)																			
	Screening		0	0.5	1	2	3	4	6	7	8	8.5	9	10	11	12	13	14	16	24 [b]	P	0	0.5	1	2	3	4	6	7	P 8	8	8.5	9	10	11	12	13	14	16	24 [b]
[redacted]																																								
Other																																								
Confinement		X ---------- Continuous ---------- X																																						

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BID: twice daily; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; FSH: follicle-stimulating hormone; [redacted]; HbsAg: hepatitis B surface antigen; metID: metabolite identification; LFT: liver function test; MRD: multiple rising dose; P: predose; PK: pharmacokinetic.

[a] Subjects will be admitted to the site on Day -2.

[b] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[c] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[d] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[e] At least 24 hours of continuous telemetry monitoring will be conducted between check-in on Day -2 and predose on Day 1.

[f] Predose time-matched telemetry extractions may take place on either Day -2 or Day -1 at the corresponding time.

[g] Wearable device will be provided to subjects at check-in and will remain on until discharge, except when being charged.

[h] Subjects will be administered study drug BID of TAK-951 or matching placebo.

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

[j] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.

[k] LFTs may be collected at additional time points based on investigator discretion.

[l] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

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

[n] Serum or urine pregnancy test for female subjects only.

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

[p] Predose blood sample for PK and metID may be drawn 10 minutes before dosing.

Table A-2 Part 2 for MRD: Screening Through Day 1; BID

	Day		Scheduled Time																																				
	-28 to -3	-2 [a]	Day -1 (Hours)																	Day 1 (Hours)																			
	Screening		0	0.5	1	2	3	4	6	7	8	8.5	9	10	11	12	13	14	16	24 [b]	P	0	0.5	1	2	3	4	6	7	P 8	8	8.5	9	10	11	12	13	14	16	24 [b]

[a] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[redacted]

Part 2 for MRD: Days 2 Through 4, BID

Table A-3 Part 2 for MRD: Days 2 Through 4; BID

	Scheduled Time																			
	Time Points (Hours) Days 2 Through 4																			
	Predose	0	0.5	1	2	3	4	6	7	Predose 8	8	8.5	9	10	11	12	13	14	16	24 [a]
Administrative Procedures																				
Prior and concomitant medication review		X----------Continuous Review----------X																		
Clinic Procedures/Assessments																				
Vital signs	X				X		X							X		X				X
Semirecumbent BP and pulse [b]	X		X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X
Standing BP and pulse [c]	X		X		X		X			X		X		X		X				X
ECG telemetry (12-lead)		X----------Continuous Monitoring----------X																		
Wearable device [d]		X----------Continuous Wear Until Discharge----------X																		
TAK-951/placebo administration [e]		X									X									
AE monitoring	X----------Continuous Review----------X																			
Laboratory Procedures/Assessments																				
Safety laboratory collection (hematology and serum chemistry) [g]	X																			X
LFTs [h]																				X (Day 2)
Serum sample for CK [i]	X																			X
Urinalysis	X															X				
Glucose finger stick	X					X														
PK Evaluations and Biomarkers																				
Plasma sample for TAK-951 PK	X [j]									X [j]										

[redacted]

Table A-3 Part 2 for MRD: Days 2 Through 4; BID

	Scheduled Time																		
	Time Points (Hours) Days 2 Through 4																		
	Predose	0	0.5	1	2	3	4	6	7	Predose 8	8	8.5	9	10	11	12	13	14	16	24 [a]
Other																				
Confinement	X----------Continuous----------X																			

AE: adverse event; BID: twice daily; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; LFT: liver function tests; MRD: multiple rising dose; PK: pharmacokinetic.

[a] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[b] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[c] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[d] Wearable device will be provided to subjects at check-in and will remain on until discharge, except when charging.

[e] Follow-up doses of TAK-951 or matching placebo should be given at the same time as on Day 1.

[f] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.

[g] Safety laboratory collection will be on Day 3 only.

[h] LFTs may be collected at additional time points based on investigator discretion.

[i] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

[j] Predose blood sample for PK may be drawn 10 minutes before dosing.

[redacted]

Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET, BID

Table A-4 Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET; BID

	Scheduled Time																							
	Day 5 (Hours)																			Day 6	Day 7 Discharge	Follow-Up Day 14 ±2	Follow-Up Day 29 ±3	ET
	Predose	0	0.5	1	2	3	4	6	7	Predose 8	8	8.5	9	10	11	12	13	14	16	24	30	48 [a]		
Administrative Procedures																								
Prior and concomitant medication review	X ----------Continuous Review---------- X																							
Clinic Procedures/Assessments																								
Full physical examination																					X			X
Vital Signs	X				X		X			X				X		X				X		X		X
Semirecumbent BP and pulse [b]	X		X	X	X	X	X	X	X	X		X		X		X		X	X	X		X		X
Standing BP and pulse [c]	X		X		X		X			X		X		X		X				X				X
12-lead ECGs																						X		
ECG telemetry (12-lead)	X ----------Continuous Monitoring ---------- X																							
Telemetry extraction	X		X	X	X	X		X		X			X	X	X	X	X	X	X	X				X
Wearable device [d]	X----------Continuous Wear Until Discharge----------X																							
TAK-951/ placebo administration [e]		X									X													
AE monitoring	X ----------Continuous Review---------- X																							
Laboratory Procedures/Assessments																								
Safety laboratory collection (hematology and serum chemistry)	X															X						X	X	X
LFTs [f]																						X	X	X
Serum sample for CK [g]																						X		X
Urinalysis	X															X						X		X
Glucose finger stick	X					X																		X
βhCG (pregnancy) test [h]																						X		X
PK Evaluations																								
Plasma sample for TAK-951 PK	X [i]		X	X	X	X		X		X [i]			X	X	X	X	X	X	X	X	X	X		X
Plasma sample for metID	X [i]		X		X			X		X [i]				X						X				X

Table A-4 Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET; BID

	Scheduled Time																							
	Day 5 (Hours)																				Day 6	Day 7 Discharge	Follow-Up Day 14 ±2	Follow-Up Day 29 ±3	ET
	Predose	0	0.5	1	2	3	4	6	7	Predose 8	8	8.5	9	10	11	12	13	14	16	24	30	48 [a]			
Immunogenicity and Biomarker Evaluations																									
Serum sample for immunogenicity [j]																							X	X	X
Blood sample for DNA (optional) [k]																						X			X
[redacted]																									
Other																									
Confinement	X----------Continuous----------X																								

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BID: twice daily; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; LFT: liver function test; metID: metabolite identification; MRD: multiple rising dose; PK: pharmacokinetic.

[a] Subjects will be confined for 48 hours after dosing (can be discharged after the 48-hour PK sample). At the 48-hour visit, additional procedures may be performed at the investigator's discretion.

[b] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[c] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[d] Wearable device will be provided to subjects at check-in and will remain on until discharge, except for charging.

[e] Follow-up doses of TAK-951 or matching placebo should be given at the same time as on Day 1.

[f] LFTs may be collected at additional time points based on investigator discretion.

[g] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

[h] Serum or urine pregnancy test for female subjects only.

[i] Predose blood sample for PK and metID may be drawn 10 minutes before dosing.

