Clinical Study Protocol

NCT Number: NCT04964258

Title: A Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-105 in Healthy Subjects

Study Number: TAK-105-1001

Document Version and Date: Version 4.0, 19 December 2022

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 PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-105 in Healthy Subjects

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA
Study Identifier:	TAK-105-1001
Compound:	TAK-105
Date:	19 December 2022
Version/Amendment Number:	Amendment 4

Amendment History:

Date	Amendment Number	Amendment Type	Region
19 December 2022	Amendment 4	Substantial	Global
23 March 2022	Amendment 3	Substantial	Global
09 September 2021	Amendment 2	Substantial	Global
29 July 2021	Amendment 1	Nonsubstantial	Global
27 May 2021	Initial protocol	Not applicable	Global

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, Massachusetts USA 02421 Telephone: +1 (617) 679-7000	TAK-105
Study Identifier: TAK-105-1001	**Phase:** 1
Protocol Title: A Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-105 in Healthy Subjects	

Study Design:

This is a phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, immunogenicity, tolerability, and pharmacokinetics (PK) of TAK-105 in healthy subjects.

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 6 parts:

- Part 1 is a first-in-human (FIH), randomized, double-blind, sponsor-open, placebo-controlled single-rising dose (SRD) design to assess the safety, immunogenicity, tolerability, and PK of TAK-105 in healthy subjects. Part 1 will consist of up to 12 sequential cohorts with 8 healthy subjects per cohort. Subjects in each cohort will be randomly assigned to receive a single dose of TAK-105-a (Process A formulation) or matching placebo via subcutaneous (SC) administration in a 3:1 ratio in a double-blind manner.
- Part 2 is a randomized, double-blind, sponsor-open, placebo-controlled, multiple-rising dose (MRD) design to assess the safety, immunogenicity, tolerability, and PK of TAK-105 in healthy subjects. Part 2 consists of sequential dosing in up to 5 ascending cohorts of healthy subjects. In each cohort, 8 healthy subjects will be randomly assigned to receive TAK-105-a or matching placebo in a 3:1 ratio in a double-blind manner.
- Part 3 is a randomized, double-blind, sponsor-open, placebo-controlled, multiple-dose, dose titration design to assess the safety, immunogenicity, tolerability, and PK of TAK-105 in healthy subjects. Part 3 will consist of up to 6 cohorts with 8 healthy subjects per cohort. Subjects will be assigned to receive TAK-105-a or matching placebo in a 3:1 ratio in a double-blind manner. The intent of the design of Part 3 is to enable a descriptive comparison (ie, without hypothesis testing) of cardiovascular (CV) tolerability profile findings between Part 3 cohorts and cohorts in Parts 1 and 2 with comparable exposures, to determine whether dose titration results in different tolerability in relation to CV observations.
- Part 4 is a randomized, double-blind, sponsor-open, placebo-controlled, redosing after a period of withholding study drug design to assess the safety, immunogenicity, tolerability, and PK of TAK-105 in healthy subjects. Part 4 will consist of up to 4 cohorts with 8 healthy subjects per cohort. Subjects will be assigned to receive TAK-105-a or matching placebo in a 3:1 ratio in a double-blind manner. The intention of the design of Part 4 is to provide an exploratory evaluation to assess the safety and CV tolerability profile of redosing with TAK-105 after a period of withholding study drug.
- Part 5 is a randomized, double-blind, sponsor-open, placebo-controlled SRD (Part 5a) and MRD (Part 5b [optional]) design to assess the safety, immunogenicity, tolerability, and PK of TAK-105 in healthy Japanese subjects. Part 5 will consist of up to 5 cohorts (3 SRD and 2 MRD [optional]) with 8 healthy Japanese subjects per cohort. Subjects will be assigned to receive TAK-105-a or matching placebo in a 3:1 ratio in a double-blind manner. The MRD cohorts in Part 5b will be optional, depending on the PK/safety data observed in Part 2 MRD.
- Part 6 is a randomized, double-blind, sponsor-open, placebo-controlled SRD design to assess the safety, immunogenicity, tolerability, and PK of a new formulation of TAK-105 in healthy subjects. Part 6 will consist of up to 2 cohorts (1 is optional) with 8 healthy subjects per cohort. Subjects will be assigned to receive TAK-105-b (Process B formulation) or matching placebo in a 3:1 ratio in a double-blind manner. The intention of Part 6 is to

evaluate safety and PK of the new formulation.

Study drug in Parts 1 to 5 is TAK-105-a (Process A formulation) or matching placebo and in Part 6 is TAK-105-b (Process B formulation) or matching placebo, which has improved stability. TAK-105-1001 Parts 1 and 2 will be initiated in advance of Parts 3 and 4. Parts 3 and 4 will be conducted at the discretion of the sponsor based on a review of available safety and PK data from Parts 1 and 2. At the discretion of the sponsor, Parts 3 and 4 may be initiated before completion of all cohorts in Parts 1 and 2 as otherwise permissible in the protocol. Part 5a/b may be performed in parallel with Parts 1 and 2 based on the review of safety and PK data at least at the matching dose from the previous parts. Part 6 with the new drug formulation of TAK-105 (TAK-105-b) may be performed in parallel with Part 1 provided that the new formulation is available and after Part 1 SRD data are available. The highest tolerable dose in Part 1 will not be exceeded in subsequent parts of the study.

Study Primary Objectives:

- Part 1:
  - To characterize the safety and tolerability of single SC doses of TAK-105-a in healthy subjects.
- Part 2:
  - To characterize the safety and tolerability of multiple SC doses of TAK-105-a in healthy subjects.
- Part 3:
  - To characterize the safety and tolerability of multiple SC dose regimens of TAK-105-a that include titration from lower doses in healthy subjects.
- Part 4
  - To characterize the safety and tolerability of multiple SC dose regimens of TAK-105-a that include weekly dosing, withholding, then redosing in healthy subjects.
- Part 5:
  - To characterize the safety and tolerability of single SC doses and of multiple SC doses of TAK-105-a in healthy Japanese subjects.
- Part 6:
  - To characterize the safety and tolerability of single SC doses of new formulation TAK 105-b in healthy subjects.

Secondary Objectives:

- Part 1:
  - To characterize the plasma PK of TAK-105 following a single SC dose of TAK-105-a in healthy subjects.
  - To assess the immunogenicity of TAK-105 following single SC doses in healthy subjects.
  - To characterize the urinary PK of TAK-105 following a single SC dose of TAK-105-a in healthy subjects.
- Part 2:
  - To characterize the plasma PK of TAK-105 following multiple SC doses of TAK-105-a in healthy subjects.
  - To assess the immunogenicity of TAK-105 following multiple SC doses in healthy subjects.
  - To characterize the urinary PK of TAK-105 following multiple SC doses of TAK-105-a in healthy subjects.
- Parts 3 and 4: To assess the immunogenicity of TAK-105-a following multiple SC dose regimens that include titration from lower doses for Part 3 and weekly dosing, withholding, then redosing for Part 4 in healthy subjects.
- Part 5:
  - To characterize the plasma PK of TAK-105 following a single SC dose and multiple SC doses of TAK-105-a in healthy Japanese subjects.
  - To assess the immunogenicity of TAK-105-a following single SC doses and multiple SC doses in healthy Japanese subjects.
  - To characterize the urinary PK of TAK-105 following a single SC dose and multiple SC doses of TAK-105-a in healthy Japanese subjects.
- Part 6:

– To characterize the plasma PK of TAK-105 following single SC doses of TAK-105-b in healthy subjects.
– To assess the immunogenicity of TAK-105 following a single SC dose of TAK-105-b in healthy subjects.

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

Planned Number of Subjects:	**Planned Number of Sites:**
Part 1: Up to approximately 96 subjects. Part 2: Up to approximately 40 subjects. Part 3: Up to approximately 48 subjects. Part 4: Up to approximately 32 subjects. Part 5: up to approximately 40 subjects. Part 6: up to approximately 16 subjects. Approximate values do not account for potential replacement of subjects who withdraw for nonsafety reasons.	4 sites.
Dose Levels: The starting dose is [redacted].	**Route of Administration:** SC
Duration of Treatment: Part 1: 1 day. Part 2: 4 weeks (once weekly [QW], 4 doses total). Part 3: 2 to 4 weeks (QW, 2 to 4 doses total). Part 4: up to 4 weeks (3 doses total). Part 5a: SRD – 1 day, Part 5b: MRD 4 weeks (QW, 4 doses total). Part 6: 1 day.	**Planned Study Duration:** Part 1 will be approximately 89 days (a 28-day screening period, a 1-day treatment period, and a follow-up period of 60 days. Part 2 will be approximately 110 days (a 28-day screening period, a 22-day treatment period, and a follow-up period of 60 days). Part 3 will be approximately 78 days (a 28-day screening period, a varying treatment period of up to 22 days, a follow-up period of 28 days). Part 4 will be approximately 85 days (a 28-day screening period, a varying treatment period with a maximum of 29 days, and a follow-up period of 28 days). Part 5a will be approximately 89 days (a 28-day screening period, a 1-day treatment period, and a follow-up period of 60 days) for SRD cohorts and Part 5b will be approximately 110 days (a 28-day screening period, a 22-day treatment period, and a follow-up period of 60 days) for MRD cohorts. Part 6 will be approximately 89 days (a 28-day screening period, a 1-day treatment period, and a follow-up period of 60 days).

Main Criteria for Inclusion:

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

<u>For All Cohorts</u>

- Be willing and able to comply with all study procedures and restrictions.
- Be a healthy male or female of nonchildbearing potential aged 18 to 55 years, inclusive, at the screening visit.
- Have a body mass index ≥18 and ≤30.0 (kg/m^2) at the screening visit.
- Continuous nonsmoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to screening and through discharge.
- 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, electrocardiogram (ECG), and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug or invasive procedure.

Additional inclusion criteria for Japanese subjects in Part 5 (Cohorts 28 to 32 only):

- The subject has 2 Japanese parents and 4 Japanese grandparents, as confirmed by interview.

Main Criteria for Exclusion:

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

For All Cohorts

- The subject has participated in another investigational study within 4 weeks (or based on local regulations) or within 5 half-lives 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 adverse event (AE) related to the study procedure 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.
- The subject has a positive pregnancy test or is lactating or breastfeeding.
- The subject is unable to refrain from or anticipates using all medications including herbal medicines beginning approximately 7 days before administration of the first dose of study drug, throughout the study until the last follow-up visit.
- 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.
- The subject has a history or presence of:
  - 3 or more incidences of syncope (eg, vasovagal) within the last 5 years prior to screening;
  - A family history of unexplained sudden death or channelopathy;
  - Brugada syndrome (ie, RBBB [right bundle branch block] pattern with ST-elevation in leads V1-V3);
  - CV or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, stroke, sick sinus syndrome, pulmonary congestion, symptomatic or significant cardiac arrhythmia, supraventricular or ventricular tachycardia, 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;
  - Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);
  - 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 >200 msec at screening or Day 1 pre-Hour 0;
  - The subject has a documented history of sinus bradycardia (<45 beats per minute [bpm]) based upon vital signs assessments, sinoatrial block as evidenced on ECG or sinus pause ≥3 seconds on ECG or predose telemetry.
- The subject has an average semirecumbent blood pressure (BP) less than 90/60 mm Hg or greater than 140/90 mm Hg from screening to predose, inclusive. Any assessments on Day -1, where 2 consecutive timepoint values do not meet this criterion, must be discussed with the medical monitor for approval.
- From screening to Day -2, subjects with an average semirecumbent heart rate (HR) <55 or >100 bpm should be excluded. From Day -2 to predose, enrollment of subjects with an average HR <55 or >100 bpm will be left to the judgment of the investigator, unless HR 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 (SBP) ≥20 mm Hg or a decrease in diastolic BP (DPB) ≥10 mm Hg at approximately 2 minutes of standing when compared with BP from the semirecumbent position at screening to predose assessments, inclusive. In asymptomatic subjects, any assessments after screening which 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 HR >120 bpm at approximately 2 minutes of standing, at screening to predose assessments, inclusive.

Any assessments after screening which 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 prior to determination that the subject is eligible to proceed.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

- All parts of the study:
  - The primary endpoint of the study is safety and tolerability as assessed through vital signs, ECG, laboratory assessments, and AEs.

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

- Parts 1, 5a, and 6: plasma PK parameters for TAK-105
  - Maximum observed plasma concentration (C_{max}).
  - Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the 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 elimination phase after extravascular administration(V_z/F).
- Parts 2 and 5b: plasma PK parameters for TAK-105 on Day 1 (the first dose):
  - C_{max}, t_{max}, and area under the concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_{τ}).
- Parts 2 and 5b: plasma PK parameters for TAK-105 on Day 22 (the fourth dose):
  - AUC_{τ}, C_{max}, t_{max}, $t_{1/2z}$, CL/F, V_z/F, observed plasma concentration at the end of a dosing interval (C_{trough}).
- Parts 1, 2, and 5a/b include the following urine PK parameters:
  - Amount of drug excreted in urine from time 0 to time t (Ae_t).
  - Amount of drug excreted in urine from time 1 to time 2 ($Ae_{t1\text{-}t2}$).
  - Amount of drug excreted in urine during a dosing interval (τ) after fourth dose (Ae_{τ}).
  - Fraction of administered dose of drug excreted from urine from time 0 to time t ($f_{e,t}$).
  - Renal clearance (CL_R).
- All parts of the study:
  - Status of subject's antidrug antibody (ADA) assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer).

Statistical Considerations:

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

Safety Analysis:

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. No formal statistical tests or inference will be performed for safety analyses. All safety summary analyses will be performed by treatment arm (TAK-105 or placebo) within each part of the study separately. In particular, the safety summary for Parts 5a (SRD) and 5b (MRD) will be provided separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for BP and HR will be provided. All data will be provided in by-subject listings.

PK Analysis:

The PK analysis set consists of all subjects who receive at least 1 dose of TAK-105 and have at least 1 measurable postdose plasma or urine concentration for TAK-105. The plasma (all parts of the study) and urine (Parts 1, 2, and 5 a/b only) concentrations of TAK-105 will be summarized by treatment arm at each scheduled sampling day/time within each part of the study separately, using descriptive statistics based on the PK analysis set. In particular, the summary of plasma concentration of TAK-105 for Parts 5a (SRD) and 5b (MRD) will be provided separately, as data allows. The plasma PK (all parts of the study) and urine PK (Parts 1, 2, and 5a/b only) parameters of TAK-105 determined using a noncompartmental analysis approach will be summarized by treatment arm, at each scheduled day where appropriate, within each part of the study separately, using descriptive statistics based on the PK analysis set. In particular, the summary of PK parameters of TAK-105 for Parts 5a (SRD) and 5b (MRD) will be provided separately. Dose proportionality may be assessed graphically (logtransformed dose-normalized C_{max} and area under the plasma concentration-time curve [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. All data will be provided in by-subject listings.

Immunogenicity Analysis:

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. The number and percentage of subjects in each category of the immunogenicity status (ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) will be tabulated by treatment arm at scheduled time points within each part of the study separately. In particular, the summary of immunogenicity for Parts 5a (SRD) and 5b (MRD) will be provided separately. The relationship between immunogenicity status (ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) and plasma drug concentration and PK parameters, and safety will be explored. All data will be provided by-subject listings.

Biomarker Analysis:

Biomarker measurements will be summarized using the safety analysis set. The baseline concentrations of [redacted] will be summarized using descriptive statistics by treatment arm within each part of the study separately. In addition, the number and percentage of subjects within each of the 4 categories defined by quartile (ie, 0 to <Q1, Q1 to <median, median to <Q3, ≥Q3) of [redacted] will be presented for each time point by treatment arm within each part of the study separately. The change from baseline in the [redacted], will be summarized using descriptive statistics by treatment arm at scheduled time points within each part of the study separately. In particular, the summary of biomarker measurements for Parts 5a (SRD) and 5b (MRD) will be provided separately. All data will be provided in by-subject listings.

In case a data-dependent decision is needed to inform the subsequent development of TAK-105 prior to database lock an interim analysis may be deemed necessary. The details about situations when such a case occurs and associated interim analyses will be provided in the SAP.

Sample Size Justification:

The selected sample sizes in all parts of the study are considered sufficient for evaluation of safety and tolerability of TAK-105 in healthy subjects. No formal statistical hypothesis testing is planned; therefore, no formal power calculations were performed in the determination of the sample size for this study.

1.1 Protocol Amendment 4 Summary of Changes

Protocol Amendment 4 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reasons for this amendment are to:

1. The protocol title was modified and language was added to modify the study to sponsor-open design.
2. Revise study design to add additional cohorts for Japanese subjects to support future studies in this population.
3. Revise study design to add additional cohorts for testing a new formulation of TAK-105, TAK-105-b, to support the use of this formulation in future studies. Unless specified "TAK-105" refers to the TAK-105-a formulation or entity.
4. Provision of an External Safety Adjudication Committee (ESAC) to monitor cardiovascular safety throughout the study.
5. Revision of the procedure for measuring orthostatic changes in heart rate (HR) and blood pressure (BP).
6. Reformat footnote styles in schedules of assessment tables and address inconsistencies in the schedule of study procedures.

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 4			
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	Added the sponsor name and address to the title page.	Updated for accuracy.
2.	Section 1.0 Study Summary	Updated number of sites.	Updated the number of sites to accommodate additional new parts added to the study.

Protocol Amendment 4			
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***
3.	Section 1.0 Study Summary Section 2.0 STUDY SCHEMATIC Section 3.7 Part 5 Japanese Subjects Section 4.2 Rationale for the Proposed Study Section 5.0 Trial Objectives And Endpoints Section 6.1 Study Design Section 6.1.6 Part 5a/b: SRD and MRD in Japanese Subjects Cohorts 28 to 32 (new section) Section 6.1.8 Study Drug Administration Section 6.4.2 Criteria for Premature Termination or Suspension of the Study Section 6.5.1 Rationale of Study Design Section 7.1 Inclusion Criteria Section 7.4.1 Diet and Fluid Section 9.2.6.2 Telemetry Section 9.3 Confinement	Modified Figures 2.a, 2.b (new), 2.c, 2.d; and Table 6.a. Updated study design, sample size and statistical analyses to include Part 5a/b, containing 5 additional cohorts. Added Section 3.7 for schedule of study procedure tables for Part 5 a/b. Modified study rationale language to clarify inclusion of Japanese populations. Updated objectives and endpoints to include Part 5 a/b. Updated study design text to include Part 5a/b cohorts as needed. Included new section 6.1.6 for new Part 5 a/b study design. Added inclusion criteria #9 for Japanese subjects.	To assess safety, tolerability, and pharmacokinetic (PK) in healthy Japanese subjects, for the determination of dose selection for future studies in this population.

Protocol Amendment 4			
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***
4.	Section 1.0 Study Summary Section 2.0 STUDY SCHEMATIC Section 3.0 Schedule of Study Procedures Section 3.8 Part 6 TAK-105-b New Formulation of Drug Product Section 4.2 Rationale for the Proposed Study Section 5.0 Trial Objectives And Endpoints Section 6.1 Study Design Section 6.1.7 Part 6: TAK-105-b New Formulation (new section) Section 6.1.8 Study Drug Administration Section 6.5.1 Rationale of Study Design Section 7.4.1 Diet and Fluid Section 8.1 Clinical Study Drug Section 9.2.6.2 Telemetry Section 9.3 Confinement	Modified Figures 2.b and 2.c and Table 6.a. Updated study design, sample size, and statistical analyses to include additional cohorts for Part 6. Added Section 3.8 for schedule of study procedure tables for Part 6. Modified language to distinguish TAK-105-a and TAK-105-b formulations, specifically in Tables 3.a through 3.r, objectives/endpoints, and as needed. Updated objectives and endpoints to include Part 6. Added text to include Part 6 cohorts as needed. Added TAK-105-b study drug and storage information. Clarified in the footnotes for the Schedule of Study Procedure tables, that the study drug is either TAK-105-a or TAK-105-b, depending on the part of the study.	To evaluate the new Process B formulation of TAK-105 (TAK- 105-b), including to assess safety and tolerability and to support the use of TAK-105-b in future studies. Included clarification of the different formulations and storage conditions.
5.	Section 3.0 Schedule of Study Procedures	Modified the language in footnote ‘r’ of Table 3.a and footnote ‘q’ Table 3.c to clarify when urine PK samples are collected.	Correction.
6.	Section 1.0 Study Summary Section 5.2.1 Primary Endpoint	Removed the word “safety” from the primary endpoint bullet.	Correction.

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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***
7.	Title page Section 1.0 Study Summary Section 6.1 Study Design Section 6.2 Dose Escalation Section 6.5.1 Rationale of Study Design Section 6.5.2.6 Rationale for MRD Dose Selection Section 8.1.3 Clinical Study Drug Blinding Section 11.2 Interim Analysis Section 12.1 Study-Site Monitoring Visits	Added/modified language to modify the study to sponsor open.	The study design is modified to sponsor-open to provide for oversight of the study for efficient evaluation of study data in an unblinded manner. The study remains blinded to investigators, study site staff, and subjects.
8.	Section 6.2 Dose Escalation	Added language that optional cohorts may not be enrolled as deemed appropriate by the investigator and the sponsor.	For clarification.
9.	Section 6.3 External Safety Adjudication Committee	Addition of an external safety adjudication committee who will perform a blinded review of ongoing cardiovascular adverse events throughout the course of the study.	To monitor cardiovascular safety throughout the study.
10.	Section 1.0 Study Summary Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria	Added subheading for inclusion and exclusion criteria.	To clarify that existing inclusion and exclusion criteria apply to all cohorts.
11.	Section 1.0 Study Summary Section 7.2 Exclusion Criteria	Modified language in exclusion criteria #14 to "…syncope (eg, vasovagal)…" Modified language to exclusion criteria #16 to include "semirecumbent".	For clarification.
12.	Section 9.2 Clinical Procedures and Assessments	Added text detailing the time window for clinical procedures and assessments.	For clarification.
13.	Section 9.2.4 Vital Signs Section 9.2.4.1 Orthostatic Measurements Section 3.0 Schedule of Study Procedures	The modified orthostatic BP and HR measurement procedure with orthostatic maneuvers has been added.	To improve assessment of orthostatic changes and safety measures to reduce risk of falls and injuries.

