Clinical Study Protocol

NCT Number: NCT04731922

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-510 in Healthy Subjects

Study Number: TAK-510-1001

Document Version and Date: Amendment 3; 21 April 2022

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

TAKEDA DEVELOPMENT CENTER AMERICAS, INC

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-510 in Healthy Subjects

Study Identifier: TAK-510-1001

Compound: TAK-510

Date: 21 April 2022

Version Number: Amendment 3

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
21 April 2022	Amendment 3	Substantial	Global
02 September 2021	Amendment 2	Substantial	Global
19 May 2021	Amendment 1	Substantial	Global
02 December 2020	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-510
Study Identifier: TAK-510-1001	**Phase:** 1
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-510 in Healthy Subjects	

Study Design:

This is a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-510 in healthy subjects.

The study will consist of 3 parts:

- Part 1 is a first-in-human, randomized, double-blind, placebo-controlled, single rising dose (SRD) design to assess the safety, immunogenicity, tolerability, and PK of TAK-510 in healthy subjects. Up to 17 cohorts may be enrolled.
- Part 2 is a randomized, double-blind, placebo-controlled, multiple rising dose (MRD) design to assess the safety, immunogenicity, tolerability, and PK of TAK-510 in healthy subjects. Up to 8 cohorts may be tested in independent subject cohorts.
- Part 3 is a randomized, double-blind, placebo-controlled, multiple-dose, dose titration and redosing design to assess the safety, immunogenicity, tolerability, and PK of TAK-510 in healthy subjects. Up to 3 cohorts may be tested in independent subject cohorts using a dose titration design, followed by redosing with a single dose of study drug after a 7-day washout (168 hours after the previous dose).

TAK-510 and matching placebo will be administered subcutaneously (SC). Safety will be assessed by monitoring for adverse events (AEs), vital signs, electrocardiogram (ECG)/telemetry, safety laboratory assessments after each dose, and immunogenicity. PK sampling times and scheme may vary based on emerging safety, tolerability and PK data, but the maximal number of samples or the maximum time point will not change. Subjects may not participate in more than 1 part or dosing cohort of the study.

Study Primary Objective:

- Part 1:
  - To characterize the safety and tolerability of single SC doses of TAK-510 in healthy subjects.
- Part 2:
  - To characterize the safety and tolerability of multiple SC doses of TAK-510 in healthy subjects.
- Part 3:
  - To characterize the safety and tolerability of multiple SC dose regimens of TAK-510 that include titration from lower doses in healthy subjects.

Secondary Objectives:

- Part 1:
  - To characterize the PK of TAK-510 in plasma following single SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-510 following single SC doses in healthy subjects.
  - To characterize the PK of TAK-510 in urine following single SC doses in healthy subjects.
- Part 2:
  - To characterize the PK of TAK-510 in plasma following multiple SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-510 following multiple SC doses in healthy subjects.

– To characterize the PK of TAK-510 in urine following multiple SC doses in healthy subjects.

- Part 3:
  – To characterize the safety and tolerability of single SC rechallenge doses of TAK-510 after a washout from multiple SC dose regimens that include titration from lower doses in healthy subjects.
  – To assess the immunogenicity of TAK-510 following multiple SC dose regimens that include titration from lower doses, washout, and redosing in healthy subjects.

Study Subject Population: Healthy male and female (nonchildbearing potential only) subjects aged 18 to 55 years, inclusive, at screening. Body mass index ≥18 and ≤30.0 (kg/m^2) at the screening.

Planned Number of Subjects:	**Planned Number of Sites:**
Part 1: Up to approximately 136 subjects. Part 2: Up to approximately 64 subjects. Part 3: Up to approximately 24 subjects. Approximate values do not account for potential replacement of subjects who withdraw for nonsafety reasons.	Up to 2 sites.
Dose Levels:	**Route of Administration:**
Part 1: TAK-510 SRD: starting dose 5 µg Part 2: TAK-510 MRD: doses to be determined based on Part 1. Part 3: TAK-510 Dose Titration and Redosing: doses to be determined based on Parts 1 and 2.	Subcutaneous (SC)
Duration of Treatment:	**Planned Study Duration:**
Part 1: 1 day. Part 2: 5 days. Part 3: 15 days (7 days plus 1 day after 7 days of washout.)	Approximately 57 days from screening (Day -28) until last follow-up visit (Day 29).

Main Criteria for Inclusion:

In order to be eligible for study participation, the subject must:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be a healthy man or woman of nonchildbearing potential 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 dosing and throughout the study.
5. Have a body mass index ≥18 and ≤30.0 (kg/m^2) at the screening visit.
6. Be judged to be in good health (eg, no evidence of psychiatric, hepatic, renal, pulmonary, or cardiovascular disease) by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug or invasive procedure.