[j] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, discharge, at ET (if applicable), and at follow-up visits on Day 14 and Day 29. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[k] If subjects have provided consent for the optional DNA collection, blood samples may be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

Part 2 TID Dosing Schema

Part 2 for MRD: Screening Through Day 1, TID

Table A-5 Part 2 for MRD: Screening Through Day 1; TID

	Day		Scheduled Time																																										
	-28 to -3	-2 [a]	Day – 1 (Hours)																				Day 1 (Hours)																						
	Screening		0	0.5	1	2	3	4	6	6.5	7	8	9	10	12	12.5	13	14	15	16	18	24 b	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24 b
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																																											
Height	X																																												
Weight and BMI	X	X																																											
Vital signs	X	X																					X				X		X																X
Semirecumbent BP and pulse [c]	X			X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X
Standing BP and pulse [d]	X					X		X	X	X		X		X	X	X		X		X	X	X	X				X		X	X		X		X		X	X		X		X		X	X	X
12-lead ECGs	X	X																					X																						X
ECG telemetry (12-lead)		X ---Continuous Monitoring [e]---X																					X ---Continuous Monitoring---X																						
Telemetry extraction [f]			X	X	X	X	X			X	X	X	X	X		X	X	X		X		X	X		X	X	X	X		X		X	X	X	X	X	X		X	X	X		X		X
Wearable device [g]		X—Continuous Wear Until Discharge—X																																											
TAK-951/ placebo administration [h]																								X							X							X							

Table A-5 Part 2 for MRD: Screening Through Day 1; TID

	Day		Scheduled Time																																									
	-28 to -3	-2 [a]	Day – 1 (Hours)																				Day 1 (Hours)																						
	Screening		0	0.5	1	2	3	4	6	6.5	7	8	9	10	12	12.5	13	14	15	16	18	24 [b]	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24 [b]
AE monitoring	X [i]	X ----------Continuous Review---------- X																																										
Laboratory Procedures/Assessments																																												
Safety laboratory collection (hematology and serum chemistry)	X	X						X [j]															X						X [j]								X								
LFTs [k]	X																						X																						
Serum sample for CK [l]																							X																						X
Urinalysis	X	X													X								X														X								
Glucose finger stick																							X					X																	
Urine drug screen	X	X																																											
Alcohol test		X																																											
Cotinine test	X	X																																											
Hepatitis screen [m]	X																																												
HIV screen	X																																												
βhCG (pregnancy) test [n]	X	X																																											
Serum FSH test [o]	X																																												
PK Evaluations																																													
Plasma sample for TAK-951 PK																							X		X	X	X	X		X [p]		X	X	X	X	X	X [p]		X	X	X		X		X
Immunogenicity and Biomarker Evaluations																																													
Serum sample for immunogenicity [q]																							X																						

Table A-5 Part 2 for MRD: Screening Through Day 1; TID

	Day		Scheduled Time																																										
	-28 to -3	-2 [a]	Day – 1 (Hours)																				Day 1 (Hours)																						
	Screening		0	0.5	1	2	3	4	6	6.5	7	8	9	10	12	12.5	13	14	15	16	18	24 [b]	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24 [b]
[redacted]																																													
Other																																													
Confinement		X																			Continuous																								X

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; [redacted] HBsAg: hepatitis B surface antigen; LFT: liver function test; metID: metabolite identification; MRD: multiple rising dose; P: predose; PK: pharmacokinetic; TID: 3 times daily.

[a] Subjects will be admitted to the site on Day -2.

[b] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[c] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[d] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[e] At least 24 hours of continuous telemetry monitoring will be conducted between check-in on Day -2 and predose on Day 1.

[f] Predose time-matched telemetry extractions may take place on either Day -2 or Day -1 at the corresponding time.

[g] Wearable device will be provided to subjects at check-in and will remain on until discharge, except when charging.

[h] Subjects will be administered study drug TID of TAK-951 or matching placebo.

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

[j] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.

[k] LFTs may be collected at additional time points based on investigator discretion.

[l] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

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

[n] Serum or urine pregnancy test for female subjects only.

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

Table A-5 Part 2 for MRD: Screening Through Day 1; TID

	Day		Scheduled Time																																										
	-28 to -3	-2 [a]	Day – 1 (Hours)																				Day 1 (Hours)																						
	Screening		0	0.5	1	2	3	4	6	6.5	7	8	9	10	12	12.5	13	14	15	16	18	24 [b]	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24 [b]

[p] Predose blood sample for PK and metID may be drawn 10 minutes before dosing.

[q] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, at ET (if applicable), and at follow-up visits on Days 14 and 29. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[redacted]

Part 2 for MRD: Days 2 Through 4, TID

Table A-6 Part 2 for MRD: Days 2 Through 4; TID

		Scheduled Time																				
		Time Points (Hours) Days 2 Through 4																				
	Predose	0	0.5	1	2	3	4	Predose 6	6	6.5	7	8	9	10	Predose 12	12	12.5	13	14	15	16	18	24 [a]
Administrative Procedures																							
Prior and concomitant medication review	X	----------Continuous Review----------																				X
Clinic Procedures/Assessments																							
Vital signs	X				X		X					X		X					X		X		X
Semirecumbent BP and pulse [b]	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X
Standing BP and pulse [c]	X		X		X		X	X		X		X		X	X		X		X		X	X	X
ECG telemetry (12-lead)	X	----------Continuous Monitoring----------																				X
Wearable device [d]	X	----------Continuous Wear Until Discharge----------																				X
TAK-951/placebo administration [e]		X							X							X							
AE monitoring	X	----------Continuous Review----------																				X
Laboratory Procedures/Assessments																							
Safety laboratory collection (hematology and serum chemistry) [f]	X																						X
LFTs [g]																							X (Day 2)
Serum sample for CK [h]	X																						X
Urinalysis	X														X								
Glucose finger stick	X					X																	
PK and Biomarker Evaluations																							
Plasma sample for TAK-951 PK	X [i]							X [i]							X [i]								
[redacted]																							

Table A-6 Part 2 for MRD: Days 2 Through 4; TID

		Scheduled Time																				
		Time Points (Hours) Days 2 Through 4																				
	Predose	0	0.5	1	2	3	4	Predose 6	6	6.5	7	8	9	10	Predose 12	12	12.5	13	14	15	16	18	24 [a]
Other																							
Confinement	X ----------Continuous----------X																						

AE: adverse event; βhCG: beta human chorionic gonadotropin; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; LFT: liver function tests; MRD: multiple rising dose; PK: pharmacokinetic; TID: 3 times daily.

[a] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[b] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[c] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[d] Wearable device will be provided to subjects at check-in and will remain on until discharge, except when charging.

[e] Follow-up doses of TAK-951 or matching placebo should be given at the same time as on Day 1.

[f] Safety laboratory collection will be on Day 3 only.

[g] LFTs may be collected at additional time points based on investigator discretion.

[h] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

[i] Predose blood sample for PK may be drawn 10 minutes before dosing.

[redacted]

Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET, TID

Table A-7 Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET; TID

	Scheduled Time																											Follow-Up		
	Day 5 (Hours)																									Day 6	Day 7 Discharge	Day 14 ±2	Day 29 ±3	ET
	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24	30	48 [a]			
Administrative Procedures																														
Prior and concomitant medication review	X ----------Continuous Review---------- X																													
Clinic Procedures/Assessments																														
Full physical examination																									X			X
Vital signs	X				X		X	X				X		X	X				X		X		X		X				X
Semirecumbent BP and pulse [b]	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X		X				X
Standing BP and pulse [c]	X		X		X		X	X		X		X		X	X		X		X		X	X	X						X
12-lead ECGs																									X				
ECG telemetry (12-lead)	X ----------Continuous Monitoring---------- X																													
Telemetry extraction	X		X	X	X	X		X		X	X	X	X	X	X		X	X	X		X		X						
Wearable device [d]	X---------- Continuous Wear Until Discharge ----------X																													
TAK-951/ placebo administration [e]		X							X							X													
AE monitoring	X ----------Continuous Review---------- X																													
Laboratory Procedures/Assessments																														
Safety laboratory collection (hematology and serum chemistry)	X															X									X	X	X	X
LFTs [f]																									X	X	X	X
Serum sample for CK [g]																									X			X
Urinalysis	X															X									X			X

Table A-7 Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET; TID

	Scheduled Time																										
	Day 5 (Hours)																							Day 6	Day 7 Discharge	Follow-Up Day 14 ±2	Follow-Up Day 29 ±3	ET
	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24	30	48 [a]			
Glucose finger stick	X					X																						X
βhCG (pregnancy) test [h]																									X			X
PK Evaluations																												
Plasma sample for TAK-951 PK	X [i]		X	X	X	X		X [i]		X	X	X	X	X	X [i]		X	X	X		X		X	X	X			X
Immunogenicity and Biomarker Evaluations																												
Serum sample for immunogenicity [j]																										X	X	X
Blood sample for DNA (optional) [k]																									X			X
[redacted]																												
Other																												
Confinement	X ----------Continuous ----------X																											

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; LFT: liver function test; MRD: multiple rising dose; P: predose; PK: pharmacokinetic; TID: 3 times daily.