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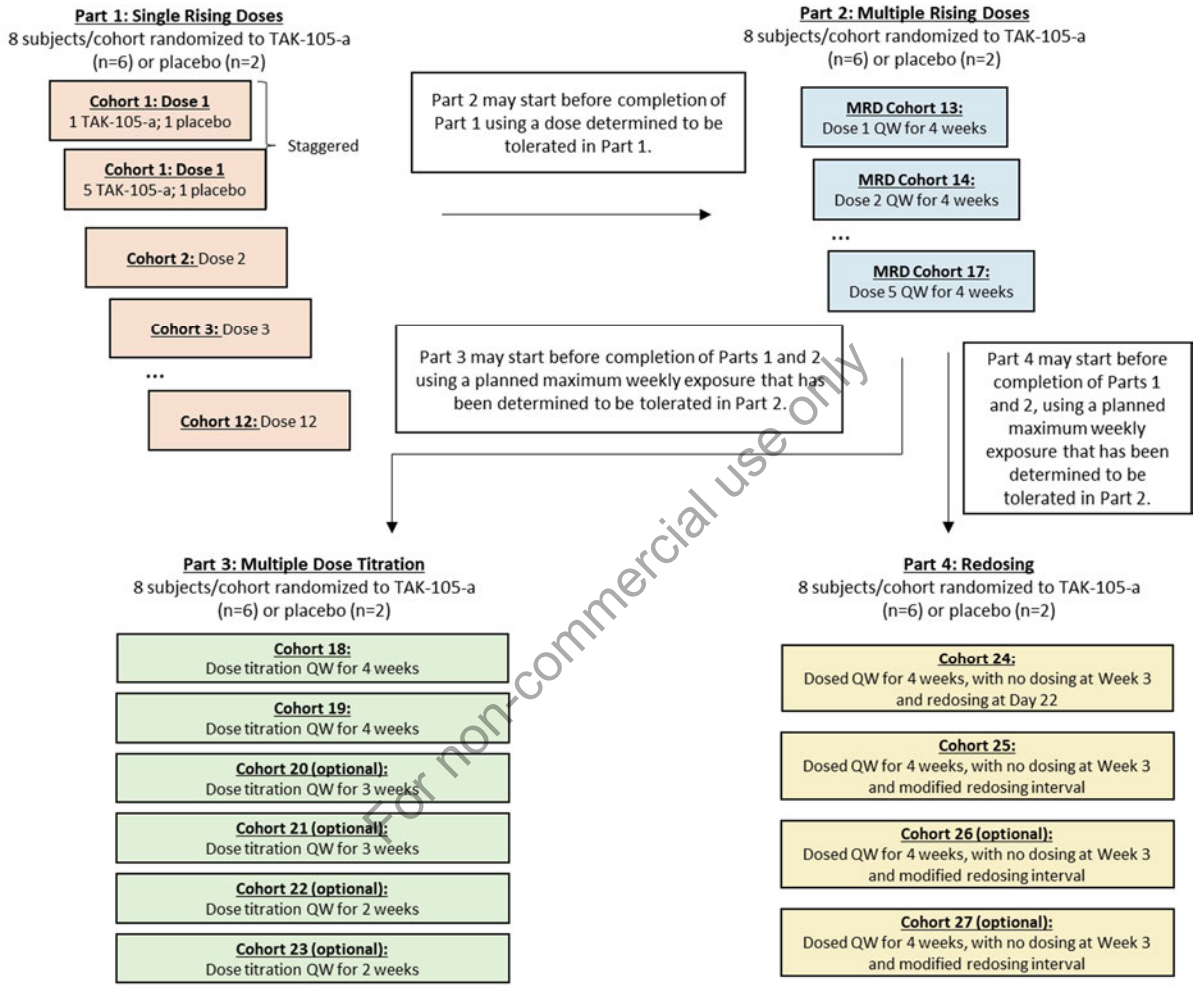
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14.	Section 9.2.6.2 Telemetry	Real-time actively monitored telemetry may be limited to less than 12 leads (ie, 2 leads for real time alerts).	This change is made to accommodate site telemetry capabilities for Parts 2 to 6 with additional investigational sites.
15.	Section 9.2.9.2 Chemistry	Added a footnote to chemistry evaluations table that samples for laboratory evaluations are collected at specified timepoints or as deemed necessary by site investigator.	For clarification for safety purposes.
16.	Section 9.2.10.1.1 Plasma for PK Measurements and MetID Section 9.2.10.2 Urine for PK Measurements	Clarified language for validated assay.	For clarification.
17.	Section 10.2.8.3 Reporting SAEs	Changed "SAE form" to "SAE eCRF entry" and "SAE form" to "SAE information".	For correction.
18.	Section 1.0 Study Summary Section 11.1 Statistical and Analytical Plans Section 11.3 Determination of Sample Size	Modified analysis plans and sample size determination language to include Parts 5a/b and 6 cohorts.	To modify analysis plans to include new cohorts in Parts 5a/b and 6.
19.	Section 7.2 Exclusion Criteria	Clarified that subjects with an average semirecumbent heart rate (HR) <55 or >100 beats per minute from screening to Day -2, should be excluded. From Day -2 to predose, such subjects can be enrolled at discretion of investigator.	To reflect that the inclusion criteria are based on blood pressure and HR measured on Day -1 and Day -2

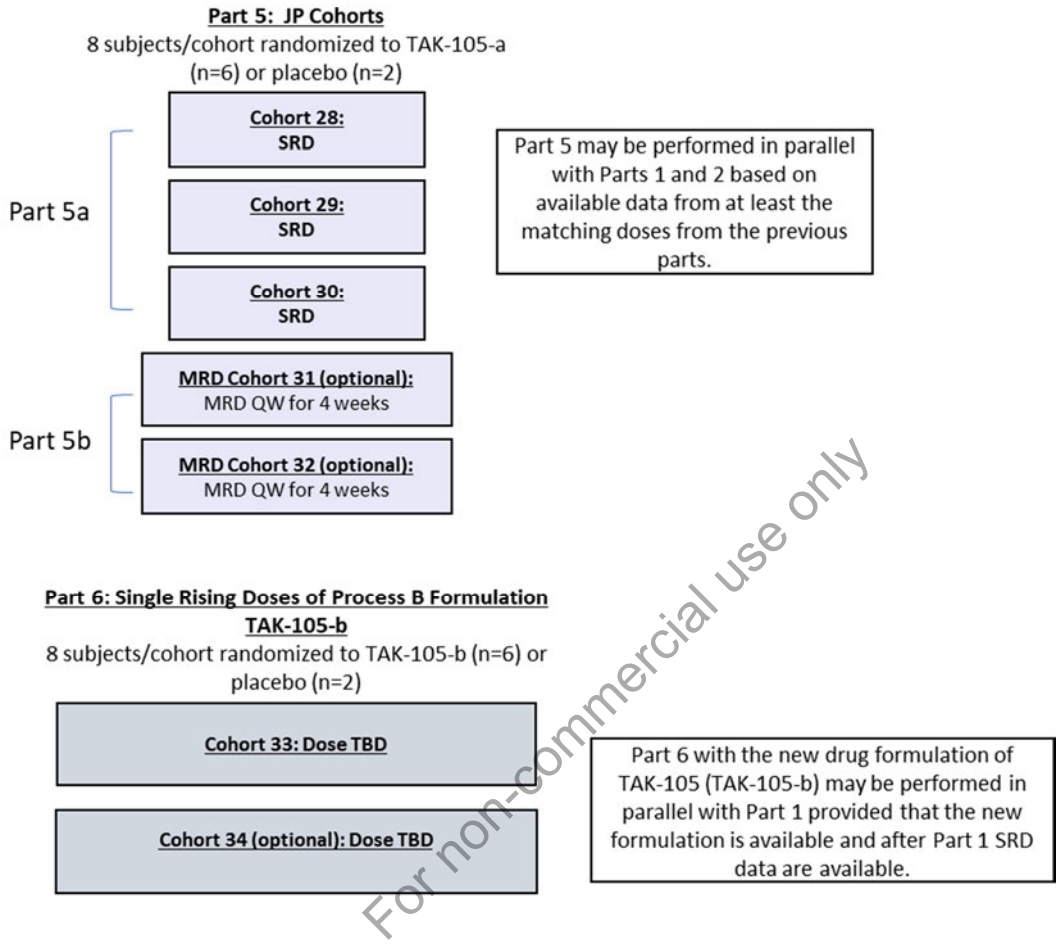
2.0 STUDY SCHEMATICS

Figure 2.a Study Schematic: Parts 1 to 4



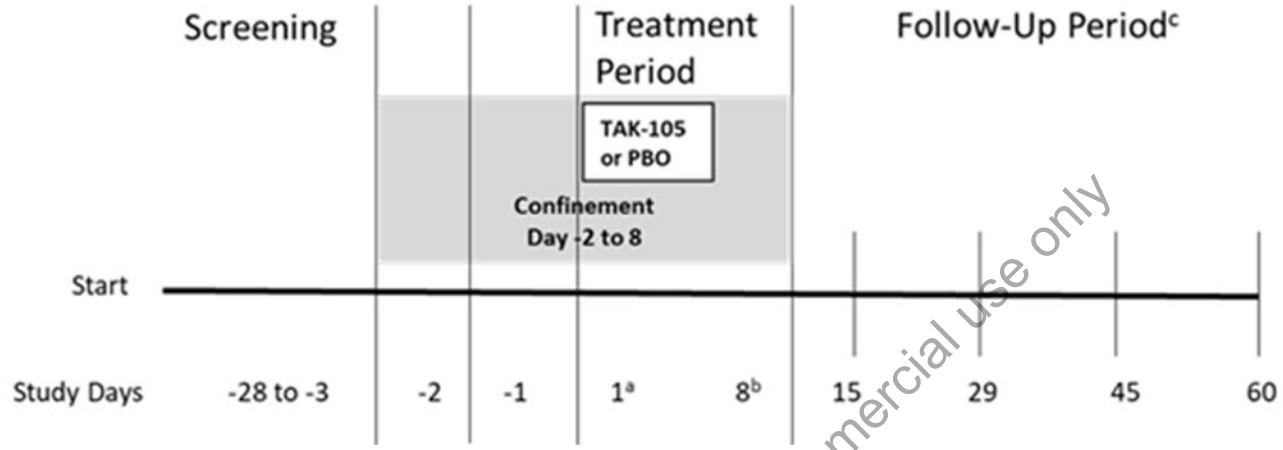
MRD: multiple-rising dose; QW: once weekly.

Figure 2.b Study Schematic: Parts 5 and 6



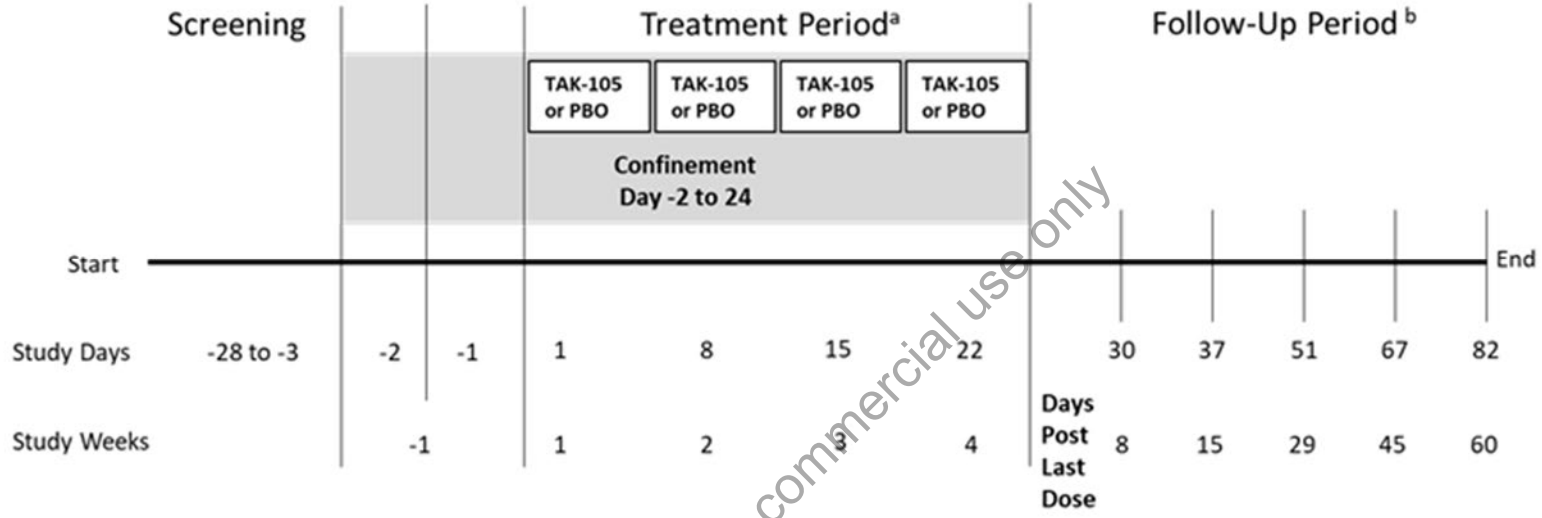
JP: Japanese; MRD: multiple-rising dose; QW: once weekly; SRD: single-rising dose; TBD: to be determined.
Part 5 will consist of subjects of Japanese origin (see Section 7.1 for details).

Figure 2.c Schematic of SRD Study Design: Part 1, Part 5a and Part 6



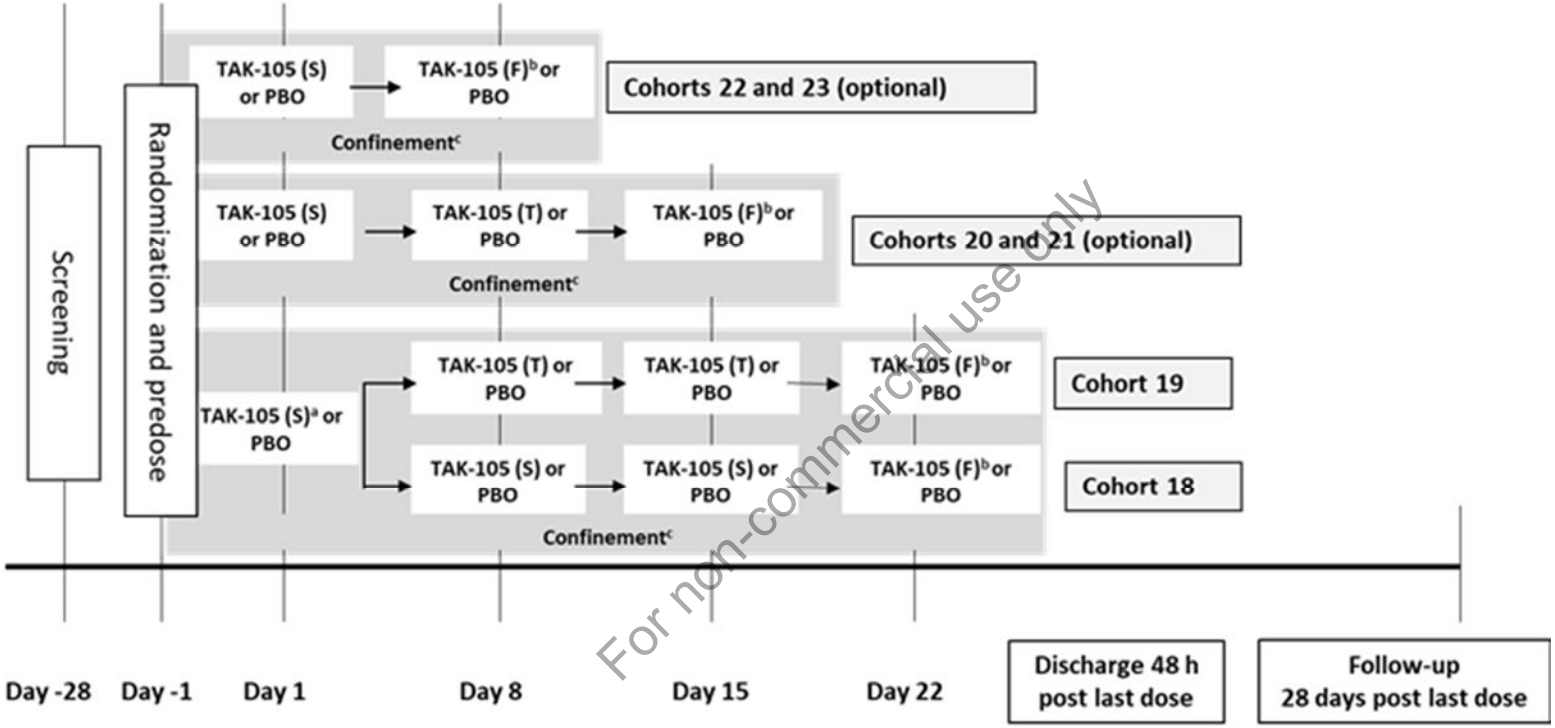
SRD study design applies to Part 1 cohorts, cohorts 28, 29, and 30 in Part 5a, and Part 6 cohorts.
PBO: placebo; SRD: single-rising dose.
[a] Subjects are dosed on Day 1 during the confinement period.
[b] Subjects are discharged on Day 8.
[c] During the follow-up period, subjects return to the clinic for assessments on specified days.

Figure 2.d Schematic of MRD Study Design: Part 2 and Part 5b



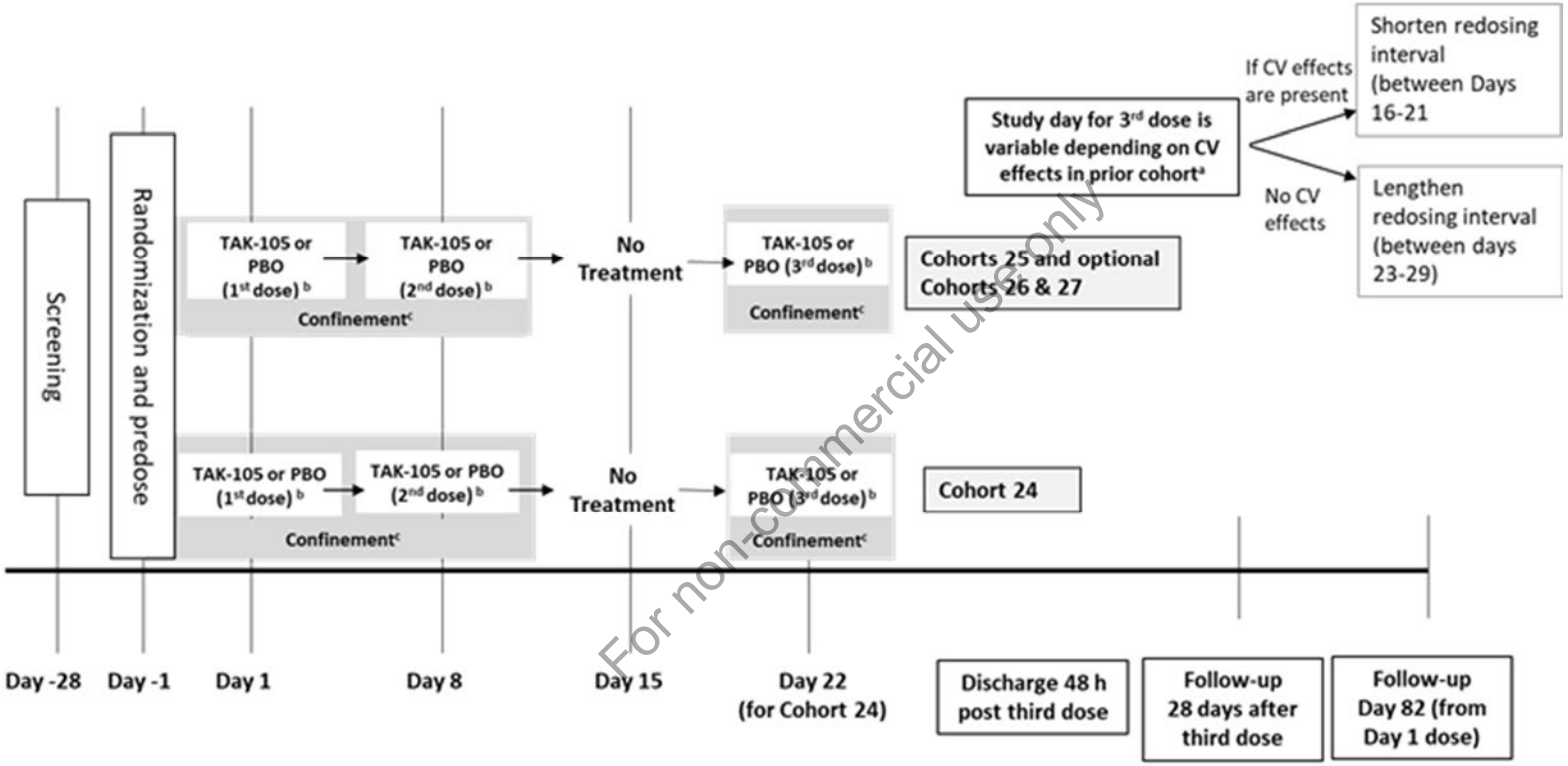
MRD study design applies to Part 2 cohorts and optional cohorts 31 and 32 in Part 5b.
MRD: multiple-rising dose; PBO: placebo.
[a] Subjects are dosed on Days 1, 8, 15, and 22 during the confined treatment period. Subjects will be discharged 48 h after the last dose.
[b] During the follow-up period, subjects return to the clinic for assessments on specified days.

Figure 2.e Schematic of Part 3 (Titration) Study Design



CV: cardiovascular; h: hours; PBO: placebo; PK: pharmacokinetic.
Starting (S), titrated (T), and final (F) doses may vary between cohorts.
[a] Starting dose for Cohorts 18 and 19 will be the same.
[b] Final (F) dose to be determined based on available safety, CV and PK data from Parts 1 and 2.
[c] Subjects will be confined from Day -1 through 48 hours post last dose (ie, until Day 10, 17, or 24 depending on the cohort assigned).

Figure 2.f Schematic of Part 4 (Redosing) Study Design



CV: cardiovascular; h: hours; PBO: placebo; PK: pharmacokinetic.

[a] Study day for third dose is variable for Cohorts 25, 26, and 27 depending on CV effects observed in prior cohort. See Section 6.1.5.1 for potential CV effects criterion.

[b] Dose to be determined based on available safety, CV and PK data from Parts 1 and 2.

[c] Subjects will be confined from Day -1 through 48 hours post second dose, then return to the clinic the day prior to the third dose (redosing day will vary for each cohort). Assessments will be performed through 48 hours after the third dose.

3.0 SCHEDULE OF STUDY PROCEDURES

3.1 Part 1 for SRD Cohort 1 to 12

3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8)

Table 3.a Part 1 for SRD Cohorts 1 to 12: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)																	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
Administrative Procedures																																		
Informed consent	X																																	
Inclusion/exclusion criteria	X	X																																
Medical history/ demographics	X																																	
Prior and concomitant medication review	X	X	X----------Continuous Review----------X																															
Clinic Procedures/Assessments																																		
Full physical examination	X	X																							X [e]									X [e]
Height	X																																	
Weight and BMI	X	X																																X
TAK-105-a/placebo administration [f]																X [f]																		
Vital signs	X	X													X				X			X					X							
Semirecumbent BP and HR [g]	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 HR [h]	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							X
ECG telemetry (12-lead)		X----------Continuous Monitoring [i]----------X													X----------Continuous Monitoring----------X																		

Table 3.a Part 1 for SRD Cohorts 1 to 12: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)														Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
Telemetry extraction [j]				X	X	X		X		X		X	X	X	X		X	X	X		X		X		X	X	X		X	X		X		X
AE monitoring	X [k]	X----------Continuous Monitoring----------X																												X	X	X	X
Laboratory Procedures/Assessments																																	
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X [l]						X		X		X			X
Urinalysis	X	X																									X						
Serum sample for CK [m]															X												X		X				X
Glucose finger stick															X					X					X								
Cortisol [n]			X																										X				X
Urine drug screen	X	X																															
Alcohol breath test		X																															
Cotinine test	X	X																															
Hepatitis screen [o]	X																																
HIV screen	X																																
βhCG (pregnancy) test [p]	X	X																															X
Serum FSH test [q]	X																																
PK Evaluations																																	
Plasma sample for TAK-105 PK															X		X	X	X		X		X		X	X	X		X	X		X		X
Urine sample for TAK-105 PK [r]															X	X					X		X		X		X		X	X	X	X	X	X
Immunogenicity and Biomarker Evaluations																																	
Serum sample for immunogenicity [s]															X																		X

Table 3.a Part 1 for SRD Cohorts 1 to 12: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
Blood sample for DNA (optional) [t]																																	X
[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; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; FSH: follicle stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure; 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 8 days after dosing (can be discharged after the Day 8 PK sample). Daily assessments on Days 5 through 8, except for urine PK collection, should occur at approximately the same time as the dosing time on Day 1. Urine PK samples will be collected per footnote r.

d At discharge, subject must meet vital sign discharge criteria as presented in Section 9.2.4.

e Physical examination at the indicated visit will be symptom-driven.

f Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

g All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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.

h For standing BP and HR assessment, a BP and HR 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 HR 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).

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

j Predose time-matched telemetry extractions may take place may take place between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.

k Collection of AEs will commence at the time the subject signs the informed consent form.

Table 3.a Part 1 for SRD Cohorts 1 to 12: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				

[l] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
[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] Morning cortisol sample should be drawn between 6 AM and 9 AM.
[o] Hepatitis panel, including HBsAg and anti-HCV.
[p] Serum pregnancy test for female subjects only.
[q] An FSH level will be obtained to assess postmenopausal status.
[r] Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 (Day 5), 96-120 (Day 6), 120-144 (Day 7), and 144-168 (Day 8) hours.
[s] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, at ET (if applicable), and at follow-up visits indicated in Table 3.b. 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.
[t] If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

3.1.2 Part 1 for SRD Cohort 1 to 12 (Follow-Up Through ET)

Table 3.b Part 1 for SRD Cohorts 1 to 12: Follow-Up Through ET

	Day 15 ±3 d	Day 29 ±3 d	Day 45 ±3 d	Day 60 ±3 d	ET
Administrative Procedures					
Prior and concomitant medication review	X	X	X	X	X
Clinic Procedures/Assessments					
Full physical examination					X
Weight and BMI				X	
Vital signs	X	X	X	X	X
Semirecumbent BP and HR [a]	X	X	X	X	X
Standing BP and HR [b]					X
12-lead ECGs	X	X	X		X
AE monitoring	X	X	X	X	X
Laboratory Procedures/Assessments					
Safety laboratory collection (hematology and serum chemistry)	X	X	X	X	X
Urinalysis		X	X	X	X
Serum sample for CK [c]					X
βhCG (pregnancy) test [d]					X
PK Evaluations					
Plasma sample for TAK-105 PK	X	X	X	X	X
Urine sample for TAK-105 PK					X
Immunogenicity and Biomarker Evaluations					
Serum sample for immunogenicity [e]	X	X	X	X	X
Blood sample for DNA (optional) [f]					X

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase;

Table 3.b Part 1 for SRD Cohorts 1 to 12: Follow-Up Through ET

	Day 15 ±3 d	Day 29 ±3 d	Day 45 ±3 d	Day 60 ±3 d	ET

ECG: electrocardiogram; ET: early termination; FSH: follicle stimulating hormone; HBsAg: hepatitis B surface antigen; HR: heart rate; LFT: liver function test; PK: pharmacokinetic; SBP: systolic blood pressure; SRD: single-rising dose.

[a] All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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.

[b] For standing BP and HR assessment, a BP and HR 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 HR 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).

[c] 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.

[d] Serum pregnancy test for female subjects only.

[e] Immunogenicity serum samples for ADA testing will be taken at ET (if applicable), and at follow-up visits on Days 15, 29, 45, and 60. 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.

[f] If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of ET (if applicable).

3.2 Part 2 for MRD Cohorts 13 to 17

3.2.1 Part 2 for MRD Cohorts 13 to 17 (Week 1)

Table 3.c Part 2 for MRD Cohorts 13 to 17: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																Day 5 (96 h)[c]	Day 6[c]	Day 7[c]
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Administrative Procedures																																	
Informed consent	X																																
Inclusion/exclusion criteria	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]							
Height	X																																
Weight and BMI	X	X																															
TAK-105-a/ placebo administration [e]																X [e]																	
Vital signs	X	X													X				X		X					X							
Semirecumbent BP and HR [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
Standing BP and HR [g]	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 [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	
AE monitoring	X [j]	X ---------- Continuous Monitoring ----------X																															

Table 3.c Part 2 for MRD Cohorts 13 to 17: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	Day 5 (96 h)[c]	Day 6[c]	Day 7[c]
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Laboratory Procedures/Assessments																																	
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X[k]						X		X			X		
Serum sample for CK [l]															X												X							
Urinalysis	X	X																									X							
Glucose finger stick															X					X					X									
Cortisol [m]			X																										X					
Urine drug screen	X	X																																
Alcohol breath test		X																																
Cotinine test	X	X																																
Hepatitis screen [n]	X																																	
HIV screen	X																																	
βhCG (pregnancy) test [o]	X	X																																
Serum FSH test [p]	X																																	
PK Evaluations																																		
Plasma sample for TAK-105 PK															X		X	X	X		X		X		X	X	X		X	X		X		
Plasma sample for metID															X		X				X		X		X	X	X		X	X	X	X		
Urine sample for TAK-105 PK [q]															X			X				X		X		X		X			X	X	X	
Immunogenicity and Biomarker Evaluations																																		
Serum sample for immunogenicity [r]															X																			
[redacted]																																		

Table 3.c Part 2 for MRD Cohorts 13 to 17: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																	
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h)[c]	Day 6 [c]	Day 7 [c]
Other																																
Confinement		X ---------- Continuous ---------- X																														

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; FSH: follicle stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; HR: heart rate; metID: metabolite identification; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

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 Daily assessments on Days 5 through 7, except for urine PK collection, should occur at approximately the same time as the dosing time on Day 1. Urine PK samples will be collected per footnote q.

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

e Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

f All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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 For standing BP and HR assessment, a BP and HR 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 HR 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 may take place between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.

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 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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

n Hepatitis panel, including HBsAg and anti-HCV.

o Serum pregnancy test for female subjects only.

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

q Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 (Day 5), 96-120 (Day 6), 120-144 (Day 7), 144-168 (Day 8 [prior to dosing]) hours.

r Immunogenicity serum samples will be collected for all subjects for ADA testing at baseline predose on Day 1.

Table 3.c Part 2 for MRD Cohorts 13 to 17: Screening Through Day 7 (Week 1)

	Day		Scheduled Time											Scheduled Time																	
	-28 to -3	-2 [a]	Day -1 (Hours)											Day 1 (Hours) through 4																	
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h)[c]	Day 6 [c]	Day 7 [c]
[redacted]																															

3.2.2 Part 2 for MRD Cohorts 13 to 17 (Week 2)

Table 3.d Part 2 for MRD Cohorts 13 to 17: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Clinic Procedures/Assessments																
Full physical examination															X [b]	
Weight and BMI	X															
TAK-105-a/placebo administration [c]		X [c]														
Vital signs	X				X		X						X			
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X daily
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X	X daily
12-lead ECGs	X												X			
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X															X [f]
Telemetry extraction	X		X		X		X				X	X	X			X [g] (72 h)
AE monitoring	X ---------- Continuous Monitoring ---------- X															
Laboratory Procedures/Assessments																
Safety laboratory collection (hematology and serum chemistry)	X						X [h]						X		X	X [i] (96 h)
Urinalysis													X			
Glucose finger stick	X					X					X					
Cortisol [j]	X															
PK Evaluations																
Plasma sample for TAK-105 PK	X [k]		X		X		X				X	X	X			X [g] (72 h)
Plasma sample for metID	X [k]															

Table 3.d Part 2 for MRD Cohorts 13 to 17: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Immunogenicity and Biomarker Evaluations																
Serum sample for immunogenicity [l]	X															
Other																
Confinement	X ---------- Continuous ---------- X															

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; BMI: body mass index; BP: blood pressure; bpm: beats per minute; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; FSH: follicle stimulating hormone; [redacted]; HR: heart rate; metID: metabolite identification; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

a Daily assessments on Days 11 through 14 should occur at approximately the same time as the dosing time on Day 8.
b Physical examination at the indicated visit will be symptom-driven.
c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 8, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 8 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
f If safety signals are identified during the study, ECG telemetry monitoring will be extended through Day 11 to 14.
g Telemetry extraction and PK sampling will be performed at 72 hours after last dose (Day 11).
h Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
i Sample for safety laboratory assessments will be taken at 96 hours after last dose (Day 12).
j Morning cortisol sample should be drawn between 6 AM and 9 AM.
k Blood samples for PK and metID may be drawn 10 minutes before dosing.
l Immunogenicity serum samples for ADA testing will be collected from all subjects at predose on Day 8.

3.2.3 Part 2 for MRD Cohorts 13 to 17 (Week 3)

Table 3.e Part 2 for MRD Cohorts 13 to 17: Day 15 Through Day 21 (Week 3)

	Scheduled Time															
	Day 15 and 16 (Hours)														Day 17	Day 18 to 21 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Clinic Procedures/Assessments																
Full physical examination															X [b]	
Weight and BMI	X															
TAK-105-a/placebo administration [c]		X [c]														
Vital signs	X				X		X						X			
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X daily
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X	X daily
12-lead ECGs	X												X			
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X															X [f]
Telemetry extraction	X		X		X		X				X	X	X			X [g] (72 h)
AE monitoring	X ---------- Continuous Monitoring ---------- X															
Laboratory Procedures/Assessments																
Safety laboratory collection (hematology and serum chemistry)	X						X [h]						X		X	X [i] (96 h)
Urinalysis													X			
Glucose finger stick	X					X					X					
Cortisol [j]	X															
PK Evaluations																
Plasma sample for TAK-105 PK	X [k]		X		X	-	X	-	-		X	X	X		-	X [g] (72 h)
Immunogenicity and Biomarker Evaluations																
Serum sample for immunogenicity [l]	X															

Table 3.e Part 2 for MRD Cohorts 13 to 17: Day 15 Through Day 21 (Week 3)

	Scheduled Time															
	Day 15 and 16 (Hours)														Day 17	Day 18 to 21 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Other																
Confinement	X ---------- Continuous ---------- X															

ADA: antidrug antibodies; AE: adverse event; BMI: body mass index; BP: blood pressure; bpm: beats per minute; DBP: diastolic blood pressure; ECG: electrocardiogram; HR: heart rate; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

[a] Daily assessments on Days 18 through 21 should occur at approximately the same time as the dosing time on Day 15.
[b] Physical examination at the indicated visit will be symptom-driven.
[c] Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
[d] All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 15, 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] For standing BP and HR assessment, a BP and HR 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 HR 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 15 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
[f] If safety signals are identified during the study, ECG telemetry monitoring will be extended through Day 18 to 21.
[g] Telemetry extraction and PK sampling will be performed at 72 hours after last dose (Day 18).
[h] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
[i] Sample for safety laboratory assessments will be taken at 96 hours after last dose (Day 19).
[j] Morning cortisol sample should be drawn between 6 AM and 9 AM.
[k] Blood sample for PK may be drawn 10 minutes before dosing.
[l] Immunogenicity serum samples for ADA testing will be taken at predose on Day 15.

3.2.4 Part 2 for MRD Cohorts 13 to 17 (Week 4, Follow-Up, and ET)

Table 3.f Part 2 for MRD Cohorts 13 to 17: Day 22 to 82 (Week 4, Follow-Up, and ET)

	Scheduled Time														Day 24 (Discharge) [a]	Follow-Up ±3d					
	Day 22 and 23 (Hours)																				
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 30	Day 37	Day 51	Day 67	Day 82	ET
Administrative Procedures																					
Prior and concomitant medication review																X	X	X	X	X	X
Clinic Procedures/Assessments																					
Full physical examination															X [b]						X
Weight and BMI															X					X	
TAK-105-a/placebo administration [c]		X [c]																			
Vital signs	X				X		X						X			X	X	X	X	X	X
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and HR [e]	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 ---------- X																				
Telemetry extraction	X		X		X		X		X		X	X	X		X						
AE monitoring	X ---------- Continuous Monitoring ---------- X															X	X	X	X	X	X
Laboratory Procedures/Assessments																					
Safety laboratory collection (hematology and serum chemistry)	X						X [f]						X		X	X	X	X	X	X	X
Serum sample for CK [g]															X						X
Urinalysis													X			X	X	X	X	X	X
Glucose finger stick	X					X					X										
Cortisol [h]															X						

Table 3.f Part 2 for MRD Cohorts 13 to 17: Day 22 to 82 (Week 4, Follow-Up, and ET)

	Scheduled Time															Follow-Up ±3d					
	Day 22 and 23 (Hours)														Day 24 (Discharge) [a]						
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 30	Day 37	Day 51	Day 67	Day 82	ET
PK Evaluations																					
Plasma sample for TAK-105 PK	X [i]		X		X		X		X		X	X	X		X	X	X	X	X	X	X
Plasma sample for metID	X [i]		X				X		X		X	X	X		X	X					X
Urine sample for TAK-105 PK [j]	X	X					X		X		X		X		X						X
Immunogenicity and Biomarker Evaluations																					
Serum sample for immunogenicity [k]	X															X		X		X	X
Blood sample for DNA (optional) [l]															X						X
[redacted]																					
Other																					
Confinement	X ---------- Continuous ---------- X																				

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; d: days; ECG: electrocardiogram; ET: early termination; HR: heart rate; metID: metabolite identification; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

a Subject must meet vital sign discharge criteria as presented in Section 9.2.4.

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

c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 22, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 22 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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 3.f Part 2 for MRD Cohorts 13 to 17: Day 22 to 82 (Week 4, Follow-Up, and ET)

																Follow-Up ±3d					
	Scheduled Time														Day 24 (Discharge) [a]						
	Day 22 and 23 (Hours)																				
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 30	Day 37	Day 51	Day 67	Day 82	ET

h Morning cortisol sample should be drawn between 6 AM and 9 AM.
i Blood samples for PK and metID may be drawn 10 minutes before dosing.
j Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-8, 8-12, 12-24, and 24-48 hours.
k Immunogenicity serum samples for ADA testing will be taken at predose on Day 22 or ET (if applicable). Serum samples will also be collected on follow-up visits on Days 30, 51, and 82. 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.
l If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

3.3 Part 3 Dose Titration Cohorts 18 and 19

3.3.1 Part 3 Dose Titration Cohorts 18 and 19 (Week 1)

Table 3.g Part 3 Dose Titration Cohorts 18 and 19: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Administrative Procedures																																	
Informed consent	X																																
Inclusion/exclusion criteria	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]							
Height	X																																
Weight and BMI	X	X																															
TAK-105-a/ placebo administration [e]																X [e]																	
Vital signs	X	X													X				X		X					X							
Semirecumbent BP and HR [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
Standing BP and HR [g]	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 [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			
AE monitoring	X [j]	X ---------- Continuous Monitoring ----------X																															

Table 3.g Part 3 Dose Titration Cohorts 18 and 19: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																			
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																			
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
Laboratory Procedures/Assessments																																		
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X [k]						X		X		X			
Serum sample for CK [l]															X												X							
Urinalysis	X	X																									X							
Glucose finger stick															X					X					X									
Cortisol [m]			X																										X					
Urine drug screen	X	X																																
Alcohol breath test		X																																
Cotinine test	X	X																																
Hepatitis screen [n]	X																																	
HIV screen	X																																	
βhCG (pregnancy) test [o]	X	X																																
Serum FSH test [p]	X																																	
PK Evaluations																																		
Plasma sample for TAK-105 PK															X		X	X	X		X				X	X	X			X				
Immunogenicity and Biomarker Evaluations																																		
Serum sample for immunogenicity [q]															X																			
[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; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; FSH: follicle stimulating hormone; [redacted]

Table 3.g Part 3 Dose Titration Cohorts 18 and 19: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																		
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]

[redacted]; HBsAg: hepatitis B surface antigen; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

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 Daily assessments on Days 5 through 7 should occur at approximately the same time as the dosing time on Day 1.
d Physical examination at the indicated visit will be symptom-driven.
e Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
f All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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 For standing BP and HR assessment, a BP and HR 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 HR 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 between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.
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 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 Morning cortisol sample should be drawn between 6 AM and 9 AM.
n Hepatitis panel, including HBsAg and anti-HCV.
o Serum pregnancy test for female subjects only.
p An FSH level will be obtained to assess postmenopausal status.
q Immunogenicity serum samples will be collected for all subjects for ADA testing at baseline predose on Day 1.

[redacted]

3.3.2 Part 3 Dose Titration Cohorts 18 and 19 (Week 2)

Table 3.h Part 3 Dose Titration Cohorts 18 and 19: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Clinic Procedures/Assessments																
Full physical examination															X [b]	
TAK-105-a /placebo administration [c]		X [c]														
Vital signs	X				X		X						X			
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X daily
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X	X daily
12-lead ECGs	X												X			
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X															X [f]
Telemetry extraction	X		X		X		X				X	X	X			X [g] (72 h)
AE monitoring	X ---------- Continuous Monitoring ---------- X															
Laboratory Procedures/Assessments																
Safety laboratory collection (hematology and serum chemistry)	X						X [h]						X		X	X [i] (96h)
Urinalysis													X			
Glucose finger stick	X					X					X					
Cortisol [j]	X															
PK Evaluations																
Plasma sample for TAK-105 PK	X [k]		X		X		X				X	X	X			X [g] (72 h)
Immunogenicity and Biomarker Evaluations																
Serum sample for immunogenicity [l]	X															

Table 3.h Part 3 Dose Titration Cohorts 18 and 19: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
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; DBP: diastolic blood pressure; ECG: electrocardiogram; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

a Daily assessments on Days 11 through 14 should occur at approximately the same time as the dosing time on Day 8.
b Physical examination at the indicated visit will be symptom-driven.
c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 8, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 8 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
f If safety signals are identified during the study, ECG telemetry monitoring will be extended through Day 11 to 14.
g Telemetry extraction and PK sampling will be performed at 72 hours after last dose (Day 11).
h Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
i Sample for safety laboratory assessments will be taken at 96 hours after last dose (Day 12).
j Morning cortisol sample should be drawn between 6 AM and 9 AM.
k Blood sample for PK may be drawn 10 minutes before dosing.
l Immunogenicity serum samples for ADA testing will be collected from all subjects at predose on Day 8.

3.3.3 Part 3 Dose Titration Cohorts 18 and 19 (Week 3)

Table 3.i Part 3 Dose Titration Cohorts 18 and 19: Day 15 Through Day 21 (Week 3)

	Scheduled Time															
	Day 15 and 16 (Hours)														Day 17	Day 18 to 21 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Clinic Procedures/Assessments																
Full physical examination															X [b]	
TAK-105-a /placebo administration [c]		X [c]														
Vital signs	X				X		X						X			
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X daily
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X	X daily
12-lead ECGs	X												X			
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X															X [f]
Telemetry extraction	X		X		X		X				X	X	X			X [g] (72 h)
AE monitoring	X ---------- Continuous Monitoring ---------- X															
Laboratory Procedures/Assessments																
Safety laboratory collection (hematology and serum chemistry)	X						X [h]						X		X	X [i] (96h)
Urinalysis													X			
Glucose finger stick	X					X					X					
Cortisol [j]	X															
PK Evaluations																
Plasma sample for TAK-105 PK	X [k]		X		X		X				X	X	X			X [g] (72 h)
Immunogenicity and Biomarker Evaluations																
Serum sample for immunogenicity [l]	X															

Table 3.i Part 3 Dose Titration Cohorts 18 and 19: Day 15 Through Day 21 (Week 3)

	Scheduled Time															
	Day 15 and 16 (Hours)														Day 17	Day 18 to 21 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Other																
Confinement	X ---------- Continuous ----------X															

ADA: antidrug antibodies; AE: adverse event; BP: blood pressure; bpm: beats per minute; DBP: diastolic blood pressure; ECG: electrocardiogram; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

a Daily assessments on Days 18 through 21 should occur at approximately the same time as the dosing time on Day 15.
b Physical examination at the indicated visit will be symptom-driven.
c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 15, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 15 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
f If safety signals are identified during the study, ECG telemetry monitoring will be extended through Day 18 to 21.
g Telemetry extraction and PK sampling will be performed at 72 hours after last dose (Day 18).
h Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
i Sample for safety laboratory assessments will be taken at 96 hours after last dose (Day 19).
j Morning cortisol sample should be drawn between 6 AM and 9 AM.
k Blood sample for PK may be drawn 10 minutes before dosing.
l Immunogenicity serum samples for ADA testing will be taken at predose on Day 15.

3.3.4 Part 3 Dose Titration Cohorts (Week 4, Follow-Up, and ET)

Table 3.j Part 3 for Dose Titration Cohorts 18 and 19: Day 22 to 82 (Week 4, Follow-Up, and ET)

	Scheduled Time														Day 24 (Discharge) [a]	Follow-Up	
	Day 22 and 23 (Hours)																
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 50±3 (28 d post last dose)	ET
Administrative Procedures																	
Prior and concomitant medication review																X	X
Clinic Procedures/Assessments																	
Full physical examination													X [b]		X [b]		X
Weight and BMI															X		
TAK-105-a /placebo administration [c]		X [c]															
Vital signs	X				X		X						X			X	X
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X		X
12-lead ECGs	X														X	X	X
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X																
Telemetry extraction	X		X		X		X		X		X	X	X		X		
AE monitoring	X ---------- Continuous Monitoring ---------- X															X	X
Laboratory Procedures/Assessments																	
Safety laboratory collection (hematology and serum chemistry)	X						X [f]						X		X	X	X
Serum sample for CK [g]															X		X
Urinalysis													X			X	X
Glucose finger stick	X					X					X						
Cortisol [h]															X		

Table 3.j Part 3 for Dose Titration Cohorts 18 and 19: Day 22 to 82 (Week 4, Follow-Up, and ET)

	Scheduled Time														Day 24 (Discharge) [a]	Follow-Up	
	Day 22 and 23 (Hours)																
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 50±3 (28 d post last dose)	ET
PK Evaluations																	
Plasma sample for TAK-105 PK	X [i]		X		X		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; BMI: body mass index; BP: blood pressure; CK: creatine kinase; DBP: diastolic blood pressure; bpm: beats per minute; ECG: electrocardiogram; ET: early termination; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

a Subject must meet vital sign discharge criteria as presented in Section 9.2.4

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

c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 22, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 22 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

i 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 22 or ET (if applicable). Serum samples will also be collected on follow-up visits on Day 50. 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 3.j Part 3 for Dose Titration Cohorts 18 and 19: Day 22 to 82 (Week 4, Follow-Up, and ET)

	Scheduled Time																
	Day 22 and 23 (Hours)														Day 24 (Discharge) [a]	Follow-Up	
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 50±3 (28 d post last dose)	ET

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

[redacted]

3.4 Part 3 Dose Titration Cohorts 20 and 21

3.4.1 Part 3 Dose Titration Cohorts 20 and 21 (Week 1)

Table 3.k Part 3 Dose Titration Cohorts 20 and 21: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Administrative Procedures																																	
Informed consent	X																																
Inclusion/exclusion criteria	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]							
Height	X																																
Weight and BMI	X	X																															
TAK-105-a / placebo administration [e]																X [e]																	
Vital signs	X	X													X				X		X					X							
Semirecumbent BP and HR [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
Standing BP and HR [g]	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 [h]----------X													X----------Continuous Monitoring----------X																	
Telemetry extraction [i]				X		X		X				X	X	X	X		X		X		X				X	X	X			X		X	
AE monitoring	X [j]	X----------Continuous Monitoring----------X																															

Table 3.k Part 3 Dose Titration Cohorts 20 and 21: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																			
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Laboratory Procedures/Assessments																																		
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X [k]						X		X		X			
Urinalysis	X	X																									X							
Serum sample for CK [l]															X												X							
Glucose finger stick															X					X					X									
Cortisol [m]			X																										X					
Urine drug screen	X	X																																
Alcohol breath test		X																																
Cotinine test	X	X																																
Hepatitis screen [n]	X																																	
HIV screen	X																																	
βhCG (pregnancy) test [o]	X	X																																
Serum FSH test [p]	X																																	
PK Evaluations																																		
Plasma sample for TAK-105 PK															X		X		X		X				X	X	X			X		X		
Immunogenicity and Biomarker Evaluations																																		
Serum sample for immunogenicity [q]															X																			
[redacted]																																		

Table 3.k Part 3 Dose Titration Cohorts 20 and 21: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																		
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
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; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; FSH: follicle stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

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 Daily assessments on Days 5 through 7 should occur at approximately the same time as the dosing time on Day 1.
d Physical examination at the indicated visit will be symptom-driven.
e Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
f All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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 For standing BP and HR assessment, a BP and HR 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 HR 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 between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.
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 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 Morning cortisol sample should be drawn between 6 AM and 9 AM.
n Hepatitis panel, including HBsAg and anti-HCV.
o Serum pregnancy test for female subjects only.
p An FSH level will be obtained to assess postmenopausal status.
q Immunogenicity serum samples will be collected for all subjects for ADA testing at baseline predose on Day 1.
[redacted]

3.4.2 Part 3 Dose Titration Cohorts 20 and 21 (Week 2)

Table 3.1 Part 3 Dose Titration Cohorts 20 and 21: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Clinic Procedures/Assessments																
Full physical examination															X [b]	
TAK-105-a /placebo administration [c]		X [c]														
Vital signs	X				X		X						X			
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X daily
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X	X daily
12-lead ECGs	X												X			
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X															X [f]
Telemetry extraction	X		X		X		X				X	X	X			X [g] (72 h)
AE monitoring	X ---------- Continuous Monitoring ---------- X															
Laboratory Procedures/Assessments																
Safety laboratory collection (hematology and serum chemistry)	X						X [h]						X		X	X [i] (96h)
Urinalysis													X			
Glucose finger stick	X					X					X					
Cortisol [j]	X															
PK Evaluations																
Plasma sample for TAK-105 PK	X [k]		X		X		X				X	X	X			X [g] (72 h)
Immunogenicity and Biomarker Evaluations																
Serum sample for immunogenicity [l]	X															

Table 3.1 Part 3 Dose Titration Cohorts 20 and 21: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Other																
Confinement	X ---------- Continuous ----------															X

ADA: antidrug antibodies; AE: adverse event; BP: blood pressure; bpm: beats per minute; DBP: diastolic blood pressure; ECG: electrocardiogram; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

a Daily assessments on Days 11 through 14 should occur at approximately the same time as the dosing time on Day 8.
b Physical examination at the indicated visit will be symptom-driven.
c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 8, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 8 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
f If safety signals are identified during the study, ECG telemetry monitoring will be extended through Day 11 to 14.
g Telemetry extraction and PK sampling will be performed at 72 hours after last dose (Day 11).
h Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
i Sample for safety laboratory assessments will be taken at 96 hours after last dose (Day 12).
j Morning cortisol sample should be drawn between 6 AM and 9 AM.
k Blood sample for PK may be drawn 10 minutes before dosing.
l Immunogenicity serum samples for ADA testing will be collected from all subjects at predose on Day 8.

3.4.3 Part 3 Dose Titration Cohorts 20 and 21 (Week 3, Follow-Up, and ET)

Table 3.m Part 3 for Dose Titration Cohorts 20 and 21: Day 15 Through Day 17 (Week 3, Follow-Up, and ET)

	Scheduled Time																
	Day 15 and 16 (Hours)														Day 17 Discharge [a]	Follow-Up	ET
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 43±3 (28 d After Last Dose)	
Administrative Procedures																	
Prior and concomitant medication review																X	X
Clinic Procedures/Assessments																	
Full physical examination															X [b]		X
Weight and BMI															X		
TAK-105-a /placebo administration [c]		X [c]															
Vital signs	X				X		X						X			X	X
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X		X
12-lead ECGs	X														X	X	X
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ----------X																
Telemetry extraction	X		X		X		X				X	X	X	X	X		
AE monitoring	X ---------- Continuous Monitoring ----------X															X	X
Laboratory Procedures/Assessments																	
Safety laboratory collection (hematology and serum chemistry)	X						X [f]						X		X	X	X
Urinalysis													X			X	X
Serum sample for CK [g]															X		X
Glucose finger stick	X					X					X						
Cortisol [h]															X		

Table 3.m Part 3 for Dose Titration Cohorts 20 and 21: Day 15 Through Day 17 (Week 3, Follow-Up, and ET)

	Scheduled Time																
	Day 15 and 16 (Hours)														Day 17 Discharge [a]	Follow-Up	
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 43±3 (28 d After Last Dose)	ET
PK Evaluations																	
Plasma sample for TAK-105 PK	X [i]		X		X		X				X	X	X	X	X	X	X
Immunogenicity and Biomarker Evaluations																	
Serum sample for immunogenicity [j]	X															X	X
Other																	
Confinement	X ---------- Continuous ---------- X																

ADA: antidrug antibodies; AE: adverse event; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; d: days; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; HR: heart rate; LFT: liver function test; PK: pharmacokinetic; SBP: systolic blood pressure.

a Subject must meet vital sign discharge criteria as presented in Section 9.2.4

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

c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 15, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 15 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

i 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 15 and on Day 43 at the follow-up visit.

3.5 Part 3 Dose Titration Cohorts 22 and 23

3.5.1 Part 3 Dose Titration Cohorts 22 and 23 (Week 1)

Table 3.n Part 3 for Dose Titration Cohorts 22 and 23: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																		
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
Administrative Procedures																																	
Informed consent	X																																
Inclusion/exclusion criteria	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]						
Height	X																																
Weight and BMI	X	X																															
TAK-105-a / placebo administration [e]																X [e]																	
Vital signs	X	X													X				X		X						X						
Semirecumbent BP and HR [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
Standing BP and HR [g]	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 [h] ----------X													X ---------- Continuous Monitoring ----------X																	
Telemetry extraction [i]				X		X		X				X	X	X	X		X		X		X					X	X	X			X			
AE monitoring	X[j]	X ---------- Continuous Monitoring ----------X																															

Table 3.n Part 3 for Dose Titration Cohorts 22 and 23: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Laboratory Procedures/Assessments																																	
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X [k]						X		X		X		
Urinalysis	X	X																									X						
Serum sample for CK [l]															X												X						
Glucose finger stick															X					X					X								
Cortisol [m]			X																										X				
Urine drug screen	X	X																															
Alcohol breath test		X																															
Cotinine test	X	X																															
Hepatitis screen [n]	X																																
HIV screen	X																																
βhCG (pregnancy) test [o]	X	X																															
Serum FSH test [p]	X																																
PK Evaluations																																	
Plasma sample for TAK-105 PK															X		X		X		X				X	X	X			X			
Immunogenicity and Biomarker Evaluations																																	
Serum sample for immunogenicity [q]															X																		
[redacted]																																	
Other																																	
Confinement		X ---------- Continuous ---------- X																															

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; ECG: electrocardiogram; FSH: follicle stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; HIV: human

Table 3.n Part 3 for Dose Titration Cohorts 22 and 23: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																						
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																						
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]

immunodeficiency virus; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

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 Daily assessments on Days 5 through 7 should occur at approximately the same time as the dosing time on Day 1.