[a] Subjects will be confined for 48 hours after dosing (can be discharged after the 48-hour PK sample). At the 48-hour visit, additional procedures may be performed at the investigator's discretion.

[b] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[c] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[d] Wearable device will be provided to subjects at check-in and will remain on until discharge, except when charging.

[e] Follow-up doses of TAK-951 or matching placebo should be given at the same time as on Day 1.

[f] LFTs may be collected at additional time points based on investigator discretion.

[g] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

Table A-7 Part 2 for MRD: Day 5 Through Discharge, Follow-Up, and ET; TID

	Scheduled Time																										
	Day 5 (Hours)																								Day 6	Day 7 Discharge	Follow-Up Day 14 ±2	Follow-Up Day 29 ±3	ET
	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24	30	48 [a]			

[h] Serum or urine pregnancy test for female subjects only.

[i] Predose blood sample for PK may be drawn 10 minutes before dosing.

[j] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, at ET (if applicable), and at follow-up visits on Days 14 and 29. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[k] If subjects have provided consent for the optional DNA collection, blood samples may be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

Part 3 Dose Titration and Redosing: Cohorts 11 to 15

Part 3 QD Dosing Schema

Part 3 Screening Through Day 1 Assessments QD

Table A-8 Part 3: Screening Through Day 1 Assessments; QD

			Scheduled Time																							
	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 (Hours)											
	Screening		0	0.5	1	2	3	4	6	8	10	12	16	24 [b]	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [b]
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																									
Vital signs	X	X													X				X		X						X
Semirecumbent BP and pulse [c]	X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [d]	X					X		X		X				X	X				X		X		X				X
12-lead ECGs	X	X													X												X
ECG telemetry (12-lead)		X----------Continuous Monitoring [e] ----------X													X----------Continuous Monitoring ----------X											

Table A-8 Part 3: Screening Through Day 1 Assessments; QD

			Scheduled Time																								
	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 (Hours)												
	Screening		0	0.5	1	2	3	4	6	8	10	12	16	24 [b]	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [b]
Telemetry extraction [f,g]			X	X	X	X	X			X		X		X	X		X	X	X	X			X		X		X
TAK-951/placebo administration																X											
AE monitoring	X [h]	X----------Continuous Review----------X																									
Laboratory Procedures/Assessments																											
Safety laboratory collection (hematology and serum chemistry)	X	X						X [i]							X						X [i]						
LFTs [j]	X														X												X
Serum sample for CK [k]															X												X
Urinalysis	X	X													X										X		
Glucose finger stick															X					X							
Urine drug screen	X	X																									
Alcohol test		X																									
Cotinine test	X	X																									
Hepatitis screen [l]	X																										
HIV test	X																										
βhCG (pregnancy) test [m]	X	X																									
Serum FSH test [n]	X																										
PK Evaluations																											
Plasma sample for TAK-951 PK [g]															X		X	X	X	X			X		X		X
Immunogenicity and Biomarkers																											
Serum sample for immunogenicity [o]															X												

Table A-8 Part 3: Screening Through Day 1 Assessments; QD

			Scheduled Time																								
	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 (Hours)												
	Screening		0	0.5	1	2	3	4	6	8	10	12	16	24 [b]	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [b]
[redacted]																											
Other																											
Confinement		X----------Continuous----------X																									

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; LFT: liver function tests; P: predose; PK: pharmacokinetic; QD: once daily.

[a] Subjects will be admitted to the site on Day -2.

[b] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[c] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[d] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[e] At least 24 hours of continuous telemetry monitoring will be conducted between check-in on Day -2 and predose on Day 1.

[f] Predose time-matched telemetry extractions may take place on either Day -2 or Day -1 at the corresponding time.

[g] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

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

[i] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.

[j] LFTs may be collected at additional time points based on investigator discretion.

[k] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

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

[m] Serum or urine pregnancy test for female subjects only.

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

Table A-8 Part 3: Screening Through Day 1 Assessments; QD

			Scheduled Time																						
	Day -28 to -3	Day -2 [a]	Day -1 (Hours)											Day 1 (Hours)											
	Screening		0	0.5	1	2	3	4	6	8	10	12	16	24 [b]	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [b]

[a] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 6 (discharge), at ET (if applicable), predose on the redosing day, and at the follow-up visit 14 days after redose. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[redacted]

Part 3 Days 2 Through 4 Assessments QD

Table A-9 Part 3: Days 2 Through 4 Assessments; QD

	Scheduled Time												
	Days 2-4 (Hours)												
	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [a]
Administrative Procedures													
Previous and concomitant medications	X----------Continuous Review----------X												
Clinic Procedures/Assessments													
Vital signs	X				X		X						X
Semirecumbent BP and pulse [b]	X		X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [c]	X		X		X		X		X				X
TAK-951/placebo administration [d]		X											
ECG telemetry (12-lead)	X----------Continuous Monitoring----------X												
Telemetry extraction [e]	X		X [f]	X [f]	X [f]	X [f]			X [f]		X [f]		X [f]
AE monitoring	X----------Continuous Review----------X												
Laboratory Procedures/Assessments													
Safety laboratory collection (hematology and serum chemistry) [g]	X												
LFTs [h]													X (Day 2)
Urinalysis	X										X		
Glucose finger stick	X					X							
PK Evaluations and Biomarkers													
Plasma sample for TAK-951 PK [e]	X [i]		X [j]	X [j]	X [j]	X [j]			X [j]		X [j]		X [j]
[redacted]													
Other													
Confinement	X----------X												

Table A-9 Part 3: Days 2 Through 4 Assessments; QD

	Scheduled Time												
	Days 2-4 (Hours)												
	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [a]

AE: adverse event; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; ECG: electrocardiogram; LFT: liver function test; PK: pharmacokinetic; QD: once daily.

[a] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[b] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[c] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[d] Follow-up doses of TAK-951 or matching placebo should be given at the same time as on Day 1.

[e] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

[f] Telemetry extractions will be performed only on day(s) when the dose has changed from the previous day, and only if PK samples are collected at the given time point.

[g] Safety laboratory collection will be on Day 3 only.

[h] LFTs may be collected at additional time points based on investigator discretion.

[i] Predose blood sample for PK may be drawn 10 minutes before dosing.

[j] Samples will be collected only on day(s) when the dose has changed from the previous day.

[redacted]

Part 3 Day 5 Through Washout Assessments QD

Table A-10 Part 3: Day 5 Through Washout Assessments; QD

	Scheduled Time													Variable Washout Period [a]
	Day 5 (Hours)												Day 6 Discharge	Day 8 to 13
	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [b]	
Previous and concomitant medications	X----------Continuous Review----------X													
Clinic Procedures/Assessments														
Full physical examination													X [c]	
Vital signs	X				X		X						X	
Semirecumbent BP and pulse [d]	X		X	X	X	X	X	X	X	X	X	X	X	
Standing BP and pulse [e]	X		X		X		X		X		X	X	X	
TAK-951/placebo administration [f]		X												
12-lead ECG	X												X	
ECG telemetry (12-lead)	X----------Continuous Monitoring----------X													
Telemetry extraction [g]	X		X [h]	X [h]	X	X [h]			X [h]		X [h]		X	
AE monitoring	X----------Continuous Monitoring----------X													
Laboratory Procedures/Assessments														
Safety laboratory collection (hematology and serum chemistry)	X												X	
LFTs [i]													X	
Serum sample for CK [j]													X	
Urinalysis	X										X		X	
Glucose finger stick	X					X								
βhCG (pregnancy) test [k]													X	
PK Evaluations														
Plasma sample for TAK-951 PK [g]	X [l]		X [m]	X [m]	X	X [m]			X		X		X	

Table A-10 Part 3: Day 5 Through Washout Assessments; QD

	Scheduled Time													Variable Washout Period [a]
	Day 5 (Hours)												Day 6 Discharge	Day 8 to 13
	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [b]	
Immunogenicity and Biomarkers														
Serum sample for immunogenicity [n]													X	
[redacted]														
Other														
Confinement	X----------Continuous----------X													

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; LFT: liver function test; PK: pharmacokinetic; QD: once daily.

[a] Based on emerging safety, tolerability, and available PK data, subjects may be confined during the 2- to 7-day variable washout at the discretion of the investigator in consultation with the sponsor and medical monitor. Duration of washout period may be shortened or lengthened for all cohorts in Part 3 based on emerging data.

[b] At the 24-hour time point, additional procedures may be performed at the investigator's discretion.

[c] Physical examination at the indicated visit will be symptom-driven.

[d] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[e] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[f] Follow-up doses of TAK-951 or matching placebo should be given at the same time as on Day 1.

[g] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

[h] Telemetry extractions will be performed only on day(s) when the dose has changed from the previous day, and only if PK samples are collected at the given time point.

[i] LFTs may be collected at additional time points based on investigator discretion.

[j] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

[k] Serum or urine pregnancy test for female subjects only.

Table A-10 Part 3: Day 5 Through Washout Assessments; QD

	Scheduled Time												Variable Washout Period [a]
	Day 5 (Hours)											Day 6 Discharge	Day 8 to 13
	Predose	0	0.5	1	2	3	4	6	8	10	12	16	24 [b]	

[l] Predose blood sample for PK may be drawn 10 minutes before dosing.

[m] Samples will be collected only on day(s) when the dose has changed from the previous day.

[n] Immunogenicity serum samples for ADA testing will be taken at discharge. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[redacted]

Part 3 Redosing Through Discharge, Follow-Up, and ET Assessments

Table A-11 Part 3: Redosing Through Discharge, Follow-Up, and ET; QD/BID/TID

	Day Before Redosing	Predose	Scheduled Time: Redosing Day (Hours) 0	0.5	1	2	3	4	6	8	10	12	13 [a]	16	Discharge 24	Follow-up Visit 14 days After Redose ±3 days	ET
Administrative Procedures																	
Inclusion/exclusion criteria	X	X															
Previous and concomitant medications	X----------Continuous Review----------X																
Clinic Procedures/Assessments																	
Full physical examination	X														X [b]	X	X
Weight and BMI	X																
Vital signs	X	X				X		X							X		X
Semirecumbent BP and pulse [c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Standing BP and pulse [d]	X	X		X		X		X		X					X		X
12-lead ECGs	X														X		X
ECG telemetry (12-lead)		X----------Continuous Monitoring----------X															
Telemetry extraction [e]		X				X		X		X		X			X		X
TAK-951/placebo administration			X														
AE monitoring	X----------Continuous Review----------X																X
Laboratory Procedures/Assessments																	
Safety laboratory collection (hematology and serum chemistry)		X										X			X	X	X
LFTs [f]		X													X	X	X
Serum sample for CK [g]															X		X
Urinalysis	X	X										X			X		X
Glucose finger stick		X					X										X

Table A-11 Part 3: Redosing Through Discharge, Follow-Up, and ET; QD/BID/TID

	Day Before Redosing	Predose	Scheduled Time: Redosing Day (Hours) 0	0.5	1	2	3	4	6	8	10	12	13 [a]	16	Discharge 24	Follow-up Visit 14 days After Redose ±3 days	ET
Urine drug screen	X																
Alcohol test	X																
Cotinine test	X																
βhCG (pregnancy) test [h]	X																X
PK Evaluations																	
Plasma sample for TAK-951 PK [e]		X				X		X		X		X			X		X
Immunogenicity and Biomarkers																	
Serum sample for immunogenicity [i]		X														X	X
[redacted]																	
Other																	
Confinement		X----------Continuous----------X															

This table applies to the Part 3 redosing day through discharge, follow-up visit, and ET for QD, BID, and TID dosing schemas.

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BID: twice daily; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; LFT: liver function test; PK: pharmacokinetic; QD: once daily; TID: 3 times daily.

[a] The 13-hour timepoint applies to BID and TID dosing regimens only.

[b] Physical examination at the indicated visit will be symptom-driven.

[c] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[d] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[e] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

[f] LFTs may be collected at additional time points based on investigator discretion.

[g] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

Table A-11 Part 3: Redosing Through Discharge, Follow-Up, and ET; QD/BID/TID

	Day Before Redosing		Scheduled Time														
			Redosing Day (Hours)													Follow-up Visit 14 days After Redose ±3 days	ET
		Predose	0	0.5	1	2	3	4	6	8	10	12	13 [a]	16	Discharge 24		

[b] Serum pregnancy tests for female subjects only.

[i] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 6 (discharge), at ET (if applicable), predose on the redosing day, and at the follow-up visit 14 days after redose. If ADAs are present, subjects may be asked to return for additional sample collections. All subjects receiving either study drug or placebo will have the same collection time points.

[redacted]

Part 3 BID Dosing Schema

Part 3 Screening Through Day 1 Assessments BID

Table A-12 Part 3: Screening Through Day 1; BID

	Day		Scheduled Time																																					
	-28 to -3	-2 [a]	Day -1 (Hours)																		Day 1 (Hours)																			
	Screening		0	0.5	1	2	3	4	6	7	8	8.5	9	10	11	12	13	14	16	24 [b]	P	0	0.5	1	2	3	4	6	7	P 8	8	8.5	9	10	11	12	13	14	16	24 [b]
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																																						
Height	X																																							
Weight and BMI	X	X																																						
Vital signs	X	X																			X				X		X													X
Semirecumbent BP and pulse [c]	X			X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X
Standing BP and pulse [d]	X					X		X				X		X	X	X				X	X				X		X			X		X		X	X	X				X
12-lead ECGs	X	X																			X													X						X
ECG telemetry (12-lead)		X------Continuous Monitoring [e]------X																			X ------ Continuous Monitoring ------X																			
Telemetry extraction [f, g]			X		X	X		X			X		X	X		X				X	X			X	X		X			X			X	X		X				X
TAK-951/ placebo administration																						X									X									
AE monitoring	X [h]	X ------ Continuous Monitoring ------X																																						

Table A-12 Part 3: Screening Through Day 1; BID

	Day		Scheduled Time																																				
	-28 to -3	-2 [a]	Day -1 (Hours)																		Day 1 (Hours)																		
	Screening		0	0.5	1	2	3	4	6	7	8	8.5	9	10	11	12	13	14	16	24 [b]	P	0	0.5	1	2	3	4	6	7	P 8	8	8.5	9	10	11	12	13	14	16	24 [b]
Laboratory Procedures/Assessments																																								
Safety laboratory collection (hematology and serum chemistry)	X	X						X [i]													X						X [i]									X				
LFTs [j]	X																				X																			X
Serum sample for CK [k]																					X																			X
Urinalysis	X	X	X																		X															X				
Glucose finger stick			X																		X					X														
Urine drug screen	X	X																																						
Alcohol test		X																																						
Cotinine test	X	X																																						
Hepatitis screen [l]	X																																							
HIV screen	X																																							
βhCG (pregnancy) test [m]	X	X																																						
Serum FSH test [n]	X																																							
PK Evaluations																																								
Plasma sample for TAK-951 PK [g]																					X			X	X		X			X [o]			X	X		X				X
Immunogenicity and Biomarker Evaluations																																								
Serum sample for immunogenicity [p]																					X																			

[redacted]

Table A-12 Part 3: Screening Through Day 1; BID

	Day		Scheduled Time																																				
	-28 to -3	-2 [a]	Day -1 (Hours)																		Day 1 (Hours)																			
	Screening		0	0.5	1	2	3	4	6	7	8	8.5	9	10	11	12	13	14	16	24 [b]	P	0	0.5	1	2	3	4	6	7	P 8	8	8.5	9	10	11	12	13	14	16	24 [b]
Other																																								
Confinement			X ---------- Continuous ---------- X																																					

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BID: twice daily; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; LFT: liver function test; P: predose; PK: pharmacokinetic.