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

e Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

f All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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 For standing BP and HR assessment, a BP and HR 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 HR 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 between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.

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 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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

n Hepatitis panel, including HBsAg and anti-HCV.

o Serum pregnancy test for female subjects only.

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

q Immunogenicity serum samples will be collected for all subjects for ADA testing at baseline predose on Day 1.

[redacted]

3.5.2 Part 3 Dose Titration Cohorts 22 and 23 (Week 2, Follow-Up, and ET)

Table 3.o Part 3 for Dose Titration Cohorts 22 and 23: Day 8 Through Day 10 (Week 2), Follow-Up, and ET

	Scheduled Time																
	Day 8 and 9 (Hours)														Day 10 (Discharge) [a]	Follow-up	
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 36±3 (28 days After Last Dose)	ET
Administrative Procedures																	
Prior and concomitant medication review																X	X
Clinic Procedures/Assessments																	
Full physical examination															X [b]		X
Weight and BMI															X		
TAK-105-a /placebo administration [c]		X [c]															
Vital signs	X				X		X						X			X	X
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X		X
12-lead ECGs	X														X	X	X
ECG telemetry (12-lead)	X---------- Continuous Monitoring ----------X																
Telemetry extraction	X		X		X		X		X		X	X	X		X		
AE monitoring	X---------- Continuous Monitoring ----------X															X	X
Laboratory Procedures/Assessments																	
Safety laboratory collection (hematology and serum chemistry)	X						X [f]						X		X	X	X
Urinalysis													X			X	X
Serum sample for CK [g]															X		X
Glucose finger stick	X					X					X						
Cortisol [h]															X		

Table 3.o Part 3 for Dose Titration Cohorts 22 and 23: Day 8 Through Day 10 (Week 2), Follow-Up, and ET

	Scheduled Time																
	Day 8 and 9 (Hours)														Day 10 (Discharge) [a]	Follow-up	
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 36±3 (28 days After Last Dose)	ET
PK Evaluations																	
Plasma sample for TAK-105 PK	X [i]		X		X		X		X		X	X	X		X	X	X
Immunogenicity and Biomarker Evaluations																	
Serum sample for immunogenicity [j]	X															X	X
Other																	
Confinement	X---------- Continuous ----------X																

ADA: antidrug antibodies; AE: adverse event; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

a Subject must meet vital sign discharge criteria as presented in Section 9.2.4

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

c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 8, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 8 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

i Blood sample for PK may be drawn 10 minutes before dosing.

j Immunogenicity serum samples for ADA testing will be collected from all subjects at predose on Day 8.

3.6 Part 4 Redosing Cohorts 24 Through 27

3.6.1 Part 4 Redosing Cohorts 24 Through 27 (Week 1)

Table 3.p Part 4 Redosing Study Cohorts 24 Through 27: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Administrative Procedures																																	
Informed consent	X																																
Inclusion/exclusion criteria	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]							
Height	X																																
Weight and BMI	X	X																															
TAK-105-a / placebo administration [e]																X [e]																	
Vital signs	X	X													X				X		X						X						
Semirecumbent BP and HR [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
Standing BP and HR [g]	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 [h]----------X													X----------Continuous Monitoring----------X																	
Telemetry extraction [i]				X		X		X				X	X	X	X		X		X		X					X	X	X			X			
AE monitoring	X [j]	X----------Continuous Monitoring----------X																															

Table 3.p Part 4 Redosing Study Cohorts 24 Through 27: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																		
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Laboratory Procedures/Assessments																																	
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X [k]						X		X		X		
Urinalysis	X	X																									X						
Serum sample for CK [l]															X												X						
Glucose finger stick															X					X					X								
Cortisol [m]		X																											X				
Urine drug screen	X	X																															
Alcohol breath test		X																															
Cotinine test	X	X																															
Hepatitis screen [n]	X																																
HIV screen	X																																
βhCG (pregnancy) test [o]	X	X																															
Serum FSH test [p]	X																																
PK Evaluations																																	
Plasma sample for TAK-105 PK															X		X		X		X				X	X	X			X			
Immunogenicity and Biomarker Evaluations																																	
Serum sample for immunogenicity [q]															X																		
[redacted]																																	
Other																																	
Confinement		X ---------- Continuous ---------- X																															

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; bpm: beats per minute; BMI: body mass index; BP: blood pressure; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; FSH: follicle stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure

Table 3.p Part 4 Redosing Study Cohorts 24 Through 27: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																		
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]

Subjects in Cohort 24 through 27 will be confined from Day -1 through 48 hours post second dose and follow the schedule of assessments for Weeks 1 and 2 as presented in Table 3.p and Table 3.q. Subjects in all cohorts will return to the clinic for fasting and confinement on the day prior to the third dose (redosing day will vary for each cohort). Assessments will be performed through 48 hours after the third dose (Table 3.r). The follow-up visit will be 28 days after the third 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 Daily assessments on Days 5 through 7 should occur at approximately the same time as the dosing time on Day 1.
d Physical examination at the indicated visit will be symptom-driven.
e Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
f All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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 For standing BP and HR assessment, a BP and HR 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 HR 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 between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.
j Collection of AEs will commence at the time the subject signs the informed consent form.
k Only chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
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 Morning cortisol sample should be drawn between 6 AM and 9 AM.
n Hepatitis panel, including HBsAg and anti-HCV.
o Serum pregnancy test for female subjects only.
p An FSH level will be obtained to assess postmenopausal status.
q Immunogenicity serum samples will be collected for all subjects for ADA testing at baseline predose on Day 1.
[redacted]

3.6.2 Part 4 Redosing Cohorts 24 Through 27 (Week 2)

Table 3.q Part 4 Redosing Study Cohorts 24 Through 27: Day 8 Through Day 10 (Week 2)

	Scheduled Time														
	Day 8 and 9 (Hours)														Day 10 (Discharge) [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48
Clinic Procedures/Assessments															
Full physical examination															X [b]
TAK-105-a /placebo administration [c]		X [c]													
Vital signs	X				X		X						X		
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X
12-lead ECGs	X														X
ECG telemetry (12-lead)	X---------- Continuous Monitoring ----------X														
Telemetry extraction	X		X		X		X				X	X	X	X	X
AE monitoring	X---------- Continuous Monitoring ----------X														
Laboratory Procedures/Assessments															
Safety laboratory collection (hematology and serum chemistry)	X						X [f]						X		X
Urinalysis													X		
Serum sample for CK [g]															X
Glucose finger stick	X					X					X				
Cortisol [h]	X														
PK Evaluations															
Plasma sample for TAK-105 PK	X [i]		X		X		X				X	X	X	X	X
Immunogenicity and Biomarker Evaluations															
Serum sample for immunogenicity [j]	X														

Table 3.q Part 4 Redosing Study Cohorts 24 Through 27: Day 8 Through Day 10 (Week 2)

	Scheduled Time														
	Day 8 and 9 (Hours)														Day 10 (Discharge) [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48
Other															
Confinement	X---------- Continuous ----------X														

ADA: antidrug antibodies; AE: adverse event; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

Subjects in Cohort 24 through 27 will be confined from Day -1 through 48 hours post second dose and follow the schedule of assessments for Weeks 1 and 2 as presented in Table 3.p and Table 3.q. Subjects in all cohorts will return to the clinic for fasting and confinement on the day prior to the third dose (redosing day will vary for each cohort). Assessments will be performed through 48 hours after the third dose (Table 3.r). The follow-up visit will be 28 days after the third dose.

a Subject must meet vital sign discharge criteria as presented in Section 9.2.4

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

c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 8, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 8 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

i Blood sample for PK may be drawn 10 minutes before dosing.

j Immunogenicity serum samples for ADA testing will be collected from all subjects at predose on Day 8.

3.6.3 Part 4 Redosing Cohorts 24 Through 27 (Third Dose Week, Follow-Up, and ET)

Table 3.r Part 4 Redosing Study Cohorts 24 Through 27: Variable Third Dose Week, Follow-Up, and ET

	Scheduled Time																
	Day Prior to Third Dose and Redosing Day (Hours)														Discharge [a]	Follow-Up	Follow-Up	
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48 h After Third Dose	28±3 days After Third Dose	Day 82±3 from Day 1 dose	ET
Administrative Procedures																		
Prior and concomitant medication review																X		X
Clinic Procedures/Assessments																		
Full physical examination															X [b]			X
Weight and BMI															X			
TAK-105-a /placebo administration [c]		X																
Vital signs	X				X		X						X			X	X	X
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X			X
12-lead ECGs	X														X	X		X
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X																	
Telemetry extraction	X		X		X		X		X		X	X	X	X	X			
AE monitoring	X ---------- Continuous Monitoring ---------- X															X	X	X
Laboratory Procedures/Assessments																		
Safety laboratory collection (hematology and serum chemistry)	X						X [f]						X		X	X	X	X
Urinalysis													X			X		X
Serum sample for CK [g]															X			X
Glucose finger stick	X					X					X							
Cortisol [h]	X														X			

Table 3.r Part 4 Redosing Study Cohorts 24 Through 27: Variable Third Dose Week, Follow-Up, and ET

	Scheduled Time																	
	Day Prior to Third Dose and Redosing Day (Hours)														Discharge [a]	Follow-Up	Follow-Up	
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48 h After Third Dose	28±3 days After Third Dose	Day 82±3 from Day 1 dose	ET
PK Evaluations																		
Plasma sample for TAK-105 PK	X		X		X		X		X		X	X	X	X	X	X		X
Immunogenicity and Biomarker Evaluations																		
Serum sample for immunogenicity [i]	X															X	X	X
Blood sample for DNA (optional) [j]															X			X
[redacted]																		
Other																		
Confinement	X ---------- Continuous ---------- X																	

ADA: antidrug antibodies; AE: adverse event; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure.

Subjects in Cohort 24 through 27 will be confined from Day -1 through 48 hours post second dose and follow the schedule of assessments for Weeks 1 and 2 as presented in Table 3.p and Table 3.q. Subjects in all cohorts will return to the clinic for fasting and confinement on the day prior to the third dose (redosing day will vary for each cohort). Assessments will be performed through 48 hours after the third dose (Table 3.r). The follow-up visit will be 28 days after the third dose

a Subject must meet vital sign discharge criteria as presented in Section 9.2.4

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

c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On redosing day, 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 For standing BP and HR assessment, a BP and HR 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 HR 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). Redosing day time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

Table 3.r Part 4 Redosing Study Cohorts 24 Through 27: Variable Third Dose Week, Follow-Up, and ET

	Scheduled Time																
	Day Prior to Third Dose and Redosing Day (Hours)														Discharge [a]	Follow-Up	Follow-Up	
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48 h After Third Dose	28±3 days After Third Dose	Day 82±3 from Day 1 dose	ET

[1] Immunogenicity serum samples for ADA testing will be taken at predose on day prior to third dose or ET (if applicable). Serum samples will also be collected on follow-up visits at 28 days after third dose and on Day 82 (from Day 1 dose). 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.

j If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

3.7 Part 5 Japanese Subjects

3.7.1 Part 5a for Japanese SRD Cohort 28 to 30: Days 1 Through 8

Table 3.s Part 5a for Japanese SRD Cohorts 28 to 30: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
Administrative Procedures																																		
Informed consent	X																																	
Inclusion/exclusion criteria	X	X																																
Medical history/ demographics	X																																	
Prior and concomitant medication review	X	X	X----------Continuous Review----------X																												X			
Clinic Procedures/Assessments																																		
Full physical examination	X	X																						X [e]										X [e]
Height	X																																	
Weight and BMI	X	X																																X
TAK-105-a/placebo administration [f]																X [f]																		
Vital signs	X	X													X				X			X					X							
Semirecumbent BP and HR [g]	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 HR [h]	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							X
ECG telemetry (12-lead)		X----------Continuous Monitoring [i]----------X													X----------Continuous Monitoring----------X																		
Telemetry extraction [j]				X	X	X		X		X		X	X	X	X		X	X	X		X		X		X	X	X		X	X		X		X

Table 3.s Part 5a for Japanese SRD Cohorts 28 to 30: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
AE monitoring	X [k]	X----------Continuous Monitoring----------X																												X	X	X	X
Laboratory Procedures/Assessments																																	
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X [l]							X		X				X
Urinalysis	X	X																										X						
Serum sample for CK [m]															X													X		X				X
Glucose finger stick															X					X					X									
Cortisol [n]			X																											X				X
Urine drug screen	X	X																																
Alcohol breath test		X																																
Cotinine test	X	X																																
Hepatitis screen [o]	X																																	
HIV screen	X																																	
βhCG (pregnancy) test [p]	X	X																																X
Serum FSH test [q]	X																																	
PK Evaluations																																		
Plasma sample for TAK-105 PK															X		X	X	X		X		X		X	X	X		X	X		X		X
Urine sample for TAK-105 PK [r]															X	X					X		X		X		X		X	X	X	X	X	X
Immunogenicity and Biomarker Evaluations																																		
Serum sample for immunogenicity [s]															X																			X
Blood sample for DNA (optional) [t]																																		X

Table 3.s Part 5a for Japanese SRD Cohorts 28 to 30: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Predose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
[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; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; FSH: follicle stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure; 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 8 days after dosing (can be discharged after the Day 8 PK sample). Daily assessments on Days 5 through 8, except for urine PK collection, should occur at approximately the same time as the dosing time on Day 1. Urine PK samples will be collected per footnote r.

d At discharge, subject must meet vital sign discharge criteria as presented in Section 9.2.4.

e Physical examination at the indicated visit will be symptom-driven.

f Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

g All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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.

h For standing BP and HR assessment, a BP and HR 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 HR 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).

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

j Predose time-matched telemetry extractions may take place may take place between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.

k Collection of AEs will commence at the time the subject signs the informed consent form.

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

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.

Table 3.s Part 5a for Japanese SRD Cohorts 28 to 30: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				

n Morning cortisol sample should be drawn between 6 AM and 9 AM.
o Hepatitis panel, including HBsAg and anti-HCV.
p Serum pregnancy test for female subjects only.
q An FSH level will be obtained to assess postmenopausal status.
r Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 (Day 5), 96-120 (Day 6), 120-144 (Day 7), and 144-168 hours (Day 8) .
s Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, at ET (if applicable), and at follow-up visits indicated in Table 3.b. 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.
t If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

3.7.2 Part 5a for Japanese SRD Cohort 28 to 30: Follow-Up Through ET

Table 3.t Part 5 for Japanese SRD Cohorts 28 to 30: Follow-Up Through ET

	Day 15 +3 d	Day 29 ±3 d	Day 45 ±3 d	Day 60 ±3 d	ET
Administrative Procedures					
Prior and concomitant medication review	X	X	X	X	X
Clinic Procedures/Assessments					
Full physical examination					X
Weight and BMI				X	
Vital signs	X	X	X	X	X
Semirecumbent BP and HR [a]	X	X	X	X	X
Standing BP and HR [b]					X
12-lead ECGs	X	X	X		X
AE monitoring	X	X	X	X	X
Laboratory Procedures/Assessments					
Safety laboratory collection (hematology and serum chemistry)	X	X	X	X	X
Urinalysis		X	X	X	X
Serum sample for CK [c]					X
βhCG (pregnancy) test [d]					X
PK Evaluations					
Plasma sample for TAK-105 PK	X	X	X	X	X
Urine sample for TAK-105 PK					X
Immunogenicity and Biomarker Evaluations					
Serum sample for immunogenicity [e]	X	X	X	X	X
Blood sample for DNA (optional) [f]					X

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase;

Table 3.t Part 5 for Japanese SRD Cohorts 28 to 30: Follow-Up Through ET

	Day 15 +3 d	Day 29 ±3 d	Day 45 ±3 d	Day 60 ±3 d	ET

ECG: electrocardiogram; ET: early termination; FSH: follicle stimulating hormone; HBsAg: hepatitis B surface antigen; HR: heart rate; LFT: liver function test; PK: pharmacokinetic; SBP: systolic blood pressure; SRD: single-rising dose.

[a] All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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.

[b] For standing BP and HR assessment, a BP and HR 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 HR 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).

[c] 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.

[d] Serum pregnancy test for female subjects only.

[e] Immunogenicity serum samples for ADA testing will be taken at ET (if applicable), and at follow-up visits on Days 15, 29, 45, and 60. 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.

[f] If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of ET (if applicable).

3.7.3 Part 5b for Japanese MRD Cohorts 31 and 32 (Week 1)

Table 3.u Part 5b for Japanese MRD Cohorts 31 and 32: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																				
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																				
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]
Administrative Procedures																																			
Informed consent	X																																		
Inclusion/exclusion criteria	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]									
Height	X																																		
Weight and BMI	X	X																																	
TAK-105-a/ placebo administration [e]																X [e]																			
Vital signs	X	X													X				X		X					X									
Semirecumbent BP and HR [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	X
Standing BP and HR [g]	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 [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			
AE monitoring	X [j]	X ---------- Continuous Monitoring ----------X																																	

Table 3.u Part 5b for Japanese MRD Cohorts 31 and 32: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																		
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	Day 5 (96 h)[c]	Day 6[c]	Day 7[c]
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72			
Laboratory Procedures/Assessments																																	
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X[k]						X		X			X		
Serum sample for CK [l]															X												X							
Urinalysis	X	X																									X							
Glucose finger stick															X					X					X									
Cortisol [m]			X																										X					
Urine drug screen	X	X																																
Alcohol breath test		X																																
Cotinine test	X	X																																
Hepatitis screen [n]	X																																	
HIV screen	X																																	
βhCG (pregnancy) test [o]	X	X																																
Serum FSH test [p]	X																																	
PK Evaluations																																		
Plasma sample for TAK-105 PK															X		X	X	X		X		X		X	X	X		X	X		X		
Urine sample for TAK-105 PK [q]															X	X					X		X		X		X		X	X	X	X	X	
Immunogenicity and Biomarker Evaluations																																		
Serum sample for immunogenicity [r]															X																			
[redacted]																																		
Other																																		
Confinement		X ---------- Continuous ---------- X																																

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase;

Table 3.u Part 5b for Japanese MRD Cohorts 31 and 32: Screening Through Day 7 (Week 1)

	Day		Scheduled Time												Scheduled Time																	
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours) through 4																	
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72	Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]

DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; FSH: follicle stimulating hormone; [redacted]; h; hours; HBsAg: hepatitis B surface antigen; HR: heart rate; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

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 Daily assessments on Days 5 through 7, except for urine PK collection, should occur at approximately the same time as the dosing time on Day 1. Urine PK samples will be collected per footnote q.

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

e Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.

f All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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 For standing BP and HR assessment, a BP and HR 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 HR 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 may take place between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.

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 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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

n Hepatitis panel, including HBsAg and anti-HCV.

o Serum pregnancy test for female subjects only.

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

q Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 (Day 5), 96-120 (Day 6), 120-144 (Day 7), 144-168 (Day 8 [prior to dosing]) hours.

r Immunogenicity serum samples will be collected for all subjects for ADA testing at baseline predose on Day 1.

[redacted]

3.7.4 Part 5b for Japanese MRD Cohorts 31 and 32 (Week 2)

Table 3.v Part 5b for MRD Japanese Cohorts 31 to 32: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Clinic Procedures/Assessments																
Full physical examination															X [b]	
Weight and BMI	X															
TAK-105-a/placebo administration [c]		X [c]														
Vital signs	X				X		X						X			
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X daily
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X	X daily
12-lead ECGs	X												X			
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ---------- X															X [f]
Telemetry extraction	X		X		X		X				X	X	X			X [g] (72 h)
AE monitoring	X ---------- Continuous Monitoring ---------- X															
Laboratory Procedures/Assessments																
Safety laboratory collection (hematology and serum chemistry)	X						X [h]						X		X	X [i] (96 h)
Urinalysis													X			
Glucose finger stick	X					X					X					
Cortisol [j]	X															
PK Evaluations																
Plasma sample for TAK-105 PK	X [k]		X		X		X				X	X	X			X [g] (72 h)

Table 3.v Part 5b for MRD Japanese Cohorts 31 to 32: Day 8 Through Day 14 (Week 2)

	Scheduled Time															
	Day 8 and 9 (Hours)														Day 10	Day 11 to 14 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Immunogenicity and Biomarker Evaluations																
Serum sample for immunogenicity [l]	X															
Other																
Confinement	X ---------- Continuous ----------															X

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; BMI: body mass index; BP: blood pressure; bpm: beats per minute; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; [redacted]; HR: heart rate; metID: metabolite identification; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

a Daily assessments on Days 11 through 14 should occur at approximately the same time as the dosing time on Day 8.
b Physical examination at the indicated visit will be symptom-driven.
c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 8, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 8 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
f If safety signals are identified during the study, ECG telemetry monitoring will be extended through Day 11 to 14.
g Telemetry extraction and PK sampling will be performed at 72 hours after last dose (Day 11).
h Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
i Sample for safety laboratory assessments will be taken at 96 hours after last dose (Day 12).
j Morning cortisol sample should be drawn between 6 AM and 9 AM.
k Blood samples for PK may be drawn 10 minutes before dosing. MetID will not be collected in Part 5b.
l Immunogenicity serum samples for ADA testing will be collected from all subjects at predose on Day 8.

3.7.5 Part 5b for Japanese MRD Cohorts 31 and 32 (Week 3)

Table 3.w Part 5b for MRD Japanese Cohorts 31 and 32: Day 15 Through Day 21 (Week 3)

	Scheduled Time															
	Day 15 and 16 (Hours)														Day 17	Day 18 to 21 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Clinic Procedures/Assessments																
Full physical examination															X [b]	
Weight and BMI	X															
TAK-105-a/placebo administration [c]		X [c]														
Vital signs	X				X		X						X			
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X daily
Standing BP and HR [e]	X		X		X		X		X		X		X	X	X	X daily
12-lead ECGs	X												X			
ECG telemetry (12-lead)	X ---------- Continuous Monitoring ----------														X	X [f]
Telemetry extraction	X		X		X		X				X	X	X			X [g] (72 h)
AE monitoring	X ---------- Continuous Monitoring ----------															X
Laboratory Procedures/Assessments																
Safety laboratory collection (hematology and serum chemistry)	X						X [h]						X		X	X [i] (96 h)
Urinalysis													X			
Glucose finger stick	X					X					X					
Cortisol [j]	X															
PK Evaluations																
Plasma sample for TAK-105 PK	X [k]		X		X	-	X	-	-		X	X	X		-	X [g] (72 h)
Immunogenicity and Biomarker Evaluations																
Serum sample for immunogenicity [l]	X															

Table 3.w Part 5b for MRD Japanese Cohorts 31 and 32: Day 15 Through Day 21 (Week 3)

	Scheduled Time															
	Day 15 and 16 (Hours)														Day 17	Day 18 to 21 [a]
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	
Other																
Confinement	X ---------- Continuous ---------- X															

ADA: antidrug antibodies; AE: adverse event; BMI: body mass index; BP: blood pressure; bpm: beats per minute; DBP: diastolic blood pressure; ECG: electrocardiogram; HR: heart rate; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

[a] Daily assessments on Days 18 through 21 should occur at approximately the same time as the dosing time on Day 15.
[b] Physical examination at the indicated visit will be symptom-driven.
[c] Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
[d] All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 15, 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] For standing BP and HR assessment, a BP and HR 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 HR 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 15 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
[f] If safety signals are identified during the study, ECG telemetry monitoring will be extended through Day 18 to 21.
[g] Telemetry extraction and PK sampling will be performed at 72 hours after last dose (Day 18).
[h] Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
[i] Sample for safety laboratory assessments will be taken at 96 hours after last dose (Day 19).
[j] Morning cortisol sample should be drawn between 6 AM and 9 AM.
[k] Blood sample for PK may be drawn 10 minutes before dosing.
[l] Immunogenicity serum samples for ADA testing will be taken at predose on Day 15.

3.7.6 Part 5b for Japanese MRD Cohorts 31 and 32 (Week 4, Follow-Up, and ET)

Table 3.x Part 5b for MRD Japanese Cohorts 31 and 32: Day 22 to 82 (Week 4, Follow-Up, and ET)

	Scheduled Time														Day 24 (Discharge) [a]	Follow-Up ±3d					
	Day 22 and 23 (Hours)																				
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 30	Day 37	Day 51	Day 67	Day 82	ET
Administrative Procedures																					
Prior and concomitant medication review																X	X	X	X	X	X
Clinic Procedures/Assessments																					
Full physical examination															X [b]						X
Weight and BMI															X					X	
TAK-105-a/placebo administration [c]		X [c]																			
Vital signs	X				X		X						X			X	X	X	X	X	X
Semirecumbent BP and HR [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and HR [e]	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 ---------- X																				
Telemetry extraction	X		X		X		X		X		X	X	X		X						
AE monitoring	X ---------- Continuous Monitoring ---------- X															X	X	X	X	X	X
Laboratory Procedures/Assessments																					
Safety laboratory collection (hematology and serum chemistry)	X						X [f]						X		X	X	X	X	X	X	X
Serum sample for CK [g]															X						X
Urinalysis													X			X	X	X	X	X	X
Glucose finger stick	X					X					X										
Cortisol [h]															X						

Table 3.x Part 5b for MRD Japanese Cohorts 31 and 32: Day 22 to 82 (Week 4, Follow-Up, and ET)

	Scheduled Time															Follow-Up ±3d					
	Day 22 and 23 (Hours)														Day 24 (Discharge) [a]						
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 30	Day 37	Day 51	Day 67	Day 82	ET
PK Evaluations																					
Plasma sample for TAK-105 PK	X [i]		X		X		X		X		X	X	X		X	X	X	X	X	X	X
Urine sample for TAK-105 PK [j]	X	X					X		X		X		X		X						X
Immunogenicity and Biomarker Evaluations																					
Serum sample for immunogenicity [k]	X															X		X		X	X
Blood sample for DNA (optional) [l]															X						X
[redacted]																					
Other																					
Confinement	X ---------- Continuous ---------- X																				

ADA: antidrug antibodies; AE: adverse event; anti-HCV: antibodies to hepatitis C virus; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; d: days; ECG: electrocardiogram; ET: early termination; HR: heart rate; metID: metabolite identification; MRD: multiple-rising dose; PK: pharmacokinetic; SBP: systolic blood pressure.

a Subject must meet vital sign discharge criteria as presented in Section 9.2.4.
b Physical examination at the indicated visit will be symptom-driven.
c Subjects will be administered a single dose of TAK-105-a or matching placebo provided subjects meet the vital sign criteria.
d All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). On Day 22, 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 For standing BP and HR assessment, a BP and HR 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 HR 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 22 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).
f Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment.
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 Morning cortisol sample should be drawn between 6 AM and 9 AM.