[a] Subjects will be admitted to the site on Day -2.

[b] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[c] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[d] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[e] At least 24 hours of continuous telemetry monitoring will be conducted between check-in on Day -2 and predose on Day 1.

[f] Predose time-matched telemetry extractions may take place on either Day -2 or Day -1 at the corresponding time.

[g] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

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

[i] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.

[j] LFTs may be collected at additional time points based on investigator discretion.

[k] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

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

[m] Serum or urine pregnancy test for female subjects only.

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

[o] Predose blood sample for PK at 8-hour may be drawn 10 minutes before dosing.

[p] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 6 (discharge), at ET (if applicable), predose on the redosing day, and at the follow-up visit 14 days after redose. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[redacted]

Part 3 Days 2 Through 4 Assessments BID

Table A-13 Part 3: Days 2 Through 4 Assessments; BID

	Scheduled Time																			
	Days 2-4 (Hours)																			
	Pre dose	0	0.5	1	2	3	4	6	7	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24 [a]
Administrative Procedures																				
Previous and concomitant medications	X----------Continuous Review----------X																			
Clinic Procedures/Assessments																				
Vital signs	X				X		X							X		X				X
Semirecumbent BP and pulse [b]	X		X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X
Standing BP and pulse [c]	X		X		X		X			X		X		X		X				X
TAK-951/placebo administration [d]		X									X									
ECG telemetry (12-lead)		X----------Continuous Monitoring----------X																		
Telemetry extraction [e]	X [f]			X [f]	X [f]		X [f]			X [f]			X [f]	X [f]		X [f]				
AE monitoring	X----------Continuous Review----------X																			
Laboratory Procedures/Assessments																				
Safety laboratory collection (hematology and serum chemistry) [g]	X																			X
LFTs [h]																				X (Day 2)
Urinalysis	X															X				
Glucose finger stick	X					X														
PK Evaluations and Biomarkers																				
Plasma sample for TAK-951 PK [e]	X [i]			X [j]	X [j]		X [j]			X [i]			X [j]	X [j]		X [j]				X
[redacted]																				

Table A-13 Part 3: Days 2 Through 4 Assessments; BID

	Scheduled Time																		
	Days 2-4 (Hours)																		
	Pre dose	0	0.5	1	2	3	4	6	7	Pre dose 8	8	8.5	9	10	11	12	13	14	16	24 [a]
Other																				
Confinement	X---------- Continuous ----------X																			

AE: adverse event; BID: twice daily; BP: blood pressure; ECG: electrocardiogram; LFT: liver function test; PK: pharmacokinetic.

[a] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[b] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[c] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

[e] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

[f] Telemetry extractions will be performed only on day(s) when the dose has changed from the previous day, and only if PK samples are collected at the given time point.

[g] Safety laboratory collection will be performed on Day 3 only.

[h] LFTs may be collected at additional time points based on investigator discretion.

[i] Predose blood samples for PK may be drawn 10 minutes before dosing.

[j] Samples will be collected only on day(s) when the dose has changed from the previous day.

[redacted]

Part 3 Day 5 Through Washout Assessments BID

Table A-14 Part 3: Day 5 Through Washout Assessments; BID

	Scheduled Time																			Variable Washout Period [a]
	Day 5 (Hours)																		Day 6	Day 8 to 13
	Pre dose	0	0.5	1	2	3	4	6	7	Pre dose 8	8	8.5	9	10	11	12	13	14	16	Discharge 24 [b]	
Previous and concomitant medications	X----------Continuous Review----------X																				
Clinic Procedures/Assessments																					
Full physical examination																				X [c]	
Vital signs	X				X		X													X	
Semirecumbent BP and pulse [d]	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Standing BP and pulse [e]	X		X		X		X			X		X		X		X			X	X	
TAK-951/placebo administration [f]		X									X										
12-lead ECG																				X	
ECG telemetry (12-lead)	X----------Continuous----------X																				
Telemetry extraction [g]	X			X [h]	X		X [h]			X			X [h]	X		X				X	
AE monitoring		X----------Continuous----------X																			
Laboratory Procedures/Assessments																					
Safety laboratory collection (hematology and serum chemistry) [i]	X															X				X	
LFTs [j]																				X	
Serum sample for CK [k]																				X	
Urinalysis	X															X				X	
Glucose finger stick	X					X															

Table A-14 Part 3: Day 5 Through Washout Assessments; BID

	Scheduled Time																			Variable Washout Period [a]
	Day 5 (Hours)																		Day 6	Day 8 to 13
	Pre dose	0	0.5	1	2	3	4	6	7	Pre dose 8	8	8.5	9	10	11	12	13	14	16	Discharge 24 [b]	
βhCG (pregnancy) test [l]																				X	
PK Evaluations																					
Plasma sample for TAK-951 PK [g]	X [m]			X [n]	X		X [n]			X [m]			X [n]	X		X				X	
Immunogenicity and Biomarker Evaluations																					
Serum sample for immunogenicity [o]																					
[redacted]																					
Other																					
Confinement	X----------Continuous----------X																				

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BID: twice daily; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; LFT: liver function test; PK: pharmacokinetic.

[a] Based on emerging safety, tolerability, and available PK data, subjects may be confined during the 2- to 7-day variable washout at the discretion of the investigator in consultation with the sponsor and medical monitor. Duration of washout period may be shortened or lengthened for all cohorts in Part 3 based on emerging data.

[b] At the 24 hour time point, additional procedures may be performed at the investigator's discretion.

[c] Physical examination at the indicated visit will be symptom-driven.

[d] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[e] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

Table A-14 Part 3: Day 5 Through Washout Assessments; BID

	Scheduled Time																			Variable Washout Period [a]
	Day 5 (Hours)																		Day 6	Day 8 to 13
	Pre dose	0	0.5	1	2	3	4	6	7	Pre dose 8	8	8.5	9	10	11	12	13	14	16	Discharge 24 [b]	

[g] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

[h] Telemetry extractions will be performed only on day(s) when the dose has changed from the previous day, and only if PK samples are collected at the given time point.

[i] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters. Additional assessments may be collected at the investigator's discretion.

[j] LFTs may be collected at additional time points based on investigator discretion.

[k] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

[l] Serum pregnancy tests for female subjects only.

[m] Predose blood sample for TAK-951 PK may be drawn 10 minutes before dosing.

[n] Samples will be collected only on day(s) when the dose has changed from the previous day.

[o] Immunogenicity serum samples for ADA testing will be taken at taken at predose on Day 1, on Day 6 (discharge), at ET (if applicable), predose on the redosing day, and at the follow-up visit 14 days after redose. If ADAs are present, subjects may be asked to return for additional sample collections. All subjects receiving either study drug or placebo will have the same collection time points.

[redacted]

Part 3 Redosing Through Discharge, Follow-Up, and ET Assessments

Refer to Table A-11 Part 3: Redosing Through Discharge, Follow-Up, and ET; QD/BID/TID for schedule of study procedures for redosing day through discharge.

Part 3 TID Dosing Schema

Part 3 Screening Through Day 1 Assessments TID

Table A-15 Part 3: Screening Through Day 1; TID

	Day		Scheduled Time																																									
	-28 to -3	-2 [a]	Day -1 (Hours)																				Day 1 (Hours)																						
	Screening		0	0.5	1	2	3	4	6	6.5	7	8	9	10	12	12.5	13	14	15	16	18	24 [b]	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24 [b]
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																																											
Height	X																																												
Weight and BMI	X	X																																											
Vital signs	X	X																					X				X		X																X
Semirecumbent BP and pulse [c]	X			X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X
Standing BP and pulse [d]	X					X		X	X	X		X		X	X	X		X		X	X		X				X		X	X		X		X		X	X		X		X		X	X	X
12-lead ECGs	X	X																					X																						X
ECG telemetry (12-lead)		X---Continuous Monitoring [e]---X																					X---Continuous Monitoring---X																						
Telemetry extraction [f, g]			X		X	X			X		X	X			X			X				X	X			X	X			X			X	X			X				X				X
TAK-951/ placebo administration																								X							X							X							
AE monitoring	X [h]	X---Continuous Review---X																																											

Table A-15 Part 3: Screening Through Day 1; TID

	Day		Scheduled Time																																										
	-28 to -3	-2 [a]	Day -1 (Hours)																				Day 1 (Hours)																						
	Screening		0	0.5	1	2	3	4	6	6.5	7	8	9	10	12	12.5	13	14	15	16	18	24 [b]	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24 [b]
Laboratory Procedures/Assessments																																													
Safety laboratory collection (hematology and serum chemistry)	X	X						X [i]															X						X [i]								X								
LFTs [j]	X																						X																						X
Serum sample for CK [k]																							X																						X
Urinalysis	X	X																					X														X								
Glucose finger stick																							X					X																	
Urine drug screen	X	X																																											
Alcohol test		X																																											
Cotinine test	X	X																																											
Hepatitis screen [l]	X																																												
HIV screen	X																																												
βhCG (pregnancy) test [m]	X	X																																											
Serum FSH test [n]	X																																												
PK Evaluations																																													
Plasma sample for TAK-951 PK [g]																							X [o]			X	X			X [o]			X	X			X [o]				X				X
Immunogenicity and Biomarker Evaluations																																													
Serum sample for immunogenicity [p]																							X																						
[redacted]																																													
Other																																													
Confinement		X------------------Continuous------------------X																																											

Table A-15 Part 3: Screening Through Day 1; TID

	Day		Scheduled Time																																												
	-28 to -3	-2 [a]	Day -1 (Hours)																					Day 1 (Hours)																						
	Screening		0	0.5	1	2	3	4	6	6.5	7	8	9	10	12	12.5	13	14	15	16	18	24 [b]	P	0	0.5	1	2	3	4	P 6	6	6.5	7	8	9	10	P 12	12	12.5	13	14	15	16	18	24 [b]

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; P: predose; PK: pharmacokinetic; TID: 3 times daily.

[a] Subjects will be admitted to the site on Day -2.

[b] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[c] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day 1, vital signs will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[d] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[e] At least 24 hours of continuous telemetry monitoring will be conducted between check-in on Day -2 and predose on Day 1.

[f] Predose time-matched telemetry extractions may take place on either Day -2 or Day -1 at the corresponding time.

[g] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

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

[i] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.

[j] LFTs may be collected at additional time points based on investigator discretion.

[k] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

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

[m] Serum or urine pregnancy test for female subjects only.

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

[o] Predose blood sample for PK may be drawn 10 minutes before dosing.

[p] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 6 (discharge), at ET (if applicable), predose on the redosing day, and at the follow-up visit 14 days after redose. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[redacted]

[redacted]

Part 3 Days 2 Through 4 Assessments TID

Table A-16 Part 3: Days 2 Through 4; TID

	Scheduled Time																						
	Time points (hours) Days 2 Through 4																						
	Predose	0	0.5	1	2	3	4	Predose 6	6	6.5	7	8	9	10	Predose 12	12	12.5	13	14	15	16	18	24 [a]
Administrative Procedures																							
Prior and concomitant medication review	X----------Continuous Review----------X																						
Clinic Procedures/Assessments																							
Vital signs	X				X		X					X		X					X		X		X
Semirecumbent BP and pulse [b]	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X
Standing BP and pulse [c]	X		X		X		X	X		X		X		X	X		X		X		X	X	X
ECG telemetry (12-lead)	X----------Continuous Monitoring----------X																						
Telemetry extraction [d]	X [e]			X [e]	X [e]			X [e]			X [e]	X [e]			X [e]				X [e]				X [e]
TAK-951/placebo administration [f]		X							X							X							
AE monitoring	X----------Continuous Review----------X																						
Laboratory Procedures/Assessments																							
Safety laboratory collection (hematology and serum chemistry) [g]	X																						
LFTs [h]																							X (Day 2)
Urinalysis	X														X								
Glucose finger stick	X					X																	
PK and Biomarker Evaluations																							
Plasma sample for TAK-951 PK [d]	X [i]			X [j]	X [j]			X [i]			X [j]	X [j]			X [i]				X [j]				X [j]
[redacted]																							

Table A-16 Part 3: Days 2 Through 4; TID

	Scheduled Time																					
	Time points (hours) Days 2 Through 4																					
	Predose	0	0.5	1	2	3	4	Predose 6	6	6.5	7	8	9	10	Predose 12	12	12.5	13	14	15	16	18	24 [a]
Other																							
Confinement	X----------Continuous----------X																						

AE: adverse event; BP: blood pressure; ECG: electrocardiogram; LFT: liver function test; PK: pharmacokinetic; TID: 3 times daily.

[a] The 24-hour sample on a given day is the same as the predose sample on the next day; only 1 assessment will be collected at this time point.

[b] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[c] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[d] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

[e] Telemetry extractions will be performed only on day(s) when the dose has changed from the previous day, and only if PK samples are collected at the given time point.

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

[g] Safety laboratory will be performed on Day 3 only.

[h] LFTs may be collected at additional time points based on investigator discretion.

[i] Predose blood samples for PK may be drawn 10 minutes before dosing.

[j] Samples will be collected only on day(s) when the dose has changed from the previous day.

[redacted]

Part 3 Day 5 Through Washout Assessments TID

Table A-17 Part 3: Day 5 Through Washout Assessments; TID

	Scheduled Time																						Variable Washout Period [a]
	Day 5 (Hours)																					Day 6	Day 8 to 13
	Predose	0	0.5	1	2	3	4	Pre dose 6	6	6.5	7	8	9	10	Pre dose 12	12	12.5	13	14	15	16	18	Discharge 24 [b]	
Administrative Procedures																							
Prior and concomitant medication review	X----------Continuous Review----------X																						
Clinic Procedures/Assessments																							
Full physical examination																						X [c]	
Vital signs	X				X		X	X							X				X		X	X	
Semirecumbent BP and pulse [d]	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	
Standing BP and pulse [e]	X		X		X		X	X		X		X		X	X		X		X		X	X	X	
12-lead ECGs																							
ECG telemetry (12-lead)	X----------Continuous Monitoring----------X																						
Telemetry extraction [f]	X			X [1]	X			X [1]			X [1]	X			X [1]				X			X	
TAK-951/ placebo administration [g]		X							X							X							
AE monitoring	X----------Continuous Review----------X																						
Laboratory Procedures/Assessments																							
Safety laboratory collection (hematology and serum chemistry) [h]	X															X						X	
LFTs [i]																						X	
Serum sample for CK [j]																						X	
Urinalysis	X															X						X	
Glucose finger stick	X					X																	

Table A-17 Part 3: Day 5 Through Washout Assessments; TID

	Scheduled Time																						Variable Washout Period [a]
	Day 5 (Hours)																					Day 6	Day 8 to 13
	Predose	0	0.5	1	2	3	4	Pre dose 6	6	6.5	7	8	9	10	Pre dose 12	12	12.5	13	14	15	16	18	Discharge 24 [b]	
PK Evaluations																							
Plasma sample for TAK-951 PK [f]	X [k]			X [l]	X			X [k]			X [l]	X			X [k]				X				X	
Immunogenicity and Biomarker Evaluations																							
Serum sample for immunogenicity [m]																							
[redacted]																							
Other																							
Confinement	X----------Continuous----------X																						

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BID: twice daily; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; LFT: liver function test; PK: pharmacokinetic; TID: 3 times daily.

[a] Based on emerging safety, tolerability, and available PK data, subjects may be confined during the 2- to 7-day variable washout at the discretion of the investigator in consultation with the sponsor and medical monitor. Duration of washout period may be shortened or lengthened for all cohorts in Part 3 based on emerging data.

[b] At the 24-hour time point, additional procedures may be performed at the investigator's discretion.