Table 3.x Part 5b for MRD Japanese Cohorts 31 and 32: Day 22 to 82 (Week 4, Follow-Up, and ET)

																Follow-Up ±3d					
	Scheduled Time														Day 24 (Discharge) [a]						
	Day 22 and 23 (Hours)																				
	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	Day 30	Day 37	Day 51	Day 67	Day 82	ET

i Blood samples for PK may be drawn 10 minutes before dosing. MetID will not be collected in Part 5.
j Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-8, 8-12, 12-24, and 24-48 hours.
k Immunogenicity serum samples for ADA testing will be taken at predose on Day 22 or ET (if applicable). Serum samples will also be collected on follow-up visits on Days 30, 51, and 82. 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.
l If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

3.8 Part 6 TAK-105-b New Formulation of Drug Product

3.8.1 Part 6 TAK-105-b Formulation - SRD Cohorts 33 and 34: Days 1 Through 8

Table 3.y Part 6 for TAK-105-b SRD Cohorts 33 and 34: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
Administrative Procedures																																		
Informed consent	X																																	
Inclusion/exclusion criteria	X	X																																
Medical history/ demographics	X																																	
Prior and concomitant medication review	X	X	X----------Continuous Review----------X																												X			
Clinic Procedures/Assessments																																		
Full physical examination	X	X																						X [e]										X [e]
Height	X																																	
Weight and BMI	X	X																																X
TAK-105-b/placebo administration [f]																X [f]																		
Vital signs	X	X													X				X			X					X							
Semirecumbent BP and HR [g]	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 HR [h]	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							X
ECG telemetry (12-lead)		X----------Continuous Monitoring [i]----------X													X----------Continuous Monitoring----------X																		
Telemetry extraction [j]				X	X	X		X		X		X	X	X	X		X	X	X		X		X		X	X	X		X	X		X		X

Table 3.y Part 6 for TAK-105-b SRD Cohorts 33 and 34: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
AE monitoring	X [k]	X----------Continuous Monitoring----------X																												X	X	X	X
Laboratory Procedures/Assessments																																	
Safety laboratory collection (hematology and serum chemistry)	X	X													X					X [l]							X		X		X				X
Urinalysis	X	X																									X								
Serum sample for CK [m]															X												X		X						X
Glucose finger stick															X					X					X										
Cortisol [n]			X																										X						X
Urine drug screen	X	X																																	
Alcohol breath test		X																																	
Cotinine test	X	X																																	
Hepatitis screen [o]	X																																		
HIV screen	X																																		
βhCG (pregnancy) test [p]	X	X																																	X
Serum FSH test [q]	X																																		
PK Evaluations																																			
Plasma sample for TAK-105 PK															X		X	X	X		X		X		X	X	X		X	X		X			X
Urine sample for TAK-105 PK [r]																																			
Immunogenicity and Biomarker Evaluations																																			
Serum sample for immunogenicity [s]															X																				X
Blood sample for DNA (optional) [t]																																			X

Table 3.y Part 6 for TAK-105-b SRD Cohorts 33 and 34: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				
[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; bpm: beats per minute; CK: creatine kinase; DBP: diastolic blood pressure; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HR: heart rate; PK: pharmacokinetic; SBP: systolic blood pressure; 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 8 days after dosing (can be discharged after the Day 8 PK sample). Daily assessments on Days 5 through 8 should occur at approximately the same time as the dosing time on Day 1.

d At discharge, subject must meet vital sign discharge criteria as presented in Section 9.2.4.

e Physical examination at the indicated visit will be symptom-driven.

f Subjects will be administered a single dose of TAK-105-b or matching placebo provided subjects meet the vital sign criteria.

g All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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.

h For standing BP and HR assessment, a BP and HR 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 HR 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).

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

j Predose time-matched telemetry extractions may take place may take place between Day -2 and Day -1 in conjunction with the 24-hour predose continuous telemetry.

k Collection of AEs will commence at the time the subject signs the informed consent form.

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

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.

Table 3.y Part 6 for TAK-105-b SRD Cohorts 33 and 34: Days 1 Through 8

	Day -28 to -3	Day -2 [a]	Day -1 (Hours)												Day 1 Through 4 (Hours)															Day 5 (96 h) [c]	Day 6 [c]	Day 7 [c]	Day 8 [c, d] (Discharge)
	Screening		0	0.5	1	2	3	4	6	8	10	12	18	24 [b]	Pre-dose	0	0.5	1	2	3	4	6	8	10	12	18	24	36	48	72				

n Morning cortisol sample should be drawn between 6 AM and 9 AM.
o Hepatitis panel, including HBsAg and anti-HCV.
p Serum pregnancy test for female subjects only.
q An FSH level will be obtained to assess postmenopausal status.
r No urine PK samples will be collected for Part 6.
s Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, at ET (if applicable), and at follow-up visits indicated in Table 3.b. 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.
t If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of discharge or at ET (if applicable).

[redacted]

3.8.2 Part 6 TAK-105-b Formulation - SRD Cohorts 33 and 34 (Follow-Up Through ET)

Table 3.z Part 6 for TAK-105-b SRD Cohorts 33 and 34: Follow-Up Through ET

	Day 15 +3 d	Day 29 ±3 d	Day 45 ±3 d	Day 60 ±3 d	ET
Administrative Procedures					
Prior and concomitant medication review	X	X	X	X	X
Clinic Procedures/Assessments					
Full physical examination					X
Weight and BMI				X	
Vital signs	X	X	X	X	X
Semirecumbent BP and HR a	X	X	X	X	X
Standing BP and HR b					X
12-lead ECGs	X	X	X		X
AE monitoring	X	X	X	X	X
Laboratory Procedures/Assessments					
Safety laboratory collection (hematology and serum chemistry)	X	X	X	X	X
Urinalysis		X	X	X	X
Serum sample for CK c					X
βhCG (pregnancy) test d					X
PK Evaluations					
Plasma sample for TAK-105 PK	X	X	X	X	X
Immunogenicity and Biomarker Evaluations					
Serum sample for immunogenicity e	X	X	X	X	X
Blood sample for DNA (optional) f					X

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; HBsAg: hepatitis B surface antigen; HR: heart rate; LFT: liver function test; PK: pharmacokinetic; SBP: systolic blood pressure; SRD: single-rising dose.

Table 3.z Part 6 for TAK-105-b SRD Cohorts 33 and 34: Follow-Up Through ET

	Day 15 +3 d	Day 29 ±3 d	Day 45 ±3 d	Day 60 ±3 d	ET

[a] All BP and HR assessments should be made in duplicate, with the subject semirecumbent, 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 (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP) between assessments (see Section 9.2.4 for details). 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.

[b] For standing BP and HR assessment, a BP and HR 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 HR 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).

[c] 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.

[d] Serum pregnancy test for female subjects only.

[e] Immunogenicity serum samples for ADA testing will be taken at ET (if applicable), and at follow-up visits on Days 15, 29, 45, and 60. 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.

[f] If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on the day of ET (if applicable).

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]

4.2 Rationale for the Proposed Study

The purpose of this first-in-human (FIH) study is to evaluate the safety, tolerability, immunogenicity, and PK of TAK-105 in healthy subjects to support further development of TAK-105. The study will be conducted in 6 parts: single-rising doses (SRD) in healthy subjects will be assessed in Part 1, multiple-rising dose (MRD) administration will be assessed in Part 2, dose titration will be assessed in Part 3, and redosing after withholding 1 dose of study drug will be

assessed in Part 4, SRD/MRD in Japanese subjects will be assessed in Part 5a/b, and a new drug product formulation (TAK-105-b) will be assessed in Part 6. Details of the study design rationale are presented in Section 6.5.1.

4.3 Benefit/Risk Profile

This study represents the first study in humans with TAK-105.

The main objective of this study is to assess the safety and tolerability of TAK-105 in healthy subjects; as such, no clinical benefit is expected for study participants. Based on nonclinical findings from studies conducted with TAK-105, and the proposed mechanism of action, the potential benefits of TAK-105 include effective treatment of nausea and vomiting that manifests downstream of all emetogenic mechanisms, regardless of the etiology of the emetic trigger. This feature differentiates TAK-105 from currently approved anti-emetic medicines.

The potential risks of TAK-105 include heart rate (HR) increase, decreased blood pressure (BP), postural (orthostatic) changes, elevated liver enzymes, immunogenicity, hypersensitivity, and injection site reaction. These potential risks are based on nonclinical safety data and the safety results from the FIH study of [redacted]

Nonclinical findings related to TAK-105 include: (1) in the rat— minimal atrophy of the adrenal gland, considered nonadverse based on low incidence and severity, (2) in the dog— decreased mean food consumption observed at all doses and increased liver enzymes (glutamate dehydrogenase, aspartate aminotransferase [AST], and/or alanine aminotransferase [ALT]) at ≥10 mg/kg/week, both of which were considered nonadverse since they presented without a coinciding change in body weights and did not have correlated liver microscopic findings, respectively. [redacted]

Safety results from the [redacted] demonstrated a transient increase in HR within the first hour of [redacted] dosing as well as decreases in systolic BP (SBP) and diastolic BP (DBP) that were more prominent with postural changes (orthostatic) in some individuals within the first 2 hours postdosing. Postural hypotension is considered to be an identified risk with [redacted]

[redacted] Assessments of antidrug antibodies (ADA) will be included as part of the risk mitigation strategy.

Subjects with a history of serious hypersensitivity to any medication or any component of TAK-105 formulation or with a history of significant multiple and/or severe allergies are excluded from this study. The potential risks related to increased HR, decreased BP, elevated liver enzymes, and injection site reactions will be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical study. Subjects will also be monitored for decrease in morning blood cortisol levels during all parts of the study.

To minimize the risks to the subjects in this study, the sponsor considers the following measures to be appropriate: selecting TAK-105 doses with appropriate safety margins based on nonclinical study data; managing study eligibility criteria; prespecifying safety monitoring procedures, such as frequent BP assessments that include orthostatic BP measurements, telemetry, and 12-lead electrocardiogram (ECG); developing guidance for investigators; and using a clinical study facility where close monitoring can be performed and urgent medical care can be initiated rapidly as appropriate. Due to a nonclinical toxicology finding of mild atrophy of the adrenal glands which was considered nonadverse, subjects will be monitored for decreases in morning blood cortisol levels during all parts of the study. Overall, the proposed risk mitigation plan is adequate to monitor subjects enrolled in the study.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Study Primary Objective

The primary objectives of the study are to characterize the safety and tolerability of:

- Part 1:
  - Single SC doses of TAK-105-a in healthy subjects.
- Part 2:
  - Multiple SC doses of TAK-105-a in healthy subjects.

- Part 3:
  - Multiple SC dose regimens of TAK-105-a that include titration from lower doses in healthy subjects.
- Part 4

  Multiple SC dose regimens of TAK-105-a that include weekly dosing, withholding, then redosing in healthy subjects.
- Part 5:
  - Single SC doses and multiple SC doses of TAK-105-a in healthy Japanese subjects.
- Part 6:
  - Single SC doses of new formulation TAK-105-b in healthy subjects.

5.1.2 Study Secondary Objective

The secondary objectives of the study are:

- Part 1:
  - To characterize the plasma PK of TAK-105 following a single SC dose of TAK-105-a in healthy subjects.
  - To assess the immunogenicity of TAK-105 following single SC doses in healthy subjects.
  - To characterize the urinary PK of TAK-105 following a single SC dose of TAK-105-a in healthy subjects.
- Part 2:
  - To characterize the plasma PK of TAK-105 following multiple SC doses of TAK-105-a in healthy subjects.
  - To assess the immunogenicity of TAK-105 following multiple SC doses in healthy subjects.
  - To characterize the urinary PK of TAK-105 following multiple SC doses of TAK-105-a in healthy subjects.
- Parts 3 and 4: To assess the immunogenicity of TAK-105 following multiple SC dose regimens that include titration from lower doses for Part 3 and weekly dosing, withholding, then redosing for Part 4 in healthy subjects.
- Part 5:
  - To characterize the plasma PK of TAK-105 following a single SC dose and multiple SC doses of TAK-105-a in healthy Japanese subjects.
  - To assess the immunogenicity of TAK-105 following single SC doses and multiple SC doses in healthy Japanese subjects.

  - To characterize the urinary PK of TAK-105 following a single SC dose and multiple SC doses of TAK-105-a in healthy Japanese subjects.

- Part 6:
  - To characterize the plasma PK of TAK-105 following single SC doses of TAK-105-b in healthy subjects.
  - To assess the immunogenicity of TAK-105 following a single SC dose of TAK-105-b in healthy subjects.

5.1.3 Study Exploratory Objectives

[redacted]

- Parts 3 and 4:
  - To characterize the PK of TAK-105 in plasma following multiple SC dose regimens that include titration from lower doses for Part 3 and weekly dosing, withholding, then redosing for Part 4 in healthy subjects.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint of the study is:

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

5.2.2 Secondary Endpoints

Secondary endpoints include:

- Parts 1, 5a, and 6: plasma PK parameters for TAK-105
  - Maximum observed plasma concentration (C_{max}).
  - Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the 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 elimination phase after extravascular administration(V_z/F).

- Parts 2 and 5b: plasma PK parameters for TAK-105 on Day 1 (the first dose):
  - C_{max}, t_{max}, and area under the concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_τ).
- Parts 2 and 5b: plasma PK parameters for TAK-105 on Day 22 (the fourth dose):

  AUCτ, C_{max}, t_{max}, $t_{1/2z}$, CL/F, V_z/F, observed plasma concentration at the end of a dosing interval (C_{trough}).
- Parts 1, 2, and 5a/b include the following urine PK parameters:
  - Amount of drug excreted in urine from time 0 to time t (Ae_t).
  - Amount of drug excreted in urine from time 1 to time 2 (Ae_{t1-t2}).
  - Amount of drug excreted in urine during a dosing interval (τ) after last dose (Ae_τ).
  - Fraction of administered dose of drug excreted from urine from time 0 to time t ($f_{e,t}$).
  - Renal clearance (CL_R).
- All parts of the study:
  - Status of subject's ADA assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer).

5.2.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

[redacted]

- Parts 3 and 4 include the following plasma PK parameters:
  - AUC_τ.
  - AUC_{last}.
  - C_{max}.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

6.1.1 Overall Study Design

This is a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, immunogenicity, tolerability, and PK of TAK-105 in healthy subjects.

The study will consist of 6 parts:

- Part 1 is a FIH, randomized, double-blind, sponsor-open, placebo-controlled SRD design to assess the safety, immunogenicity, tolerability, and PK of TAK-105-a in healthy subjects. Up to 12 cohorts may be enrolled.
- Part 2 is a randomized, double-blind, sponsor-open, placebo-controlled, MRD design to assess the safety, immunogenicity, tolerability, and PK of TAK-105-a in healthy subjects. Up to 5 cohorts may be enrolled.
- Part 3 is a randomized, double-blind, sponsor-open, placebo-controlled, multiple-dose, dose titration design to assess the safety, immunogenicity, tolerability, and PK of TAK-105-a in healthy subjects. Up to 6 cohorts may be enrolled.
- Part 4 is a randomized, double-blind, sponsor-open, placebo-controlled, redosing after a period of withholding study drug design to assess the safety, immunogenicity, tolerability, and PK of TAK-105-a in healthy subjects. Up to 4 cohorts may be enrolled.
- Part 5 is a randomized, double-blind, sponsor-open, placebo-controlled SRD (Part 5a) and MRD (Part 5b) design to assess the safety, immunogenicity, tolerability, and PK of TAK-105-a in healthy Japanese subjects. Up to 5 cohorts may be enrolled.
- Part 6 randomized, double-blind, sponsor-open, placebo-controlled SRD design to assess the safety, immunogenicity, tolerability, and PK of a new formulation of TAK-105-b in healthy subjects. Up to 2 cohorts may be enrolled.

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).

Study drug in Parts 1 to 5 is TAK-105-a (Process A formulation) or matching placebo and in Part 6 is TAK-105-b (Process B formulation) or matching placebo, which will be administered SC.

While Parts 1 (SRD) and 2 (MRD) of TAK-105-1001 are intended to be completed as planned, subsequent parts of the study (ie, Parts 3 or 4) may not be conducted at the discretion of the sponsor. Parts 1 and 2 will be initiated in advance of Parts 3 and 4. Parts 3 and 4 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 3 and 4 may be initiated before completion of all cohorts in Parts 1 and 2 as otherwise permissible in the protocol. Part 5 may be performed in

parallel with Parts 1 and 2 based on the review of safety and PK data at least at the matching dose from the previous parts. Part 6 with the new drug formulation of TAK-105 (TAK-105-b) may be performed in parallel with Part 1 provided that the new formulation is available and after Part 1 SRD data are available.

Safety will be assessed by monitoring for AEs, vital signs including orthostatic assessments, 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. Subjects may not participate in more than 1 part or more than 1 dosing cohort of the study.

A schematic of the overall study design is presented in Figure 2.a (Parts 1 to 4) and Figure 2.b (Parts 5a/b and 6). A schematic of the SRD study design (Parts 1, 5a, and 6), the MRD study design (Parts 2 and 5b), Part 3 (titration), and Part 4 (redosing) study designs are presented in Figure 2.c, Figure 2.d, Figure 2.e, and Figure 2.f, respectively.

An overview of treatment cohorts is presented in Table 6.a. Healthy subjects will be enrolled in Cohorts 1 to 12 (Part 1), 13 to 17 (Part 2), 18 to 23 (Part 3), 24 to 27 (Part 4), and 33 to 34 (Part 6). Healthy Japanese subjects will be enrolled in Cohorts 28 to 30 (Part 5a – SRD), and 31 and 32 (Part 5b – MRD [optional]). The schedules of study procedures are presented in Section 3.0.

The study may be conducted at 3 phase 1 units to support recruitment of all cohorts.

Table 6.a Overview of Treatment Cohorts

Cohort	Regimen	TAK-105 formulation	Treatment	
			TAK-105	Placebo
Part 1				
1	SRD	TAK-105-a	6	2
2			6	2
3			6	2
4			6	2
5			6	2
6			6	2
7			6	2
8			6	2
9			6	2
10			6	2
11			6	2
12			6	2

Table 6.a Overview of Treatment Cohorts

Cohort	Regimen	TAK-105 formulation	Treatment	
			TAK-105	Placebo
Part 2				
13	MRD	TAK-105-a	6	2
14			6	2
15			6	2
16			6	2
17			6	2
Part 3				
18	Dose Titration	TAK-105-a	6	2
19			6	2
20 (optional)			6	2
21 (optional)			6	2
22 (optional)			6	2
23 (optional)			6	2
Part 4				
24	Redosing	TAK-105-a	6	2
25			6	2
26 (optional)			6	2
27 (optional)			6	2
Part 5a (Japanese subjects)				
28	SRD	TAK-105-a	6	2
29			6	2
30			6	2
Part 5b (Japanese subjects) [a]				
31 (optional)	MRD	TAK-105-a	6	2
32 (optional)			6	2
Part 6				
33	SRD	TAK-105-b	6	2
34 (optional)			6	2

MRD: multiple-rising dose; PK: pharmacokinetic; SRD: single-rising dose.

The starting dose in Part 1 (SRD) will be [redacted]. The starting doses of subsequent cohorts in Parts 1, 2, 3, and 4, will be determined at the dose escalation meeting based on emerging safety, tolerability, and available PK data. Additional cohorts may be included in any part of the study, as determined at the dose escalation meeting based on emerging safety, tolerability, and available PK data during the study.

[a] The MRD cohorts in Part 5b will be optional, depending on the PK/safety data observed in Part 2 MRD.

6.1.2 Part 1: SRD Cohorts 1 to 12

Part 1 will consist of up to 12 sequential cohorts with 8 healthy subjects per cohort. Subjects in each cohort will be randomly assigned to receive a single dose of TAK-105-a or matching placebo via SC administration in a 3:1 ratio in a double-blind, sponsor-open manner. Up to approximately 96 healthy subjects will be randomized in Part 1 (the number of subjects is approximate and does not account for potential replacement of subjects who withdraw for nonsafety reasons).

The schedule of study assessments for Part 1 (SRD) are presented in Table 3.a (Days 1 through 8) and Table 3.b (follow-up or early termination [ET]).

Subjects will be admitted into the study unit on Day -2. Baseline HR and BP assessments, including postural measurements, will be taken on Day -1, and will be time-matched to the Day 1 assessments. Subjects will be dosed with TAK-105-a or matching placebo on Day 1 after a minimum of 8 hours of fasting. Subjects will be confined for 8 days after dosing (ie, they can be discharged after completion of the Day 8 assessments). Assessments of postural hypotension will be measured on Day 1 predose, and at the time points specified postdose, including at the time-matched time points on Day -1. Blood and urine samples for assessment of TAK-105 concentrations and PK will be collected predose and at the specified time points in the schedule of events. [redacted] Immunogenicity will be assessed predose and at the specified follow-up visits as detailed in Table 3.a and Table 3.b.

Cohort 1 will use a staggered dosing scheme. The starting dose will be [redacted] as approved by the sponsor safety board. After dosing the first 2 subjects (1 receiving TAK-105-a and 1 receiving placebo), the investigator will review all available safety and tolerability data up to at least 48 hours postdose before dosing the remaining subjects in Cohort 1. A staggered dosing approach may be used for subsequent cohorts in Part 1. Only the starting dose will be prespecified in the protocol. Subsequent doses 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, but will have a corresponding top dose that does not exceed the maximal defined exposure based on nonclinical safety studies.

The current projected exposure levels [redacted] with a planned maximum dose escalation factor of 5-fold between lower exposures and 2-fold at high exposures. The actual dose [redacted] may change based on emerging human PK data. The sponsor may decide to administer lower doses, repeat doses, and cancel cohort(s) if deemed appropriate.

6.1.3 Part 2: MRD Cohorts 13 to 17

Part 2 may start before the completion of Part 1. If Part 2 is started before the completion of Part 1, the starting dose in Part 2 will be at a total weekly exposure at or below the highest completed cohort in Part 1. The starting dose will be decided in the dose escalation meeting (see Section 6.2).

The weekly maximum exposure will not exceed an exposure established as tolerated in Part 1. Similar to Part 1, a staggered dosing approach may be used for cohorts in Part 2. Part 2 consists of sequential dosing in up to 5 ascending cohorts of healthy subjects. In each cohort, 8 healthy subjects will be randomly assigned to receive TAK-105-a 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 2 (the number of subjects is approximate and does not account for potential replacement of subjects who withdraw for nonsafety reasons).

The schedule of study assessments for Part 2 (MRD) are presented in Table 3.c (screening through Day 7; Week 1), Table 3.d (Days 8 through 14; Week 2), Table 3.e (Days 15 through 21; Week 3), and Table 3.f (Days 22 to 82; Week 4, follow-up and ET).

Subjects will be admitted to the study unit on Day -2. Baseline HR and BP assessments will be taken on Day -1, and will be time-matched to the Day 1 assessments. Subjects will be dosed on Days 1, 8, 15, and 22 in each cohort after a minimum of 8 hours of fasting. Subjects will be confined until Day 24, 48 hours after the fourth dose, to assess safety, tolerability, immunogenicity, and PK. Assessments of postural hypotension will be measured on Day 1 predose, and at the time points specified postdose, including at the time-matched time points on Day -1. Blood and urine samples for assessment of TAK-105 concentrations and PK will be collected predose and at the specified time points postdose as described in schedule of events. [redacted]
Optional DNA samples will also be collected from subjects that provide consent for collection through a separate procedure. Immunogenicity assessments will be assessed predose and prior to discharge, and during the specified follow-up visits.

In Part 2, up to 5 tolerated doses [redacted] will be studied in an ascending manner. The weekly maximum exposure in Part 2 will not exceed exposures determined to be tolerated in Part 1. Doses in Part 2 are planned to be administered SC QW for 4 weeks. Doses will be determined in the dose escalation meeting based on emerging safety, tolerability, and available PK data. The sponsor may decide to administer lower doses, repeat doses, and cancel cohort(s) if deemed appropriate.

6.1.4 Part 3: Dose Titration Cohorts 18 to 23

The intent of the design of Part 3 is to enable a descriptive comparison (ie, without hypothesis testing) of cardiovascular (CV) tolerability profile findings between Part 3 cohorts and cohorts in Parts 1 and 2 with comparable exposures, to determine whether dose titration results in different tolerability in relation to CV observations.

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 maximum weekly exposure in Part 3 will be at a total weekly exposure level below or at the highest completed cohorts in Parts 1 and 2. The weekly maximum exposure will not exceed an exposure established as tolerated in Parts 1 and 2.