[c] Physical examination at the indicated visit will be symptom-driven.

[d] All BP 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. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[e] Standing BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should perform the modified orthostatic maneuver with measurement of standing BP and pulse as detailed in Section 9.2.4.1. Standing assessments must not be performed if semirecumbent SBP 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). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

[f] Telemetry extractions and PK sampling may be changed or omitted based on emerging data.

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

[h] Additional safety laboratory assessments may be collected at the investigator's discretion.

[i] LFTs may be collected at additional time points based on investigator discretion.

[j] If CK is elevated in an individual subject after dosing, additional serum samples for CK may be collected at the investigator's discretion. The medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.

[k] Predose blood sample for TAK-951 PK may be drawn 10 minutes before dosing.

Table A-17 Part 3: Day 5 Through Washout Assessments; TID

	Scheduled Time																					Variable Washout Period [a]
	Day 5 (Hours)																				Day 6	Day 8 to 13
	Predose	0	0.5	1	2	3	4	Pre dose 6	6	6.5	7	8	9	10	Pre dose 12	12	12.5	13	14	15	16	18	Discharge 24 [b]	

[l] PK samples will be collected only on day(s) when the dose has changed from the previous day. Telemetry extractions will be performed only if PK samples are collected at the given time point.

[m] Immunogenicity serum samples for ADA testing will be taken at taken at predose on Day 1, on Day 6 (discharge), at ET (if applicable), predose on the redosing day, and at the follow-up visit 14 days after redose. If ADAs are present, subjects may be asked to return for additional sample collections. All subjects receiving either study drug or placebo will have the same collection time points.

[redacted]

Part 3 Redosing Through Discharge, Follow-Up, and ET Assessments

Refer to Table A-11 Part 3: Redosing Through Discharge, Follow-Up, and ET; QD/BID/TID for schedule of study procedures for redosing day through discharge.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB 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 (e)consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each subject who participates in the study, and document the date of (e)consent in the subject's medical chart. Valid informed (e)consent is the most current version approved by the IRB. Each informed (e)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 (e)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 C Elements of the Subject Informed Consent

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

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

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

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A subject authorization (either contained within the informed (e)consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for 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. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed (e)consent throughout the duration of the study, and for 30 days after the last dose of study drug. If the partner of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Guidance on Abnormal Liver-associated Test Result Monitoring, Evaluation, and Follow-up

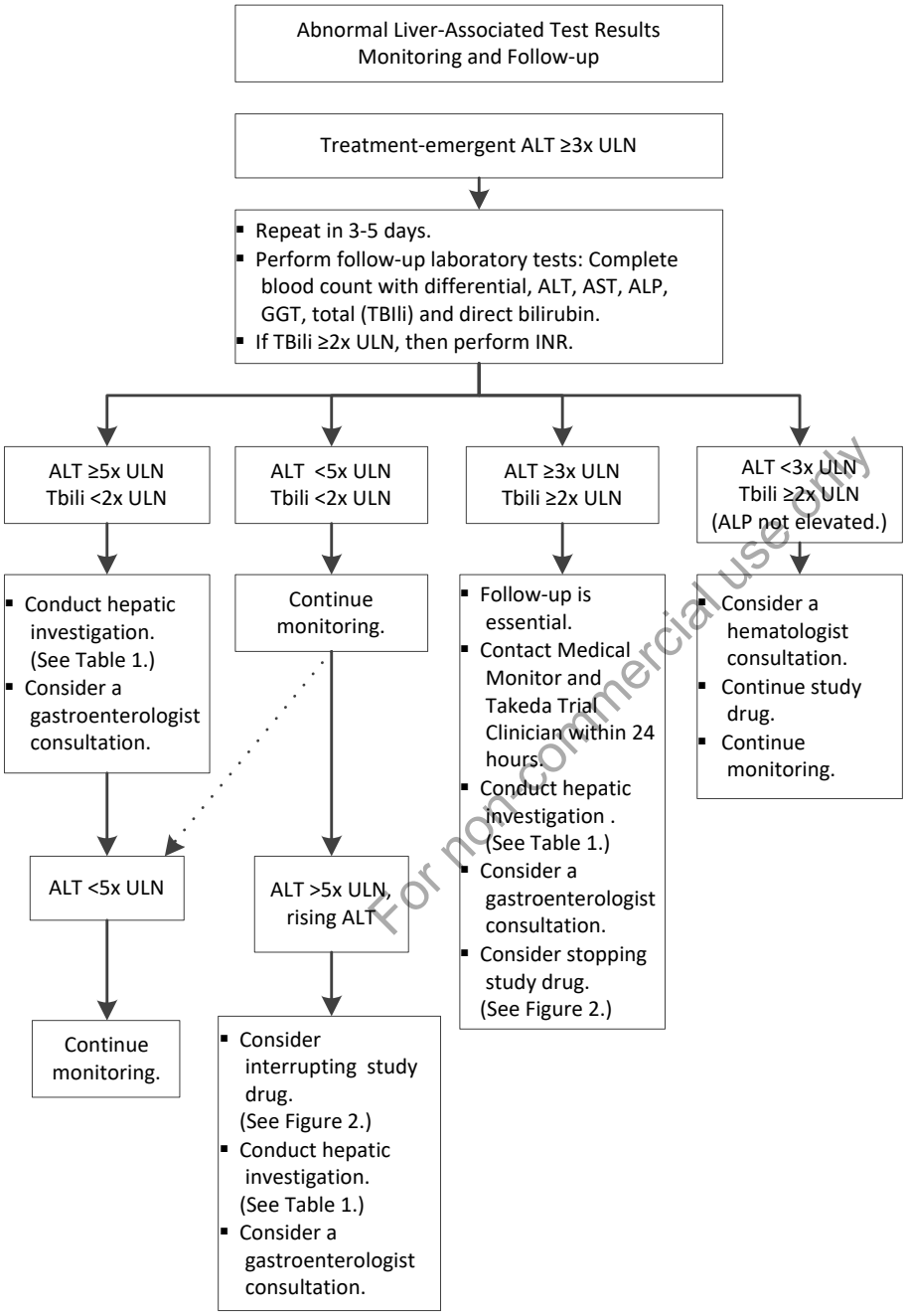
Investigators must be vigilant for abnormal liver test results in subjects during the clinical trial. Transient fluctuations in serum aminotransferases occur commonly in clinical trial subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver test results in clinical trial subjects who had no known liver disease and had either normal or near normal baseline liver test results (ie, ALT <2 × ULN, total bilirubin <1.5 × ULN, and alkaline phosphatase <1.5 × ULN) at the time of enrollment.

In evaluating trial subjects with abnormal liver test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 1. Suggested hepatic investigations are listed in Table 1. Criteria for considering discontinuation of study drug are shown in Figure 2.

Subjects with Combined Elevations in Aminotransferase and Bilirubin

If a subject has elevated ALT >3 × ULN **with concurrent** elevated total bilirubin >2 × ULN **or** elevated INR >1.5, the investigator must contact the Medical Monitor and Takeda Trial Clinician within 24 hours. Hepatic investigations as suggested in Table 1 should be initiated. Any event of elevated ALT ≥3 × ULN with concurrent elevated total bilirubin >2 × ULN or elevated INR >1.5 for which an alternative etiology has not been identified must be reported as an SAE.