Part 3 will consist of up to 6 cohorts with 8 healthy subjects per cohort. Subjects will be assigned to receive TAK-105-a or matching placebo in a 3:1 ratio in a double-blind, sponsor-open manner. Up

to approximately 48 healthy subjects will be randomized in Part 3 (the number of subjects is approximate and does not account for potential replacement of subjects who withdraw for nonsafety reasons).

The TAK-105-a doses for Part 3 will consist of a starting low dose (for Cohorts 18 and 19) that will be either held constant or titrated for 2 additional doses, followed by a final (fourth) dose, which will be determined by the available safety, CV, and PK data from Parts 1 and 2. The starting doses will be chosen with the objective of minimizing CV effects and allow for attenuation of CV effects following the next titrated dose. The goal is to achieve attenuation of CV effects with the fewest doses. Review of the data from Cohorts 18 and 19 will determine which if any of the additional optional cohorts with fewer weeks of treatment (ie, 3 weeks for Cohorts 20 and 21 and 2 weeks for Cohorts 22 and 23) will be enrolled. As applicable, the CV and available PK data from Cohorts 18 and 19 will be used to determine starting dose and titrated doses for Cohorts 20 to 23. The starting, titrated, and final doses chosen between cohorts may vary based on emerging available PK and CV data.

For cohorts in Part 3, doses will be determined in the dose escalation meeting based on emerging safety, tolerability, and available PK data. The sponsor may decide to administer lower doses, repeat doses, and cancel cohort(s) if deemed appropriate.

Subjects from each cohort will be admitted into the study unit on Day -2. On Day 1, after randomization and all predose procedures have been performed, subjects will be dosed according to the cohort, titration schema, and randomized treatment assignment after a minimum of 8 hours fasting. Subjects will be confined for the duration of dosing and discharged 48 hours post last dose, on Day 10, 17, or 24, depending on the cohort assigned.

The proposed dose titration design for the 6 cohorts are presented in Figure 2.e and are described in the following Sections 6.1.4.1, 6.1.4.2, and 6.1.4.3.

6.1.4.1 Cohorts 18 and 19

After randomization and Day -1 assessments have been performed, Cohorts 18 and 19 will start with a low TAK-105 dose on Day 1. Doses for Cohorts 18 and 19 will be based on emerging safety, tolerability, and available PK and CV data, but will have a corresponding dose that does not exceed the weekly maximum exposure established as tolerated in Parts 1 and 2. The second dose on Day 8 will be either the same starting dose (Cohort 18) or a titrated dose (Cohort 19). The subjects will receive a third dose on Day 15, which may either be the same starting dose (Cohort 18) or a titrated doses (Cohort 19). Subjects will receive a fourth dose (final dose) on Day 22, which will not exceed the weekly maximum exposure established as tolerated in Parts 1 and 2. Subjects will be discharged after 48 hours assessments are taken after the last dose. A follow-up visit will occur 28 days after the last dose.

The assessments for Cohorts 18 and 19 will follow the schedule of assessments in Table 3.g (Week 1), Table 3.h (Week 2), Table 3.i (Week 3), and Table 3.j (Week 4, follow-up, ET).

The sponsor has the option to add additional cohorts following the same dosing schedule as Cohorts 18 and 19, but with modified doses.

6.1.4.2 Cohorts 20 and 21 (optional)

Cohorts 20 and 21 are optional. After randomization and Day -1 assessments have been performed, Cohorts 20 and 21 will begin with a starting dose on Day 1. Doses for these cohorts will be determined in the dose escalation meeting before dosing begins and will be based on emerging safety, tolerability, and available PK and CV data during the study, but will have a corresponding weekly dose that does not exceed the weekly maximum exposure established as tolerated in Parts 1 and 2.

The second dose on Day 8 will be a titrated dose. Subjects will receive a third and final dose on Day 15, which will not exceed the weekly maximum exposure established as tolerated in Parts 1 and 2. Subjects will be discharged after 48 hours assessments are taken after the last dose. A follow-up visit will occur 28 days after the last dose for both cohorts.

The assessments for Cohorts 20 and 21 will follow the schedule of assessments in Table 3.k (Week 1), Table 3.l (Week 2), and Table 3.m (Week 3).

6.1.4.3 Cohort 22 and 23 (optional)

Cohorts 22 and 23 are optional. After randomization and Day -1 assessments have been performed, Cohorts 22 and 23 will begin with a starting dose on Day 1. Doses for these cohorts will be determined in the dose escalation meeting before dosing begins and will be based on emerging safety, tolerability, and available PK and CV data during the study, but will have a corresponding dose that does not exceed the weekly maximum exposure established as tolerated in Parts 1 and 2.

Subjects will receive a second and final dose on Day 8, which will not exceed the weekly maximum exposure established as tolerated in Parts 1 and 2. Subjects will be discharged after 48 hour assessments are taken. A follow-up visit will occur 28 days after the last dose for both cohorts.

The assessments for Cohorts 22 and 23 will follow the schedule of assessments in Table 3.n (Week 1) and Table 3.o (Week 2, follow-up, and ET).

6.1.5 Part 4: Redosing Study Cohorts 24, 25, 26, and 27

The intention of the design of Part 4 is to provide an exploratory evaluation to assess the safety and CV tolerability profile of redosing with TAK-105-a after a period of withholding study drug. A schematic of the Part 4 study design is presented in Figure 2.f.

Part 4 may start before the completion of Parts 1 and 2, and may start before Part 3 is initiated. If Part 4 is started before the completion of Part 2, the starting dose will be decided in the dose escalation meeting (see Section 6.2). The maximum weekly exposure in Part 4 will be at a total weekly exposure level below or at the highest completed cohort in Parts 1 and 2. The weekly maximum exposure will not exceed an exposure established as tolerated in Parts 1 and 2.

Part 4 will consist of up to 4 cohorts with 8 healthy subjects per cohort. Subjects will be assigned to receive TAK-105-a or matching placebo in a 3:1 ratio in a double-blind, sponsor-open manner. Up

to approximately 32 healthy subjects will be randomized in Part 4 (the number of subjects is approximate and does not account for potential replacement of subjects who withdraw for nonsafety reasons).

Subjects from each cohort will be admitted into the study unit on Day -2. On Day 1, after randomization and all predose procedures have been performed, subjects will be dosed according to the cohort and redosing schema they have been randomized to after a minimum of 8 hours fasting. Subjects will be confined until Day 10. Subjects will return to the clinic the day prior to the third dose and will be confined until 48 hours post third dose. The total duration of confinement is 14 days.

The proposed redosing study design for the 4 cohorts are presented in Figure 2.f and are as described in the following Sections 6.1.5.1 and 6.1.5.2.

Doses will be determined in the dose escalation meeting based on emerging safety, tolerability, and available PK data. The sponsor may decide to administer lower doses, repeat doses, and cancel cohort(s) if deemed appropriate.

6.1.5.1 Cohort 24

Cohort 24 will receive a dose of TAK-105-a or matching placebo on Day 1 and 8, which will be determined by the available safety, tolerability, CV, and PK data from Parts 1 and 2. Subjects will be discharged 48 hours after Day 8 dose. Subjects will not be treated on Day 15, as the third dose will be withheld until Day 22. Subjects will return to the clinic on Day 21 for fasting and confinement before Day 22 dosing and assessments. Subjects will be monitored for 48 hours post third dose for CV effects and safety, tolerability, and PK. If CV effects are found, the redosing interval may be shortened for the subsequent cohorts (ie, days between second and third dose will be less days). If no CV effects are found, the redosing interval may be lengthened for the subsequent cohorts (ie, days between second and third dose will be more days). The modified redosing interval will be changed based on emerging PK and CV data.

A potential CV effect will be monitored using the following criteria based on cohort level data:

- Maximal increase in mean change from baseline HR ≥10 bpm when compared to baseline predosing value on same day of dosing in semirecumbent vital signs, or
- Maximal decrease in mean change from baseline SPB or DBP ≥5 mmHg when compared to baseline predosing value in semirecumbent vital signs.

These monitoring criteria are empirically derived from [redacted] human data [redacted]. Nonclinical data in dogs demonstrates that molecules within this class impart a similar magnitude of maximal HR and BP effects. These monitoring criteria may be modified based on evolving hemodynamic data from this study. Orthostatic data will also be reviewed by cohort to determine the maximal change from baseline in orthostatic vital sign measurements upon redosing.

6.1.5.2 Cohorts 25, 26, and 27

The dosing scheme for subsequent optional cohorts will follow that of Cohort 24. However, the redosing interval (ie, third dose) for Cohorts 25, 26 (optional), and 27 (optional) may be shortened to Day 16 to 21 or lengthened up to Day 29 based on the available PK and CV data.

The schedule of study procedures for Part 4 are presented in Table 3.p (Week 1), Table 3.q (Week 2), and Table 3.r (variable third dose week, follow-up, and ET).

6.1.6 Part 5a/b: SRD and MRD in Japanese Subjects Cohorts 28 to 32

Parts 5a (SRD) and 5b (MRD) may be performed in parallel with Parts 1 and 2 based on the review of safety and PK data at least at the matching dose from the previous parts. Part 5a/b will consist of up to 5 cohorts (up to 3 cohorts in SRD and 2 cohort in MRD [optional]) with 8 healthy subjects of Japanese descent per cohort. Subjects in each cohort will be randomly assigned to receive a single dose of TAK-105-a or matching placebo via SC administration in a 3:1 ratio in a double-blind, sponsor-open manner. Up to approximately 40 healthy Japanese subjects will be randomized in Part 5 (the number of subjects is approximate and does not account for potential replacement of subjects who withdraw for nonsafety reasons). The MRD cohorts in Part 5b will be optional, depending on the PK/safety data observed in Part 2 MRD.

The schedule of study assessments for Part 5a SRD cohorts (Cohorts 28 to 30) are presented in Table 3.s (Days 1 through 8) and Table 3.t (follow-up or early termination [ET]) and Part 5b MRD cohorts (Cohorts 31 and 32; [optional]) are presented in Table 3.u (Screening through Day 7; Week 1), Table 3.v (Days 8 through 14; Week 2), Table 3.w (Days 15 through 21; Week 3), and Table 3.x (Days 22 to 82; Week 4, follow-up and ET).

The overall study designs will follow that of Part 1 for SRD (see Section 6.1.2) and Part 2 for MRD (see Section 6.1.3).

The cohorts in Part 5 will be dosed with doses of TAK-105-a that are determined during the dose escalation meeting and based on emerging safety, tolerability, and available PK data during the study, but will have a corresponding top dose that does not exceed the maximal defined exposure based on nonclinical safety studies. The dose planned for the optional Japanese MRD cohorts will be based on emerging PK, tolerability, and safety data.

6.1.7 Part 6: TAK-105-b New Formulation

A new formulation of TAK-105 (Process B), called TAK-105-b, was generated for improved stability of TAK-105 and will be evaluated in Part 6. This part will consist of up to 2 cohorts with 8 healthy subjects per cohort. Subjects in each cohort will be randomly assigned to receive a single dose of new formulation TAK-105-b or matching placebo via SC administration in a 3:1 ratio in a double-blind, sponsor-open manner. Up to approximately 16 healthy subjects will be randomized in Part 6 (the number of subjects is approximate and does not account for potential replacement of subjects who withdraw for nonsafety reasons).

The cohorts in Part 6 (Cohorts 33 and 34 [optional]) will follow the SRD study design (Figure 2.c) and schedule of assessments presented in Table 3.y (Days 1 through 8) and Table 3.z, and Table 3.b (follow-up or early termination [ET]).

If formulation differences between TAK-105-a and TAK-105-b are observed in Part 5, additional Japanese cohort(s) may be added to assess PK and safety of the new formulation in Japanese subjects.

6.1.8 Study Drug Administration

The study drug used in Parts 1 to 5 is TAK-105-a (Process A formulation) or matching placebo and in Part 6 is TAK-105-b (Process B formulation) or matching placebo.

In Parts 1, 5a, and 6, the single SC dose of study drug (TAK-105-a/b or matching placebo) should be administered in the abdomen at least 2 cm away from the umbilicus. 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 until requested to stand for orthostatic BP and HR measurements.

In Parts 2, 3, 4, and 5b 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 until requested to stand for orthostatic BP and HR measurements.

In Part 6, the new formulation of TAK-105 (Process B), TAK-105-b, will be administered the same as the single SC dose of TAK-105-a, using the same administration instructions above (see Parts 1, 5a, and 6).

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

6.2 Dose Escalation

A dose escalation meeting will occur with representatives from the sponsor, including Clinical Sciences, Clinical Pharmacologist, Global Patient Safety Evaluation, the investigator, and possibly other members of the site study team. The representatives will review the safety, tolerability, and

laboratory data of at least 7 days after the last dose, and available PK data will be evaluated to decide on the dose and regimen to be administered in the subsequent cohorts. Available PK data will also be assessed to ensure no dose exceeds the maximal defined exposure.

As outlined in the operational plan for blinding, 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).

Additional cohorts may be enrolled if it is deemed appropriate by the investigator and the sponsor. Dose levels may also be repeated or lowered based on emerging data. Optional cohorts may not be enrolled as deemed appropriate by the investigator and the sponsor.

All decisions will be documented in the study file.

6.3 External Safety Adjudication Committee

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.

6.4 Stopping Rules

6.4.1 Stopping Criteria for Individual Subjects

Subjects will permanently discontinue study drug for any study drug-related AEs that are rated Grade ≥3 in severity on the Common Terminology Criteria for Adverse Events (CTCAE) scale.

6.4.2 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require premature termination of the study (across all parts):

- Any subject experiences a Hy's Law reaction (defined as ALT or 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-105, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises subject 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.

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 >120 bpm at rest while semirecumbent with symptoms of palpitation or lightheadedness requiring medical intervention and considered related to TAK-105/placebo, or
- Two or more subjects experience a CTCAE v5.0 Grade ≥3 hypotension (ie, requiring medical intervention) and considered related to TAK-105/placebo, or
- One subject experiences a CTCAE v5.0 Grade ≥3 syncope (fainting or orthostatic collapse) and considered related to TAK-105/placebo, or
- Two or more subjects experience a CTCAE v5.0 Grade 3 event considered related to TAK-105 administration, or
- One subject experience a CTCAE Grade 4 event considered related to TAK-105 administration, or
- One subject with ALT or AST >5 × ULN after TAK-105 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 a serious adverse event (SAE) considered related to TAK-105 administration, 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 the sponsor once the dosing is paused. If a safety concern is 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.

During Study Drug Dosing in MRD

If the criteria for pausing occurs in SRD Part 1 at a higher level than is being dosed in MRD Part 2, dosing in Part 2 or Part 5b may continue provided it is at a lower weekly dose than in Part 1 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 and 4 (Titration and Redosing)

If the criteria for pausing occurs in MRD Part 2 or SRD Part 1 at a higher level than is being dosed in Parts 3 and 4, dosing in Parts 3 and 4 may continue provided it is at a lower weekly 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.

6.5 Rationale for Study Design, Dose, and Endpoints

6.5.1 Rationale of Study Design

Part 1 of the study is a randomized, double-blind, sponsor-open, placebo-controlled SRD design which is intended to characterize the safety, tolerability, and PK of single doses of TAK-105. [redacted]

Part 2 of the study is a randomized, double-blind, sponsor-open, placebo-controlled, sequential panel MRD design which is intended to characterize the safety, tolerability, and PK of multiple doses of TAK-105. Up to 5 cohorts may be enrolled.

[redacted], the duration of follow-up for Parts 1 and 2 will be 60 days after the last dose to enable additional safety, PK, and immunogenicity assessments.

Part 3 of the study is a randomized, double-blind, sponsor-open, placebo-controlled design which is intended to explore whether dose titration results in different tolerability in relation to CV observations by examining the CV tolerability profile findings between Part 3 cohorts and cohorts in Parts 1 and 2 with comparable exposures. This will be a descriptive comparison, that is, without hypothesis testing. Up to 6 cohorts may be enrolled. [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.

Part 4 of the study is a randomized, double-blind, sponsor-open, placebo-controlled design which is intended to explore the safety and CV tolerability of redosing after a period of withholding study drug. Up to 4 cohorts may be enrolled. Part 4 of this study is designed to determine the kinetics of attenuation of CV effects by evaluating CV effects in subjects following repeated dosing of TAK-105, a period of withholding study drug, then redosing.

Part 5 of the study is a randomized, double-blind, sponsor-open, placebo-controlled SRD (Part 5a) and MRD (Part 5b [optional]) design to assess the safety, immunogenicity, tolerability, and PK of

TAK-105 in healthy Japanese subjects. Part 5 will consist of up to 5 cohorts (3 SRD and 2 MRD [optional]).

Part 6 of the study is a randomized, double-blind, sponsor-open, placebo-controlled SRD design to assess the safety, immunogenicity, tolerability, and PK of a new formulation of TAK-105 (Process B) in healthy subjects to support the use of TAK-105-b in future studies. Part 6 will consist of up to 2 cohorts (1 is optional) . TAK-105-b has improved stability compared to TAK-105-a. The dose(s) that will be evaluated will be determined based on available data from Part 1.

6.5.2 Rationale for Dose

The starting dose for this FIH study is [redacted]. The 4 considerations for the selection of the starting dose for the FIH study are summarized here and described in more detail below:

1. Nonclinical safety data and Food and Drug Administration (FDA) maximum safe starting dose guidance (FDA 2005).
2. Nonclinical CV safety pharmacology data for TAK-105.
3. Benchmarking to [redacted] CV findings.
4. Lowest projected anti-emetic effect and insulin secretion effect as demonstrated in nonclinical species.

6.5.2.1 FIH Starting Dose Consideration Based on Nonclinical Safety Study Results, Published [redacted] Experience

The principle of the FDA Guidance "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (FDA 2005) is to use a 10-fold safety factor on the no-observed-adverse-effect level (NOAEL) from nonclinical data to identify a starting clinical dose.

For TAK-105, NOAELs were identified in the 29-day GLP-compliant, repeat-dose toxicity studies, and no-observed-effect levels (NOELs) were identified in the respiratory and central nervous system safety pharmacology studies.

The NOAEL in the rat was 100 mg/kg/week (highest dose investigated); mild decreases in spleen weights and minimal atrophy of the adrenal gland were considered nonadverse. The NOAEL in the dog was 30 mg/kg/week (highest dose investigated); decreased food consumption and minimal to moderate elevations in liver enzymes were considered nonadverse. [redacted]

CV effects in dogs were the principal finding in the safety pharmacology studies. In the CV safety pharmacology study, the lowest dose of [redacted] TAK-105 elicited a mild increase in HR, and a NOEL was not identified.

Given the mild and reversible nature of the CV changes, and the lack of other significant safety findings at this dose level, the [redacted] TAK-105 dose is not anticipated to result in clinically significant effects. The HED to this dose is 0.011 mg/kg/week; based on body surface area, this equates to a [redacted] as per FDA guidance.

[redacted]

Additionally, in the SRD portion of the [redacted] No clinically significant mean changes in HR were observed and a single AE of abdominal pain was reported. Based on TAK-105 human PK simulations, [redacted]

The selected FIH dose is [redacted] which equates to an approximate [redacted] safety factor from the HED derived from the dog CV safety pharmacology study. A [redacted] safety factor was selected based on the duration of CV effects observed in dog and potential translatability to the clinic. A [redacted] FIH starting dose provides the following calculated margins:

[redacted]

6.5.2.2 Other Supporting Estimated Pharmacologically Active Exposures

[redacted] However, this is not a pharmacologically active dose for anti-emetic effects. [redacted] his reflects the intended pharmacology in the most sensitive

species and model. This assumes linear human PK for TAK-105 and that drug concentration at the time of emetic challenge is the minimum concentration to ablate emesis.

For the dosing escalations, predicted pharmacologically active drug exposures and doses were considered. From nonclinical pharmacology models, the estimated pharmacologically-active dose range, [redacted]

6.5.2.3 Summary of FIH Starting Dose Consideration

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

6.5.2.4 FIH Maximum Dose Consideration

As described in the International Council for Harmonisation (ICH) M3 (R2) guidance, without toxicity in both species, the maximum clinical dose should not exceed one-tenth the lower NOAEL area under the plasma concentration-time curve (AUC) exposure of the 2 species. The NOAEL in the 29-day toxicity study in rats and dogs was 100 mg/kg/week and 30 mg/kg/week corresponding to an area under the concentration curve [redacted], respectively. Since the rat NOAEL AUC is less than the dog NOAEL AUC, the FIH maximum dose will not exceed an AUC exposure of [redacted] and will enable exploration of the available anticipated pharmacologically active dose range while limiting the maximum clinical exposure below the rat NOAEL AUC exposure cap.

6.5.2.5 FIH Proposed Dose Regimen for the SRD Cohorts

The proposed dose regimen with target PK and safety margins for select proposed doses is presented in Table 6.b.

Table 6.b [redacted]

[redacted]

It is planned that up to 12 doses may be explored with a maximum escalation factor between cohorts of 5-fold at lower exposures and 2-fold at high exposures.

Dose levels will be determined based on emerging safety, tolerability, and available PK data from previous cohorts, and after discussion between the sponsor and investigator. Doses may be repeated if safety and tolerability are acceptable, or lower doses may be studied to increase data within the dose range. Any decision to resume dosing at the current dose level or to escalate the dose will be made jointly by the investigator and the sponsor after careful evaluation of all available blinded data.

6.5.2.6 Rationale for MRD Dose Selection

MRD consisting of up to 5 dosing cohorts will be studied. In each cohort, 8 healthy subjects will be randomly assigned to receive TAK-105 or matching placebo in a 3:1 ratio in a double-blind manner. Up to approximately 40 healthy subjects may be randomized in the sponsor open, double-blind Part 2 of the study (the number of subjects is approximate and do not account for potential replacement of subjects who withdraw for nonsafety reasons).

The weekly maximum exposure in MRD will not exceed exposures determined to be well tolerated in SRD. Doses in MRD are planned to be administered SC QW for 4 doses. Similar to SRD, a staggered dosing approach may be used for cohorts in MRD. Based on safety, tolerability, and emerging PK data from SRD, reductions in dose and in repeat dosing duration may be implemented.

The dosing regimens selected for MRD will have a projected AUC [redacted], as outlined above for SRD, or the highest AUC determined to be well tolerated in SRD. After completion of each cohort, assessment of the blinded safety and tolerability, laboratory, and available PK data will be performed to decide on the dose to be administered in the subsequent cohorts.

6.5.2.7 Rationale for Dose Titration and Redosing

The intent of the dose titration design is to enable a descriptive comparison (ie, without hypothesis testing) of the CV tolerability profile findings between cohorts in the dose titration part and cohorts in the SRD and MRD with comparable exposures, to determine whether dose titration results in different tolerability in relation to CV observations. The dose titration part consists of up to 6 cohorts with 8 healthy subjects per cohort. Subjects will be assigned to receive TAK-105 or matching placebo in a 3:1 ratio in a double-blind manner. Up to approximately 48 healthy subjects will be randomized in the dose titration part.

The intention of the redosing design is to provide an exploratory evaluation to assess the safety and CV tolerability profile of redosing with TAK-105 after a period of withholding study drug. The redosing part will consist of up to 4 cohorts with 8 healthy subjects per cohort. Subjects will be assigned to receive TAK-105 or matching placebo in a 3:1 ratio in a double-blind manner. Up to approximately 32 healthy subjects will be randomized in the redosing part.

Similar to SRD and MRD, a staggered dosing approach may be used for cohorts in dose titration (Part 3) and redosing (Part 4) parts.

[redacted] will be studied as determined by the prior dosing regimen in the SRD and MRD. The weekly exposure will not exceed an exposure established as well tolerated in SRD and MRD. Doses in dose titration and redosing parts are planned to be administered SC QW. Based on emerging PK data from SRD and MRD, and available PK data from prior cohorts in dose titration and redosing part, adjustments to dose and to repeat dosing duration may be implemented.

The dosing regimens selected for MRD and dose titration and redosing will have a [redacted], which is one-tenth the NOAEL in the most sensitive species as outlined above for SRD, or the highest AUC determined to be well tolerated in SRD.

6.5.3 Rationale for Endpoints

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

6.5.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For all parts of this study, the following procedures are critical:

- Timing of PK, BP, and telemetry assessments.
- All other procedures should be performed as close as possible (either before or after) the scheduled times.
- The order of priority can be changed during the study with joint agreement of the investigator and the sponsor.

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

6.6 Procedure Modifications Permitted Within Protocol Parameters

This is a phase 1 study of TAK-105 in humans, and the PK and safety profiles of the compound are still being elucidated. This protocol is written to accommodate the dependence on evolving data and the inherent dynamic nature of phase 1 clinical studies. Minor changes in procedures, eg, changes to the specific dose regimen in any cohort or the specific timing of assessments, will be documented and may not require a protocol amendment or ICF update if the changes do not impact the burden of subjects or safety monitoring.

6.7 Study Beginning and End/Completion

6.7.1 Definition of Beginning of the Study

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

6.7.2 Definition of End of the Study

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

6.7.3 Definition of Study Discontinuation

Study discontinuation because of safety reasons:

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

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

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

6.7.4 Criteria for Premature Termination or Suspension of the Study

6.7.4.1 Criteria for Premature Termination or Suspension of Study

See Section 6.4 for study-specific stopping rules and additional criteria for premature termination or suspension of the study.

6.7.4.2 Procedures for Premature Termination or Suspension of the Study

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

6.7.5 Criteria for Premature Termination or Suspension of a Site

6.7.5.1 Criteria for Premature Termination or Suspension of a Site

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.

6.7.5.2 Procedures for Premature Termination or Suspension of a Site

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

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

For All Cohorts

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be a healthy male or WONCBP (woman of nonchildbearing potential) female subject aged 18 to 55 years, inclusive, at the screening visit.
4. Continuous nonsmoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to screening and through discharge.
5. Subject has not had frequent or heavy use (ie, near-daily) of medical or recreational cannabis for at least 3 months prior to screening and through discharge.
6. Have a body mass index (BMI) $\geq$18 and $\leq$30.0 (kg/m^2) at the screening visit.
7. 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.

8. Meet the following birth control requirements (see Appendix D):
   - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 5 half-lives (approximately 46 days for TAK-105) 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. Male subjects should agree to use condom with spermicide from screening time point if they cannot bring documentation for bilateral vasectomy.
   - Is a male subject who agrees not to donate sperm from the first dose of study drug until 5 half-lives after the last dose of study drug.
   - Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
     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.

Additional inclusion criteria for Japanese subjects in Part 5 (Cohorts 28 to 32 only):

9. The subject has 2 Japanese parents and 4 Japanese grandparents, as confirmed by interview.

7.2 Exclusion Criteria

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

For All Cohorts

1. The subject has participated in another investigational study within 4 weeks (or based on local regulations) or within 5 half-lives 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.
4. The subject has a known hypersensitivity or contraindication to any component of TAK-105.
5. The subject has a positive pregnancy test or is lactating or breastfeeding.
6. 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. 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.
8. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.
9. The subject is unable to refrain from or anticipates using all medications including herbal medicines beginning approximately 7 days before administration of the first dose of study drug, throughout the study until the last follow-up visit.
10. The subject has a history or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
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 breath test or urine drug screen results at screening or check-in.
13. The subject with previous major psychotic disorder.
14. The subject has a history or presence of:
    - 3 or more incidences of syncope (eg, vasovagal) within the last 5 years prior to screening;
    - A family history of unexplained sudden death or channelopathy;
    - Brugada syndrome (ie, RBBB [right bundle branch block] pattern with ST-elevation in leads V1-V3);
    - CV or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, stroke, sick sinus syndrome, pulmonary congestion, symptomatic or significant cardiac arrhythmia, supraventricular or ventricular tachycardia, 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;
    - Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);

- 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 >200 msec at screening or Day 1 pre-Hour 0;
- The subject has a documented history of sinus bradycardia (<45 bpm) based upon vital signs assessments, sinoatrial block as evidenced on ECG or sinus pause ≥3 seconds on ECG or predose telemetry.

15. The subject has an average semirecumbent BP less than 90/60 mm Hg or greater than 140/90 mm Hg from screening to predose, inclusive. Any assessments on Day -1, where 2 consecutive timepoint values do not meet this criterion, must be discussed with the medical monitor for approval.
16. From screening to Day -2, subjects with an average semirecumbent HR <55 or >100 bpm should be excluded. From Day -2 to predose, enrollment of subjects with an average HR <55 or >100 bpm will be left to the judgment of the investigator, unless HR 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 2 minutes of standing when compared with BP from the semirecumbent position at screening to predose assessments, inclusive. In asymptomatic subjects, any assessments after screening which 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 HR >120 bpm at approximately 2 minutes of standing, at screening to predose assessments, inclusive. Any assessments after screening which 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 prior to determination that the subject is eligible to proceed.

7.3 Excluded Medications, Supplements, Dietary Products

7.3.1 Concomitant Medications

The use of concomitant medications approximately 7 days before administration of the first dose of study drug, throughout the study until the last follow-up visit 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 Seville oranges, pomelos, grapefruit juice, grapefruits, and products containing grapefruit beginning approximately 2 weeks before administration of the first dose of study drug, throughout the study until discharge.

7.3.3 Alcohol

Subjects will refrain from consuming alcohol, 24 hours before admission until discharge. Subjects may undergo an alcohol breath test at the discretion of the investigator.

7.3.4 Caffeine

In Part 1, subjects will refrain from consuming caffeinated beverages from the evening of Day -2 until discharge 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 3 months prior to screening to discharge after last scheduled dose.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

7.4.1.1 Parts 1, 5a and 6

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 HR 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 safety ECGs.

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 Parts 2, 3, 4, and 5b

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 HR and BP assessments. In all

parts of the study, 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 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.

- Pretreatment event or AE. The subject has experienced a pretreatment event or AE that requires ET because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pretreatment event or AE.
- Liver testing abnormalities.
  - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN without findings of cholestasis or other alternate etiology.
- Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
- Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

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

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

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

If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for subject withdrawal in the eCRF. The reason for discontinuation should be entered on the eCRF including unavoidable circumstances such as the COVID-19 pandemic.

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 ET visit.

7.7 Subject Replacement

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

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Study drug in Parts 1 to 5a/b is TAK-105-a (Process A formulation) or matching placebo and in Part 6 is TAK-105-b (Process B formulation) or matching placebo, which will be administered SC. The study drug will be supplied to the study site by the sponsor in dose strengths of [redacted] and its matching placebo in the single-use vials for injection with open label manner. The matching placebo will be also used as the diluent for active vials to dilute [redacted] active vials to target concentration for dose strength at each study cohort.

Details regarding the dosage form description, composition, compounding process, or dosing syringe preparation can be found in the pharmacy manual. Study drug will be packaged to support enrollment and replacement of subjects as required.

8.1.1 Clinical Study Drug Labeling

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

The label description 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.

8.1.2 Clinical Study Drug Inventory and Storage

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

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

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-105-a and matching placebo must be stored at -25°C to -15°C (-13°F to 5°F) with protection from light. TAK-105-b and matching placebo must be stored at 2°C to 8°C (36°F to 46°F) with protection from light.

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

8.1.3 Clinical Study Drug Blinding

This is a double-blind, sponsor-open study; the investigator and subjects are blinded to treatment assignment. The sponsor may be open to treatment assignment in the evaluation of data including safety and PK for efficient oversight of the study, however will remain blinded in study drug preparation and drug dispensing during dosing of each cohort. 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.

All members of the sponsor team will be blinded during randomization and dosing of each cohort (ie, in preparation for dosing of subjects while members of the sponsor team may be unblinded in review of data). Discussions within the dose escalation meetings will be conducted in a blinded manner (ie, such that no unblinded information is communicated to other members of the meeting). The subjects and investigators (including the site staff) will remain blinded.

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 prior to the database lock.

8.1.4 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-105 or matching placebo in a 3:1 ratio in a double-blind, sponsor-open manner. Subject randomization will not be stratified.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

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

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator or designee must ensure that the study drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study drug (TAK-105 or matching placebo), the investigator or designee must maintain records of all study drug deliveries to the site, site inventory, dispensation and use by each subject, destruction of drug supply at the site, and/or study drug returned to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must promptly verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct and that the study drug is in good condition. If there are any discrepancies between the packing list versus the actual product received, the sponsor (or representative) must be contacted to resolve the issue as outlined in the pharmacy manual. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all study drugs during his or her entire participation in the study. Proper drug accountability includes, but is not limited to, the following:

- Frequent verification that actual inventory matches documented inventory.
- Verification that the log is completed for the drug lot (or medication ID number) used to prepare each dose.
- Verification that all containers used are documented accurately on the log.
- Verification that required fields are completed accurately and legibly.

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

The investigator or designee must record the current inventory of all study drugs (TAK-105 or matching placebo) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title; name of investigator; site identifier and number; description of sponsor-supplied drugs; expiry date; date and amount dispensed including initials, seal, or signature of the person dispensing the drug; and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The site destruction SOP will be approved by the sponsor. If the site will return the drug to the depot, instructions will be provided by Clinical Supplies.

9.0 STUDY PROCEDURES

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

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.1.1 Assignment of Screening and Randomization Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur before randomization or allocation. Each subject will be assigned only 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.

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-105 or placebo, according to the randomization schedule generated before the study. Each subject will be dispensed blinded study drug, labeled with his/her unique randomization number, throughout the study.

9.1.2 Inclusion and Exclusion

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

9.1.3 Medical History/Demography

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

9.1.4 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

The time window for all measurements is ±10 minutes. If a 10 minute deviation occurs in any measurement, subsequent measurements may deviate by up to 10 minutes and the ±10 minutes window will apply.

9.2.1 Full Physical Exam

Qualified site personnel will conduct full or symptom-driven physical examinations as indicated in the Schedule of Study Procedures (Section 3.0).

9.2.2 Height and Weight

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

9.2.3 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 Signs

Body temperature will be measured with either an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (ie, oral or tympanic) must be used for all measurements for each individual subject and should be the same for all subjects. 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 -2, Day -1, and predose on Day 1) vital signs including orthostatic BP and HR 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, HR, orthostatic BP, and orthostatic HR assessments immediately prior to dosing (the single dose in Part 1, first dose in Part 2, first dose in Part 3, and first dose in Part 4) 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, 3, and 4, the investigator may exercise discretion related to appropriateness of the subject's ongoing study participation based on 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 (Parts 2, 3, and 4) or vital sign criteria defined in Section 7.2. Should dosing be delayed in Parts 2, 3, or 4 of the study, adjustment should be made on subsequent days to administer the dose as close as possible to the originally planned TAK-105 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 HR rate (bpm), respiratory rate, SDP, and DBP in all parts of the study. BP and HR 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 HR assessment if results are inconsistent (ie, a difference >10 bpm in HR or a difference >10 mmHg in SBP or DBP between assessments). If 3 measurements are obtained, the final BP and HR readout should be the average of the 2 more consistent assessments. All original values (all 3) should be entered into the database and the average will be derived in the datasets.

Subjects in each study part will have baseline HR 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 prior to Hour 0 time points, BP and HR will be measured within 1 hour ±10 minutes prior to dosing or 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.

Prior to discharge, vital signs will be assessed and must meet the following criteria: semirecumbent HR <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 HR readout should be the average of the 2 more consistent assessments**.**

9.2.4.1 Orthostatic Measurements

Orthostatic BP and HR assessment will be performed in the outlined sequence as follows:

1. After resting for 5 minutes in a semirecumbent position, BP and HR 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 HR 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 HR 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.

Subjects will remain semirecumbent for the first 4 hours with vital signs obtained at 0.5, 1, 2, 3, and 4 hours post dosing, 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.

9.2.4.2 Follow-Up Safety Monitoring

All subjects who early terminate the study 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 form will be provided to the subject prior to discharge from the CRU.

Any subject who early terminates the study 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, 3, and 4 and will also be monitored using safety laboratory testing.

9.2.6 ECG Procedure

9.2.6.1 Screening and Safety ECGs

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

For all parts of the study, cardiac monitoring (HR and ECG) will be assessed via telemetry and will be performed for at least 24 hours before dosing and from dosing through the hours postdose as described below:

- Part 1, 5a, and 6 (SRD)- Continuous ECG telemetry (monitoring) will continue through to Day 8.

- Part 2 and Part 5b (MRD)- Continuous ECG telemetry (monitoring) will continue through at least Day 10, and at least 48 hours postdose on Days 15 and 22.
- Part 3 Continuous ECG telemetry (monitoring) will continue through at least Day 10, and for some cohorts at least 48 hours postdose on Days 15 and 22.
- Part 4 Continuous ECG telemetry (monitoring) will continue through at least Day 10, and at least 48 hours post the third dose.

Real-time actively monitored telemetry may be limited to less than 12 leads (ie, 2 leads for real time alerts).

All subjects who terminate early from the study will have remote blood pressure monitoring and real-time continuous single lead telemetry (monitoring) for the duration of the protocol-specified observation period included in the protocol (see Section 9.2.4.2 for details).

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.

Extractions of the 12-lead telemetry will be captured with a minimum of 48 hours of cardiac monitoring (24 hours predose and 24 hours postdose) (see Section 3.0). The purpose of the telemetry extraction data is to support future detailed concentration-QT (c-QT) 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 prior to 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 future through QT (TQT) 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-105 exposure. If conducted, the results from these analyses will not be included in the CSR but will be reported in a standalone report.

9.2.7 Study Drug Administration

Study drug (TAK-105 or matching placebo) will be administered as shown in the Schedule of Study Procedures in Section 3.0.

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.

9.2.9 Laboratory Procedures and Assessments

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

9.2.9.1 Hematology

Hematology will consist of the following tests:

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

9.2.9.2 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 ULN, total bilirubin will be fractionated
Protein (total)	Creatine kinase
Other Assessments	
Cortisol (6:00 – 9:00 AM collection)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
Samples for laboratory evaluations are collected at specified timepoints or as deemed necessary by site investigator.

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, 3, and 4, 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.

9.2.9.3 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.

9.2.9.4 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; HIV: human immunodeficiency virus.

Alcohol Screen

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

Urine

The urine drug screening assessment will include the following tests:

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

9.2.10 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 (Section 3.0). Please refer to the laboratory manual for information on the collection, processing, and shipment of samples to the central laboratory.

The decision as to which plasma samples collected will be assayed for evaluation of PK will be determined by the sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). 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-105 PK	Blood	Plasma	PK analysis	Mandatory
Plasma sample for metID	Blood	Plasma	metID analysis	Mandatory
Urine sample for TAK-105 PK	Urine	N/A	PK 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; N/A: not applicable; PK: pharmacokinetic.

During the confinement period, the sponsor's expectation is that the investigators will ensure that every effort is made to collect all blood samples at the precise protocol-scheduled time (as shown in the schedule of study procedures, Section 3.0). PK blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes. In case of repeat vital sign measurements, PK samples may be collected within ±10 minutes of nominal time.

During the confinement period, the collection time of samples collected for the assessment of [redacted], hematology, and chemistry, must not deviate from the nominal collection time set in the protocol (Section 3.0) by more than ±10 minutes.

Follow up laboratory assessments can be taken at any time during the follow-up visit.

Samples drawn outside these parameters will be considered a protocol deviation but may be considered on case by case basis.

9.2.10.1 PK Measurements

The PK parameters of TAK-105 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 and urine samples to determine the metabolites of TAK-105. If conducted, these data will be reported separately and not be reported in the CSR.

Plasma PK parameters that will be determined after single dose and at steady state in different parts of the study 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 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 $(CL/F)/\lambda_z$.

The following urine PK parameters of TAK-105 will be determined after SC administration in Parts 1 and 2:

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

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

9.2.10.1.1 Plasma for PK Measurements and MetID

Plasma samples for PK analysis of TAK-105 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 dipotassium ethylenediaminetetraacetic acid (K_2EDTA). 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.

[redacted] 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 (Section 3.0). These data will be reported separately and will not be reported in the CSR.

9.2.10.2 Urine for PK Measurements

Urine concentrations of TAK-105 will be measured by a validated LC/MS/MS. A full description of urine sample collection, handling, storage, and shipping can be found in the laboratory manual. The collected urine samples may be archived following bioanalysis of TAK-105 levels for exploratory characterization of potential urinary metabolites.

9.2.10.3 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 (Section 3.0). Other [redacted] have reported the formation of ADAs; however, an ADA assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, the incidences of ADA formation cannot be directly compared with the other products. ADA samples will be taken in all parts of the study across all cohorts.

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 future potential further 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-105 in this study as well as the regulatory request if it is applied.

9.2.10.4 Biomarker Measurements

9.2.10.4.1 [redacted]

[redacted]

9.2.10.4.2 [redacted]

[redacted]

9.2.10.5 DNA Measurements

9.2.10.5.1 Blood Sample for DNA

Sampling of blood for DNA analysis is optional in this study and both 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 (Section 3.0).

[redacted]

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

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

9.2.10.5.2 Biological Sample Retention and Destruction

In this study, samples of blood for DNA analysis will be collected as described in Section 9.2.10.5.1. 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.

9.3 Confinement

9.3.1 SRD (Parts 1, 5a, and 6)

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until discharge on Day 8 (7 days after last dose of study drug). At the discretion of the investigator, subjects may be requested to remain in the clinical site longer.

9.3.2 MRD (Parts 2 and 5b)

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until discharge on Day 24 (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.

9.3.3 Part 3 (Dose Titration)

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until discharge either on Day 10, 17, or 24 depending on the cohort (ie, 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.

9.3.4 Part 4 (Redosing)

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until discharge on Day 10 (48 hours after second dose of study drug) and will return to the clinic the day prior to the third dose and will be confined until 48 hours post third (last) dose. At the discretion of the investigator, subjects may be requested to remain in the study site longer.

9.4 Childbearing Status and Methods of Contraception

9.4.1 Women of Childbearing Potential

Women of childbearing potential (WOCBP) will be excluded from this study.

9.4.1.1 Definition of WOCBP

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

9.4.2 Women of Nonchildbearing Potential

WONCBP are defined as satisfying at least 1 of the following criteria:

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

9.4.2.1 Contraception for WONCBP

No contraception is required for WONCBP.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of…”).
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or

severe in nature, that is, investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE case report form(s) (CRF[s]) according to Section 10.0.
- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT 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 and 10.1.1).

10.1.2 AEs of Special Interest

AEs of special interest (AESIs) for TAK-105 include injection site reactions, hypotension including postural hypotension, and tachycardia.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

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

Table 10.a NCI-CTCAE

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

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(s) will be assessed using the following categories:

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

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

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the 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 1 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, SAEs, Special Interest AEs, and Abnormal Liver Function Tests

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, special interest AEs, and abnormal liver function tests [LFTs]) will commence at the time the subject signs the informed consent and continue until the last follow up visit (see Schedule of Study Procedures s Section 3.0). For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

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

10.2.8.3 Reporting SAEs

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

A Takeda SAE eCRF entry 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 information should be transmitted within 24 hours to the attention of the contact listed in Appendix 14.1.1.

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

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

10.2.8.3.1 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. The site must use the eCRF to report an SAE within 24 hours, and, only if the eCRF is unavailable, should the site send a safety reporting form. 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.
[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 subjects should be advised to lie flat, and HR 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, HR, 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-105 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 HR and BP 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 3 (ulceration or necrosis; severe tissue damage; need for operative intervention) or Grade 4 (life-threatening consequences; urgent intervention indicated), discontinue administration of TAK-105, provide immediate treatment, and contact the medical monitor.

10.2.8.4.4 Hypersensitivity

If anaphylaxis or other serious allergic reactions occur, TAK-105 administration will be discontinued immediately and appropriate management initiated (eg, epinephrine, antihistamines, and further immediate care as necessary).

10.2.8.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN the event should be recorded as an SAE and reported as per Section 10.2.8.3. Treatment with TAK-105 should be discontinued. 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 9.2.9 must also be performed.

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

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

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

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

The impact due to COVID-19 will be summarized and listed based on all randomized subjects, where appropriate.

If an optional dose level/dose regimen/study part in Table 6.a is not actually investigated in this study, no statistical analysis specified in Section 11.0 will be applied to that dose level/dose regimen/study part. In addition, the following conventions will be applied to present the analyses results, unless otherwise specified.

- Descriptive statistics:
  - For continuous data (study drug exposure and compliance, clinical laboratory data, vital signs, ECGs, etc.):
    - n, mean, standard deviation, median, minimum, and maximum.
  - For PK and biomarkers:
    - n, arithmetic mean, standard deviation, percent coefficient of variation [%CV], geometric mean, geometric %CV, median, minimum, and maximum.
  - For categorical data:
    - frequency counts and percentages.
  - Percentages will be reported to 1 decimal place. For the calculation of summary statistics and statistical analysis, unrounded data will be used.
- By treatment arm (TAK-105 or placebo):
  - For PK:
    - by dose level (Parts 1, 2, 5 and 6 only)/dose regimen (Parts 3 and 4 only) of TAK-105, as appropriate, within each part of the study separately. The dose levels in Parts 5a (SRD) and 5b (MRD) will be grouped separately.
  - For AEs and impact due to COVID-19:
    - by placebo, each TAK-105 dose level (Parts 1, 2, 5 and 6 only)/dose regimen (Parts 3 and 4 only), TAK-105 overall (ie, combining all TAK-105 arms), and total (ie, combining placebo and TAK-105 arms), as appropriate, within each part of the study separately. The dose levels in Parts 5a (SRD) and 5b (MRD) will be grouped separately.

- For all other analyses:
    - by placebo, dose level (Parts 1, 2, 5 and 6 only)/dose regimen (Parts 3 and 4 only) of TAK-105, as appropriate, within each part of the study separately. The dose levels in Parts 5a (SRD) and 5b (MRD) will be grouped separately.
- Treatment arm pooling:
    - For Parts 1, 2, 3, 4, and 6, placebo will be pooled across cohorts within each part of the study where appropriate. The placebo will be pooled across cohorts in Parts 5a (SRD) and 5b (MRD) separately.
    - The same dose level (Parts 1, 2, and 6 only)/dose regimen (Parts 3 and 4 only) of TAK-105 will be pooled across cohorts within each part of the study separately where appropriate. The same dose levels of TAK-105 will be pooled across cohorts in Parts 5a (SRD) and 5b (MRD) separately.

11.1.1 Analysis Sets

11.1.1.1 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.

11.1.1.2 PK Analysis Set

The PK analysis set consists of all subjects who receive at least 1 dose of TAK-105 and have at least 1 measurable postdose plasma or urine concentration for TAK-105.

11.1.1.3 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.

11.1.2 Analysis of Demography 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) by treatment arm in Parts 1, 2, 3, 4, 5 and 6 separately. In particular, these descriptive statistics for Part 5a (SRD) and 5b (MRD) will be provided separately. The count and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (eg, gender, ethnicity, race) will be tabulated by treatment arm in Parts 1, 2, 3, 4, 5, and 6 separately. In particular, these frequency summaries for Part 5a (SRD) and 5b (MRD) will be provided separately. The safety analysis set will be used to summarize the demographics and baseline characteristics. All data will be provided in by-subject listings.

11.1.3 PK Analysis

The plasma (all parts of the study) and urine (Parts 1, 2, and 5 a/b only) concentrations of TAK-105 will be summarized by treatment arm at each scheduled sampling day/time within each part of the study separately, using descriptive statistics based on the PK analysis set. In particular, the summary of plasma concentration of TAK-105 for Parts 5a (SRD) and 5b (MRD) will be provided separately, as data allows. The plasma PK (all parts of the study) and urine PK (Parts 1, 2, and 5 a/b only) parameters of TAK-105 determined using a noncompartmental analysis approach will be summarized by treatment arm, at each scheduled day where appropriate, within each part of the study separately, using descriptive statistics based on the PK analysis set. In particular, the summary of PK parameters of TAK-105 for Parts 5a (SRD) and 5b (MRD) will be provided separately. 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. 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 will be a standalone report.

11.1.4 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 summary analyses will be performed by treatment arm within each part of the study separately. In particular, the safety summaries for Part 5a (SRD) and 5b (MRD) will be provided separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for BP and HR will be provided. All data will be provided in by-subject listings.

11.1.4.1 AEs

The summary of treatment-emergent adverse events (TEAEs) will include the number and percentage of subjects with at least 1 TEAE by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term and by treatment arm within each part of the study separately. Similar summary analyses will be provided for treatment-related TEAEs, SAEs, AESIs, and TEAEs leading to permanent treatment discontinuation as well.

11.1.4.2 Clinical Laboratory Evaluation

Clinical laboratory parameters will be summarized using descriptive statistics for baseline, postdose, and change from baseline to postdose by treatment arm at each study scheduled visit 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 treatment arm within each part of the study separately.

11.1.4.3 Vital Signs

Typically, BP and HR assessments are made in duplicate with an interval of approximately 2 minutes between the 2 assessments. The investigator can take a third BP and HR assessment if results are inconsistent (as defined in Section 9.2.4). If the assessments are made in duplicate, the average value of the duplicate assessments will be used in the summary analysis. If the investigator takes a third BP and HR assessment when results are inconsistent, the average value of the 2 more consistent corresponding assessments (details will be provided in the SAP) will be used in the summary analysis.

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 treatment arm at each study scheduled visit 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 by not limited to BP) will be presented by treatment arm within each part of the study separately. Meanwhile, the time-matched difference between Day 1 and Day -1 values of vital signs will summarized using descriptive statistics by treatment arm at each nominal time point within each part of the study separately where appropriate. For each orthostatic vital sign parameter, the difference between standing and semirecumbent (ie, standing vital sign measurement –semirecumbent vital sign measurement) will be summarized by treatment arm at each study scheduled visit within each part of the study separately.

11.1.4.4 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 treatment arm at each study scheduled visit 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 treatment arm within each part of the study separately.

11.1.4.5 Other Safety Parameters

Physical examination findings will be presented in the data listings.

11.1.5 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 transiently and persistently ADA-positive, and low or high ADA titer) will be tabulated by treatment arm at scheduled time points within each part of the study separately. In particular, the summary of immunogenicity for Parts 5a (SRD) and 5b (MRD) will be provided separately. ADA negative is defined as subjects who do not have a confirmed positive ADA status in any postbaseline assessment. Transiently ADA positive will be defined as subjects who have confirmed positive ADA status in 1 or 2 postbaseline assessments. Persistently ADA positive will be defined as subjects who have confirmed positive ADA status in more than 2 postbaseline

assessments. For ADA positive (transiently ADA positive or persistently ADA positive) only, high ADA titer is defined as subject who has at least 1 postbaseline ADA titer >16; low ADA titer is defined as subject whose postbaseline ADA titers are all ≤16.

The relationship between immunogenicity status (ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) and plasma drug concentration and PK parameters, and safety will be explored. All data will be provided by subject listings.

11.1.6 Biomarker Analysis

Biomarker measurements will be summarized using the safety analysis set. The baseline concentrations of [redacted] will be summarized using descriptive statistics by treatment arm within each part of the study separately. In addition, the number and percentage of subjects within each of the 4 categories defined by quartile (ie, 0 to <Q1, Q1 to <median, median to <Q3, ≥Q3) of [redacted] concentrations will be presented for each time point by treatment arm within each part of the study separately. The change from baseline in the [redacted] will be summarized using descriptive statistics by treatment arm at scheduled time points within each part of the study separately. In particular, the summary of biomarker measurements for Parts 5a (SRD) and 5b (MRD) will be provided separately. All data will be provided in by-subject listings.