Figure 1: Abnormal Liver-associated Test Results: Monitoring and Follow-up

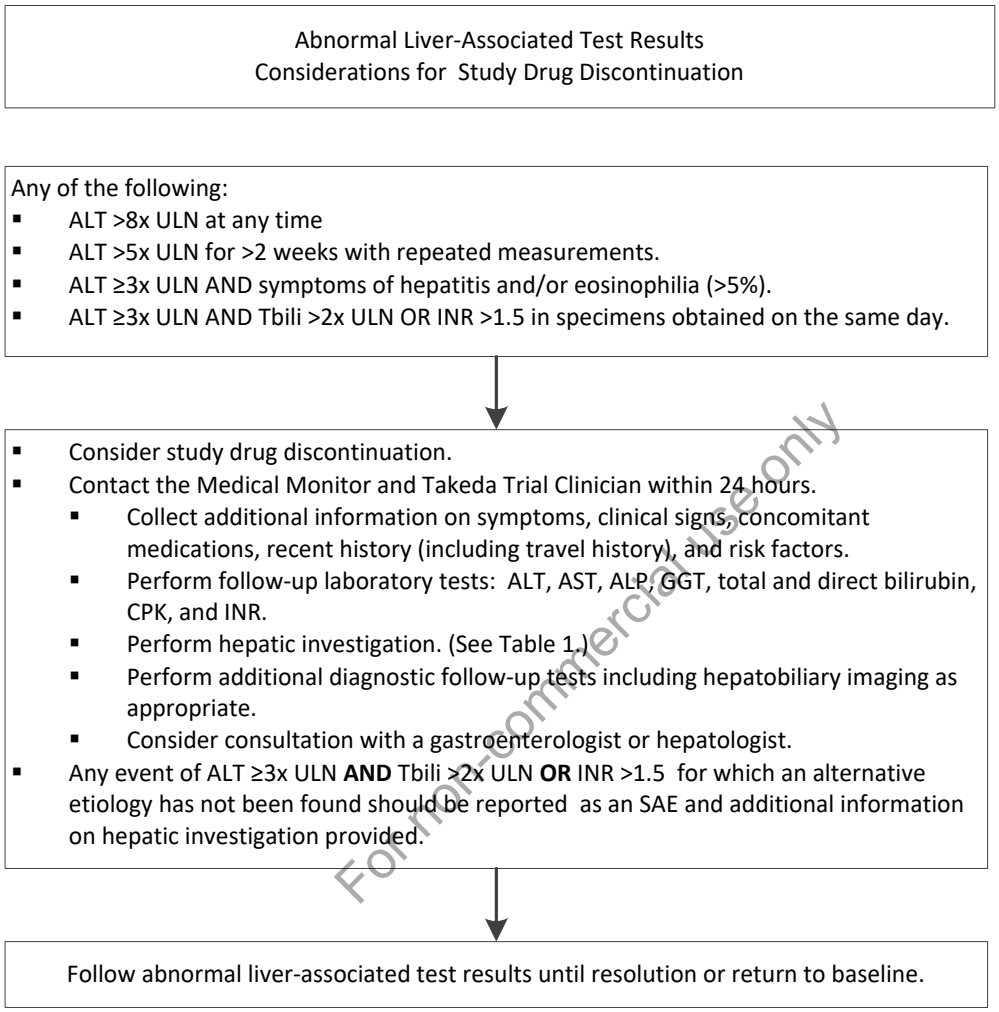


ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

Table 1: Hepatic Investigation

Medical History	• Concomitant medications (including over-the-counter medications, such as acetaminophen, and herbal supplements). • Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis). • Alcohol intake. • Hepatobiliary disorder. • Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia). • Travel history.
Physical Examination (symptoms, signs, and laboratory results)	• General malaise, fatigue, nausea, or vomiting. • Right upper quadrant pain or tenderness, fever, jaundice, rash. • Eosinophilia >5%.
Hepatic/Hepatobiliary imaging	Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging).
Viral hepatitis serology	• Hepatitis A antibody (total and IgM). • Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (anti-HBs), Hepatitis B core antibody (IgM anti-HBc), Hepatitis C antibodies (anti-HCV). • Hepatitis E (IgG and IgM). • Consider PCR for Hepatitis B, C, and E. • Consider Epstein-Barr virus serology (viral capsid antigen [VCA] nuclear antigen [EBNA], early antigen [EA]). • Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	• Anti-nuclear antibody (ANA). • Anti-smooth muscle antibody (ASMA). • Anti-liver-kidney microsomal antibody (anti-LKM).

Figure 2: Abnormal Liver-associated Test Results: Considerations for Study Drug Discontinuation



ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

Appendix E Protocol History

Date	Amendment Number	Amendment Type	Region
16 March 2023	Amendment 2	Substantial	United States
24 January 2023	Amendment 1	Substantial	United States
23 November 2021	Initial protocol	Not applicable	United States

Protocol Amendment 1 Summary and Rationale:

The primary reasons for this amendment are:

- Study design modified to be sponsor-open; the study remains blinded to investigators, study site staff, and subjects.
- Removal of the 0.5 hour timepoint for assessing orthostatic vital signs (standing blood pressure and pulse) on Day 1 of Parts 1, 2 and 3.
- Addition of early termination remote monitoring safety measures.
- Addition of a safety step to reduce the risk of syncope while comprehensively assessing semirecumbent and standing vital signs.
- Addition of steps to reduce the risks of orthostatic vital signs as follows:
  - Require subjects to be supine/semirecumbent for the first 2 hours after dosing.
  - Implementation of an external safety adjudication committee before reinitiating dosing.
  - Use of a modified orthostatic challenge whereby subjects will be semirecumbent for 5 minutes; then, after semirecumbent vital signs are recorded, they will sit for 3 minutes with legs crossed, then stand for 2 minutes before collecting vital signs in this position.
- Clarification of timing of the proposed interim analysis.

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

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Title page Section 2.0 STUDY SUMMARY	Wording "sponsor-open" was added to the protocol title.	The protocol title was updated because the study has been modified to sponsor-open.
2.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 6.2 Dose Escalation Section 6.4.1 Justification for	Added language to modify the study to sponsor open.	The study design is modified to sponsor-open for oversight of the study for efficient evaluation of study data in an unblinded manner. The study remains

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Study Design Section 8.3 Randomization Code Creation and Storage Section 8.4 Blinding		blinded to investigators, study site staff, and subjects.
3.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added "semirecumbent" to exclusion criteria #16.	To clarify that this criteria is for semirecumbent, and not standing measurements.
4.	Section 6.3 Study Drug Administration Appendix A Schedules of Study Procedures	Parts 1, 2, and 3 – removal of standing blood pressure and pulse measurement at the 0.5 hour timepoint on Day -1 and Day 1.	Additional risk mitigation for prevention of syncope. Removal of the 0.5 hour post-dose orthostatic challenge addresses the observation that symptomatic orthostatic adverse events mainly take place before the 2 hour assessment timepoint.
5.	Section 9.2.4 Vital Sign Procedure Section 9.2.4.1 Orthostatic Measurements Appendix A Schedules of Study Procedures	Use of a modified orthostatic challenge: Subjects will be semirecumbent for 5 minutes; then, after semirecumbent vital signs are recorded, they will sit for 3 minutes with legs crossed, then stand for 2 minutes before collecting vital signs.	Takeda proposes an additional safety step to reduce the risk of syncope while comprehensively assessing semirecumbent and standing vital signs.
6.	Section 9.2.4.3 Follow-up Safety Monitoring	Addition of early termination remote monitoring safety measures.	To ensure that telemetry monitoring is provided for the confinement period outlined in the protocol even if the subject early terminates.
7.	Section 9.2.6 ECG Procedure	QRS interval changed to QRS duration.	Wording change
8.	Section 9.3.3 Urinalysis	Urinalysis nitrite rather than nitrate will be determined.	Correction of typographical error.
9.	Section 9.6.5 Documentation of Screen Failure	Clarification that screen failures will be captured outside of the clinical database as part of the study source documentation.	Clarification of where screen failures will be reported.
10.	Section 10.2.9 Collection and Reporting of SAEs	Updated SAE form language.	Updated language for accuracy.
11.	Section 11.0 STUDY-SPECIFIC COMMITTEES	Inclusion of an external safety adjudication	Takeda determined that an external safety event

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		committee that will review ongoing CV adverse events during the conduct of study.	adjudication committee is an appropriate additional risk mitigation and assessment step, which is therefore added in this protocol to be specified in the charter for the external safety adjudication committee.
12.	Section 13.2 Interim Analysis	Clarification of timing of proposed interim analysis. Updates to the plan for interim analysis and clarification of the potential timing of the interim analysis.	To update the plan of the interim analysis and clarify its potential timing.