11.2 Interim Analysis

Safety, tolerability, and available PK data will be reviewed after completion of each cohort in the dose escalation meetings and before next dose escalation stage in the study (see Section 6.0).

In case a data-dependent decision is needed to inform the subsequent development of TAK-105 prior to database lock an interim analysis may be deemed necessary. The details about situations when such a case occurs and associated interim analyses will be provided in the SAP.

11.3 Determination of Sample Size

The selected sample sizes in all parts of the study are considered sufficient for evaluation of safety and tolerability of TAK-105 in healthy subjects. No formal statistical hypothesis testing is planned; therefore, no formal power calculations were performed in the determination of the sample size for this study.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC. 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 subject 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 in this sponsor-open, double-blind study), including but not limited to the Investigator's Binder, trial drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that have a deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) for medical and safety assessments.

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

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the European Medicines Agency [EMA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

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

13.1 IRB and/or IEC Approval

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

and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the 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 or IEC for approval. The IRB's or IEC'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 or IEC 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 trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

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

The investigator is responsible for the preparation, content, and IRB or IEC 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 prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. 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 prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

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

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

13.3 Subject Confidentiality

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

of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

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

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

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site

requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

13.4.3 Clinical Trial Results Disclosure

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

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

14.1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International 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 SAEs defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

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

_____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State/Province)

_____
Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

%CV	percent coefficient of variation
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
Ae_t	amount of drug excreted in urine from time 0 to time t
$Ae_{t1\text{-}t2}$	amount of drug excreted in urine from time 1 to time 2
Ae_τ	amount of drug excreted in urine during a dosing interval (τ) at steady state
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_τ	area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval
AV	atrioventricular
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	observed plasma concentration at the end of a dosing interval
CV	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ET	early termination

[redacted]	[redacted]
FDA	Food and Drug Administration
$f_{e,t}$	fraction of administered dose of drug excreted from urine from time 0 to time t
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
GLP	Good Laboratory Practice
[redacted]	[redacted]
HED	human equivalent dose
HR	heart rate
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LFT	liver function test (LFT includes AST, ALT, alkaline phosphatase, and bilirubin)
MedDRA	Medical Dictionary for Regulatory Activities
metID	metabolite identification
MRD	multiple-rising dose
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PPB	plasma protein binding
PK	pharmacokinetic(s)
QTcF	QT interval with Fridericia correction method
QW	once weekly
$R_{ac(AUC)}$	accumulation ratio based on AUC_{τ}
$R_{ac(Cmax)}$	accumulation ratio based on C_{max}
RBBB	right bundle branch block
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal

V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
WBC	white blood cell
WOCBP	women of childbearing potential
WONCBP	woman of nonchildbearing potential

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 CRFs (Electronic and Paper)

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

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

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

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

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

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

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site

and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6(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 Clinical Study Site Agreement between the investigator and sponsor.

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

16.0 REFERENCES

[redacted]

FDA 2005. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. Rockville, MD: US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research.

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]

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform 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, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

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

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

Appendix B Elements of the Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC 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 DNA analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

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

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and auditing of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

[For Americas- and Europe-conducted studies include text below as applicable.]

Male Subjects and Their Female Partners

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

In studies with no risk of fetotoxicity/teratogenicity/genotoxicity: Male subjects are not required to use barrier contraception.

Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives 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 (investigational medicinal product 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/1 highly effective and 1 effective method (from the list below).

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

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a WOCBP, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral tubal ligation, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A 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 year 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. They should agree to use condom with spermicide from first dose if they cannot bring documentation for bilateral vasectomy.

The following procedures apply for contraception and pregnancy avoidance.

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

    - Non-Hormonal Methods:
        - 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).
    - 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 prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
            - Oral.
            - Injectable.
            - Implantable.
2. If genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drug, comparator, background therapy or standard of care medications effective methods of contraception (there may be a higher than 1% failure rate) are:

    - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).

- Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.

3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, 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.
4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
5. During the course of the study, regular serum/urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for WOCBP and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?

Pregnancy

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

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug [list all that apply] should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 5 half-lives after the last dose, should also be recorded following authorization from the subject's partner.

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

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

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

Appendix E Protocol History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
19 December 2022	Amendment 4	Substantial	Global
23 March 2022	Amendment 3	Substantial	Global
09 September 2021	Amendment 2	Substantial	Global
29 July 2021	Amendment 1	Nonsubstantial	Global
27 May 2021	Initial protocol	Not applicable	Global

Protocol Amendment 3 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary reasons for this amendment are to:

1. Add follow-up monitoring for subjects who early terminate from the study.
2. Add safety measures at follow-up visits for COVID monitoring.
3. Add collection windows for PK sampling.
4. Remove buccal epithelial cell sampling from the study.
5. Address inconsistencies in the schedule of study procedures.

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 3			
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 1.0 Study Summary Section 6.1.2 Part 1: SRD Cohorts 1 to 12 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 Section 6.1.4 Part 3: Dose Titration Cohorts 18 to 23 Section 6.1.5 Part 4: Redosing Study Cohorts 24, 25, 26, and 27 Section 6.4.2.6 Rationale for MRD Dose Selection	Updated description of planned number of subjects and of interim analysis.	To correct inaccuracies in approximation of subjects and to correct interim analysis language in summary to match main body.
2.	Section 2.0 Study Schematic	Modified language in box for Cohort 24.	For clarification that the third dose is on Day 22 for Cohort 24.
3.	Section 3.2.4 Part 2 for MRD Cohorts 13 to 17 (Week 4, Follow-Up, and ET)	Table 3.b, 3.f, 3.j, 3.m, 3.o, 3.r Added temperature and respiratory rate and vital sign	Additional safety measures added at follow-up visits due to COVID-19 pandemic.

Protocol Amendment 3			
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***
	Section 3.3.4 Part 3 Dose Titration Cohorts (Week 4, Follow-Up, and ET) Section 3.4.3 Part 3 Dose Titration Cohorts 20 and 21 (Week 3, Follow-Up, and ET) Section 3.5.2 Part 3 Dose Titration Cohorts 22 and 23 (Week 2, Follow-Up, and ET) Section 3.6.3 Part 4 Redosing Cohorts 24 Through 27 (Third Dose Week, Follow-Up, and ET)	measurements to each follow-up visit.	
4.	Section 3.1.2 Part 1 for SRD Cohort 1 to 12 (Follow-Up Through ET)Section 3.2.4 Section 3.3.4 Part 3 Dose Titration Cohorts (Week 4, Follow-Up, and ET) Section 3.4.3 Part 3 Dose Titration Cohorts 20 and 21 (Week 3, Follow-Up, and ET) Section 3.5.2 Part 3 Dose Titration Cohorts 22 and 23 (Week 2, Follow-Up, and ET) Section 3.6.3 Part 4 Redosing Cohorts 24 Through 27 (Third Dose Week, Follow-Up, and ET)	Table 3.b, 3.f, 3.j, 3.m, 3.o, 3.r Removed glucose finger stick assessments at ET visit.	To remove procedures that are not considered necessary at the early termination visit and for consistency.
5.	Section 3.0 Schedule of Study Procedures Section 9.2.10 PK, Immunogenicity, Biomarker, and DNA Samples Section 9.2.10.5 DNA Measurements	Table 3.a, 3.b, 3.f, 3.j, 3.r, 9.a, Removed collection of buccal epithelial cell sample from the study.	Buccal sampling removed due to technical issues with the sample for the assay.
6.	Section 3.0 Schedule of Study Procedures Section 9.2.4 Vital Signs Section 11.1.4.3 Vital Signs	All tables in Section 3.0. Updated language for repeat BP and HR assessments.	Modified footnote for repeat BP and HR assessments to be in agreement with Standard Operating Procedures for entry of data into the electronic database.
7.	Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.2.1 Part 2 for MRD	Table 3.a, 3.c, 3.g, 3.k, 3.n, 3.p Modified language in footnote for predose time-matched	For clarification of time period for time-matched extractions.

Protocol Amendment 3			
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***
	Cohorts 13 to 17 (Week 1) Section 3.3.1 Part 3 Dose Titration Cohorts 18 and 19 (Week 1) Section 3.4.1 Part 3 Dose Titration Cohorts 20 and 21 (Week 1) Section 3.5.1 Part 3 Dose Titration Cohorts 22 and 23 (Week 1) Section 3.6.1 Part 4 Redosing Cohorts 24 Through 27 (Week 1)	telemetry.	
8.	Section 6.1.1 Overall Study Design	Table 6.a Added note stating the planned starting dose.	For flexibility in the protocol.
9.	Section 6.1.2 Part 1: SRD Cohorts 1 to 12 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 Section 6.1.4 Part 3: Dose Titration Cohorts 18 to 23 Section 6.1.5 Part 4: Redosing Study Cohorts 24, 25, 26, and 27 Section 6.2 Dose Escalation Section 6.3.2 Criteria for Premature Termination or Suspension of the Study Section 8.1.3 Clinical Study Drug Blinding Section 11.2 Interim Analysis	Changed terminology of "Dose Escalation Committee" to "dose escalation meeting".	Modified terminology for clarification.
10.	Section 6.3.2 Criteria for Premature Termination or Suspension of the Study	a. Added language clarifying that criteria apply when related to study drug administration. b. Removed "vasovagal" from "vasovagal syncope". Removed greater than equal sign in bullet for: "Two or more subjects experience a CTCAE v5.0 Grade ≥ 3 event considered related to TAK-105 administration". Added bullet for Grade ≥2 injection site reaction	a. To clarify criteria apply when related to study drug administration and for better consistency. b. For correction.

Protocol Amendment 3			
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***
		criterion.	
11.	Section 6.5 Procedure Modifications Permitted Within Protocol Parameters	Removed details of Section 6.5 and provided general guidance.	For correction following the guidance of other studies in the program to document changes in the study file.
12.	Section 1.0 Study Summary Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria Appendix D Pregnancy and Contraception	Modified inclusion criteria #8 to clarify male subjects birth control criteria. Modified language in exclusion criteria #1 "last dose". Modified language in exclusion criteria #14 and #15.	For clarification of male birth control criteria #8. For correction of exclusion criteria #1 that criteria is after last dose of study drug. For clarification of exclusion criteria #14 and #15.
13.	Section 9.2.4.1 Follow-Up Safety Monitoring (new section) Section 9.2.6.2 Telemetry	Added language to define "inconsistent" BP measurements and to describe follow-up safety monitoring procedures.	For clarification and to continue safety monitoring of subjects who terminate early from the study.
14.	Section 9.2.9.3 Urinalysis	Changed "nitrate" to "nitrite".	To correct an error.
15.	Section 9.2.10 PK, Immunogenicity, Biomarker, and DNA Samples	Table 9.a Added note including language for sampling windows.	Notes added for clarification to provide time sampling windows for protocol-specified assessments.
16.	Section 10.2.8.3.1 SAE Follow-Up	Added: "The site must use the eCRFs to report SAE within 24 hours, and only if the eCRF is unavailable, should the site send a safety reporting form."	To clarify SAE reporting.
17.	Section 12.2 Protocol Deviations	Modified language to clarify protocol deviation.	For clarification of protocol deviation language.
18.	Section 15.1 CRFs (Electronic and Paper)	Remove sentence regarding CRFs are required for each subject who signs an informed consent.	To correct an error.
19.	Appendix D Pregnancy and Contraception	Removed true abstinence as a form of birth control.	To correct discrepancies.

Protocol Amendment 2 Summary and Rationale:

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

1. Add at least 24 hours of continuous telemetry monitoring before the first dose.
2. Add serum sampling for measurement of creatine kinase levels.
3. Include additional guidance for the investigator regarding vital sign assessments collected before dosing.
4. Specify that only serum electrolytes (sodium, potassium, chloride, and carbon dioxide) are measured at the 4-hour postdose time point on Day 1.
5. Add collection of a blood sample for DNA at discharge or at early termination in all applicable study parts.
6. Add footnotes for cortisol sample, blood sample for pharmacokinetics (PK), and metabolite identification.
7. Address inconsistencies in the early termination visits in the schedule of study procedures.

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 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 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.2.1 Part 2 for MRD Cohorts 13 to 17 (Week 1) Section 3.3.1 Part 3 Dose Titration Cohorts 18 and 19 (Week 1) Section 3.4.1 Part 3 Dose Titration Cohorts 20 and 21 (Week 1) Section 3.5.1 Part 3 Dose Titration Cohorts 22 and 23 (Week 1) Section 3.6.1 Part 4 Redosing Cohorts 24 Through 27 (Week 1) Section 9.2.6.2 Telemetry	Table 3.a, Table 3.c, Table 3.g, Table 3.k, Table 3.n, Table 3.p: Added at least 24 hours of continuous telemetry monitoring before the first dose of TAK-105 or placebo. Added predose telemetry extractions time-matched to extractions on Day 1. Section 9.2.6.2 Telemetry: Changed "approximately 2 hours before dosing through the hours postdose" to "at least 24 hours before dosing and from dosing through the hours postdose" of cardiac monitoring. Revised "23.5 hours of continuous cardiac monitoring" to "48 hours of cardiac monitoring (24 hours predose and 24 hours postdose)."	To extend baseline telemetry measurements to a period of at least 24 hours before dosing to aid in evaluation of any rhythm findings following dosing. To add predose telemetry extraction time points to support future concentration-QT analysis.
2.	Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.2 Part 2 for MRD	Table 3.a, Table 3.c, Table 3.d, Table 3.e, Table 3.f, Table 3.g, Table 3.h, Table 3.i, Table 3.j, Table 3.k, Table	Clarification

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***
	Cohorts 13 to 17 Section 3.3 Part 3 Dose Titration Cohorts 18 and 19 Section 3.4 Part 3 Dose Titration Cohorts 20 and 21 Section 3.5 Part 3 Dose Titration Cohorts 22 and 23 Section 3.6 Part 4 Redosing Cohorts 24 Through 27 Section 9.2.6.2 Telemetry	3.l, Table 3.m, Table 3.n, Table 3.o, Table 3.p, Table 3.q, Table 3.r: Clarified that telemetry is ECG 12-lead telemetry.	
3.	Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.1.2 Part 1 for SRD Cohort 1 to 12 (Follow-Up Through ET) Section 3.2.1 Part 2 for MRD Cohorts 13 to 17 (Week 1) Section 3.2.4 Part 2 for MRD Cohorts 13 to 17 (Week 4, Follow-Up, and ET) Section 3.3.1 Part 3 Dose Titration Cohorts 18 and 19 (Week 1) Section 3.3.4 Part 3 Dose Titration Cohorts (Week 4, Follow-Up, and ET) Section 3.4.1 Part 3 Dose Titration Cohorts 20 and 21 (Week 1) Section 3.4.3 Part 3 Dose Titration Cohorts 20 and 21 (Week 3, Follow-Up, and ET) Section 3.5.1 Part 3 Dose Titration Cohorts 22 and 23 (Week 1) Section 3.5.2 Part 3 Dose Titration Cohorts 22 and 23 (Week 2, Follow-Up, and ET) Section 3.6.1 Part 4 Redosing Cohorts 24 Through 27 (Week 1) Section 3.6.2 Part 4 Redosing Cohorts 24 Through 27 (Week 2) Section 3.6.3 Part 4 Redosing Cohorts 24 Through 27 (Third	Table 3.a, Table 3.b, Table 3.c, Table 3.f, Table 3.g, Table 3.j, Table 3.k, Table 3.m, Table 3.n, Table 3.o, Table 3.p, Table 3.q, and Table 3.r: Added serum sample collection of creatine kinase (CK) at predose and 24 hours postdose on Day 1, at discharge, and at early termination for all parts of the study; also at 48 hours after the first dose for Part 1 (SRD). Added footnote to allow for additional serum samples for CK at the investigator's discretion if CK is elevated in an individual subject after dosing, and to note that the medical monitor will be updated regularly on any findings of elevated CK and plans for continued monitoring.	To enable assessment of potential changes in CK levels following TAK-105 dosing and to evaluate any association with events of myalgia.

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***
	Dose Week, Follow-Up, and ET) Section 9.2.9.2 Chemistry		
4.	Section 3.1.2 Part 1 for SRD Cohort 1 to 12 (Follow-Up Through ET) Section 3.2.4 Part 2 for MRD Cohorts 13 to 17 (Week 4, Follow-Up, and ET) Section 3.3.4 Part 3 Dose Titration Cohorts (Week 4, Follow-Up, and ET) Section 3.4.3 Part 3 Dose Titration Cohorts 20 and 21 (Week 3, Follow-Up, and ET) Section 3.5.2 Part 3 Dose Titration Cohorts 22 and 23 (Week 2, Follow-Up, and ET) Section 3.6.3 Part 4 Redosing Cohorts 24 Through 27 (Third Dose Week, Follow-Up, and ET)	Table 3.b, Table 3.f, Table 3.j, Table 3.m, Table 3.o, Table 3.r: Added safety laboratory sample collection; temperature and respiratory rate; and standing blood pressure and HR assessments at the early termination visit.	To collect safety and pharmacokinetic (PK) information for subjects with early termination and to be consistent with the rest of the protocol.
5.	Section 6.1.2 Part 1: SRD Cohorts 1 to 12 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.1.2 Part 1 for SRD Cohort 1 to 12 (Follow-Up Through ET) Section 3.2.4 Part 2 for MRD Cohorts 13 to 17 (Week 4, Follow-Up, and ET) Section 3.3.4 Part 3 Dose Titration Cohorts (Week 4, Follow-Up, and ET) Section 3.6.3 Part 4 Redosing Cohorts 24 Through 27 (Third Dose Week, Follow-Up, and ET) Table 9.a Primary Specimen Collections Section 9.2.10.5 DNA Measurements	Table 3.a, Table 3.b, Table 3.f, Table 3.j, Table 3.r: Added collection of optional blood samples for DNA at discharge or at early termination in all applicable study parts. Revised text to indicate if subjects have provided consent for the optional DNA collection, both buccal swabs and blood samples should be collected.	Inclusion of optional blood samples for DNA sequencing.

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***
6.	Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.2 Part 2 for MRD Cohorts 13 to 17 Section 3.3 Part 3 Dose Titration Cohorts 18 and 19 Section 3.4 Part 3 Dose Titration Cohorts 20 and 21 Section 3.5 Part 3 Dose Titration Cohorts 22 and 23 Section 3.6 Part 4 Redosing Cohorts 24 Through 27	Table 3.a, Table 3.c, Table 3.d, Table 3.e, Table 3.f, Table 3.g, Table 3.h, Table 3.i, Table 3.j, Table 3.k, Table 3.l, Table 3.m, Table 3.n, Table 3.o, Table 3.p, Table 3.q, and Table 3.r: Revised footnote for safety laboratory assessments at the 4-hour postdose time point to specify that only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed.	To clarify the footnote by stating the measurements to be performed at 4 hours postdose and removing the list of excluded measurements.
7.	Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.2.1 Part 2 for MRD Cohorts 13 to 17 (Week 1) Section 3.3.1 Part 3 Dose Titration Cohorts 18 and 19 (Week 1) Section 3.4.1 Part 3 Dose Titration Cohorts 20 and 21 (Week 1) Section 3.5.1 Part 3 Dose Titration Cohorts 22 and 23 (Week 1) Section 3.6.1 Part 4 Redosing Cohorts 24 Through 27 (Week 1) Section 6.1.2 Part 1: SRD Cohorts 1 to 12 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 Section 6.1.4 Part 3: Dose Titration Cohorts 18 to 23 Section 6.1.5 Part 4: Redosing Study Cohorts 24, 25, 26, and 27 Section 9.3 Confinement	Removed the option to admit subjects to the site on Day -1 if the Day -2 assessments can be performed on Day -1.	To specify that subjects must be admitted to the site on Day -2 to allow for at least 24 hours of continuous telemetry monitoring before the first dose of study drug.
8.	Section 3.3 Part 3 Dose Titration Cohorts 18 and 19 Section 3.4 Part 3 Dose Titration Cohorts 20 and 21 Section 3.5 Part 3 Dose Titration Cohorts 22 and 23 Section 3.6 Part 4 Redosing Cohorts 24 Through 27	Table 3.g, Table 3.h, Table 3.i, Table 3.j, Table 3.k, Table 3.l, Table 3.m, Table 3.n, Table 3.o, Table 3.p, Table 3.q, Table 3.r: Added footnote to cortisol test indicating the collection period.	To be consistent with the rest of the protocol.

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***
9.	Section 3.2.2 Part 2 for MRD Cohorts 13 to 17 (Week 2) Section 3.2.3 Part 2 for MRD Cohorts 13 to 17 (Week 3) Section 3.2.4 Part 2 for MRD Cohorts 13 to 17 (Week 4, Follow-Up, and ET) Section 3.3.2 Part 3 Dose Titration Cohorts 18 and 19 (Week 2) Section 3.3.3 Part 3 Dose Titration Cohorts 18 and 19 (Week 3) Section 3.3.4 Part 3 Dose Titration Cohorts (Week 4, Follow-Up, and ET) Section 3.4.2 Part 3 Dose Titration Cohorts 20 and 21 (Week 2) Section 3.4.3 Part 3 Dose Titration Cohorts 20 and 21 (Week 3, Follow-Up, and ET) Section 3.5.2 Part 3 Dose Titration Cohorts 22 and 23 (Week 2, Follow-Up, and ET) Section 3.6.2 Part 4 Redosing Cohorts 24 Through 27 (Week 2)	Table 3.d, Table 3.e, Table 3.f, Table 3.h, Table 3.i, Table 3.j, Table 3.l, Table 3.m, Table 3.o, Table 3.q: Added footnote to plasma sampling for PK and/or metabolite identification to indicate that blood draw may occur 10 minutes before dosing.	To give flexibility in blood collection period during predosing period to be consistent with studies within the same program. Applies to non–first dose predose sampling and non–redosing dose (Part 4).
10.	Section 9.1.1.1 Assignment of Screening and Randomization Numbers	Added statement that rescreening of subjects will be considered on a case-by-case basis by the sponsor.	To ensure that a discussion with the sponsor occurs before a subject is rescreened.
11.	Section 9.2.4 Vital Signs	Added additional guidance for the investigator regarding vital sign assessments collected before each dose.	To allow for the investigator's clinical assessment of vital signs before subsequent days of dosing and to provide a window for discussion on a case-by-case basis between the investigator and the sponsor.
12.	Section 12.1 Study-Site Monitoring Visits	Added a statement that allows for alternative monitoring approaches in the event a monitor cannot visit the site in a timely manner.	To allow remote source data verification in extenuating circumstances.

Protocol Amendment 1 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to:

1. Revise the number of planned investigational sites.
2. Update the Schedule of Study Procedures tables to correct discrepancies.
3. Correct discrepancy in exclusion criterion #9.
4. Clarify continuous telemetry time periods.
5. Clarify timing of adverse event (AE) collection period.

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	Section 1.0 Study Summary	Updated the planned number of sites from 2 to 3.	Increased the maximal number of sites for flexibility in study operations.
2	Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8) Section 3.2.1 Part 2 for MRD Cohorts 13 to 17 (Week 1) Section 3.3.1 Part 3 Dose Titration Cohorts 18 and 19 (Week 1) Section 3.4.1 Part 3 Dose Titration Cohorts 20 and 21 (Week 1) Section 3.5.1 Part 3 Dose Titration Cohorts 22 and 23 (Week 1) Section 3.6.1 Part 4 Redosing Cohorts 24 Through 27 (Week 1)	Table 3.a, 3.c, 3.g, 3.k, 3.n, and 3.p: Removed the column for 96-hour timepoint and shifted 96-hour assessments to Day 5. Relabeled the Day 5 heading to include 96 hours. Updated footnote 'm' and 'p' in Table 3.a; 'm' and 'o' in Table 3.c; 'm' in Table 3.g, 3.k, 3.n, and 3.p for urine pharmacokinetic (PK) samples and biomarker samples to align with updated tables.	To correct error since 96 hours is the same as Day 5 timepoint.
3	Section 3.1.1 Part 1 for SRD Cohort 1 to 12 (Days 1 Through 8)	Table 3.a: Added collection of standing blood pressure (BP) and HR at Day 5 and removed BP and HR collection at Time 0.	To be consistent with the other parts of the study.
4	Section 3.6.3 Part 4 Redosing Cohorts 24 Through 27 (Third Dose Week, Follow-Up, and ET)	Revised footnote 'f' for immunogenicity serum samples.	Corrected error to clarify that collections are at follow-up visits at 28 days after third dose in addition to Day 82.
5	Section 6.3.2 Criteria for Premature Termination or Suspension of the Study	Added language "at rest while semirecumbent."	To clarify the stopping criteria related to sinus tachycardia.

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***
6	Section 7.2 Exclusion Criteria Section 1.0 Study Summary	Updated language in exclusion criterion #9 regarding concomitant medications.	Updated language for consistency with language in Section 7.3.1 as recommended by the United States Food and Drug Administration (US FDA).
7	Section 9.2.6.2 Telemetry	Added language for each part of the study extending telemetry monitoring beyond 24 hours postdose.	To clarify that telemetry is collected beyond 24 hours postdose in each part of the study.
8	10.2.8.1 Collection Period	Modified language for adverse event (AE) collection period.	To correct that AE collection period should follow the Schedule of Study Procedures not 30 days after last dose.
9	Section 11.1.5 Immunogenicity Analysis Section 1.0 Study Summary	Modified the language to read "plasma drug concentration."	Revised language for accuracy.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	20-Dec-2022 18:52 UTC
[redacted]	Biostatistics Approval	20-Dec-2022 19:42 UTC
[redacted]	Pharmacovigilance Approval	21-Dec-2022 08:49 UTC
[redacted]	Clinical Science Approval	21-Dec-2022 14:27 UTC