Main Criteria for Exclusion:

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

- The subject has participated in another investigational study within 4 weeks (or based on local regulations) or within 5 half-lives of the investigational product before the screening visit. The 4-week or 5 half-lives window will be derived from the date of the last study dose and/or 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 2 days after discharge.
- The subject has a history or presence of:
  - 3 or more incidences of vasovagal syncope within the last 5 years prior to screening; or
  - A family history of unexplained sudden death or channelopathy; or
  - Brugada syndrome (ie, RBBB pattern with ST-elevation in leads V1-V3); or
  - Cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, stroke, sick sinus syndrome, pulmonary congestion, symptomatic or significant cardiac arrhythmia, second-degree atrioventricular (AV) block type 2, third degree AV block, prolonged QT interval with Fridericia correction method (QTcF) interval, hypokalemia, hypomagnesemia, or conduction abnormalities; or
  - Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome); or
  - Any clinically significant ECG findings or medical history including: long or short QTcF (over 450 msec or less than 360 msec), bifascicular block or QRS ≥120 msec or PR interval >210 msec at screening or Day -1 pre-Hour 0; or
  - The subject has a documented history of sinus bradycardia (<45 beats per minute [bpm]) 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 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 time point values do not meet this criterion, must be discussed with the medical monitor for approval.
- The subject has an average HR <55 or >100 bpm from screening to predose, inclusive. Subjects with an average HR <55 bpm can be enrolled only with medical monitor approval. Any assessments after admission with an average HR <55 bpm, from Day -2 to predose (inclusive), 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 ≥20 mm Hg or a decrease in diastolic BP ≥10 mm Hg at approximately 3 minutes of standing when compared with BP from the semirecumbent position at screening to predose assessments, inclusive. In asymptomatic subjects, any assessments after screening that do not meet this criterion may be repeated after the subject has remained in the semirecumbent or supine position for 15 minutes. If the repeat assessment is exclusionary based on the above criterion, the subject will not be eligible. If the repeat assessment is not exclusionary, the subject will be eligible.
- The subject has postural orthostatic tachycardia, defined as an increase of >30 bpm or HR >120 bpm at approximately 3 minutes of standing, at screening to predose assessments, inclusive. Any assessments after screening that do not meet this criterion may be repeated with the subject remaining standing for up to a total of 5 minutes, provided that the subject remains asymptomatic. If the repeat assessment occurring within 5 minutes is exclusionary based on the above criterion, the subject will not be eligible. A confirmed orthostatic increase of >30 bpm, but <40 bpm, on 1 or more Day -1 assessments may not be considered exclusionary if not considered clinically significant by the investigator and the medical monitor. Such assessments must be discussed with the medical monitor prior to determination that the subject is eligible to proceed.

Main Criteria for Evaluation and Analyses:

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:

- Part 1: plasma PK parameters for TAK-510
  - Maximum observed plasma concentration (C_{max}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration

(AUC_{last}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Terminal disposition phase half-life ($t_{1/2z}$).
  - Apparent clearance after extravascular administration (CL/F).
  - Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Part 2: plasma PK parameters for TAK-510 on Day 1
  - C_{max}, t_{max}, and area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_τ).
- Part 2: plasma PK parameters for TAK-510 at steady state
  - 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}), accumulation ratio based on AUC_τ ($R_{ac[AUC]}$), calculated as AUC_τ at steady state/AUC_τ after a single dose, and accumulation ratio based on C_{max} ($R_{ac[Cmax]}$), calculated as C_{max} at steady state/C_{max} after a single dose.
- Parts 1 and 2: urine PK parameters for TAK-510
  - 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) at steady state (Ae_τ).
  - Fraction of administered dose of drug excreted from urine from time 0 to time t ($f_{e,t}$).
  - Renal clearance (CL_R).
- Part 3:
  - Safety and tolerability of single SC rechallenge doses after a washout from multiple SC dose regimens of TAK-510 as assessed through vital signs, ECG, laboratory assessments, and AEs.
- All parts of the study:
  - Status of subject's antidrug antibody (ADA) assessment (ie, ADA-negative or ADA-positive, and low or high ADA titer).

Statistical Considerations:

Safety analyses will be based on the safety analysis set (defined as all subjects who are randomized and receive at least 1 dose of study treatment). No formal statistical tests or inference will be performed for safety analyses. All summary analyses will be performed by placebo, TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. In particular, the number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for BP and HR will be provided. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) will be pooled across cohorts within each part of the study where appropriate. For Part 3 only, similar safety summary analyses (excluding ADA assessments) will be performed for the single dose after washout from multiple dose regimens of TAK-510 by placebo, TAK-510 single dose level after washout, and TAK-510 single dose overall after washout.

The plasma (all parts of the study) and urine (Parts 1 and 2 only) concentrations of TAK-510 will be summarized by dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) at each scheduled sampling day/time within each part of the study separately, using descriptive statistics based on the PK analysis set (defined as all subjects who receive at least 1 dose of TAK-510 and have at least 1 measurable postdose plasma or urine concentration for TAK-510). The PK parameters of TAK-510 determined using a noncompartmental analysis approach will be summarized by dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) of TAK-510, as appropriate, within each part of the study separately, using descriptive statistics based on the PK analysis set. Dose proportionality may be assessed graphically (log-transformed dose-normalized C_{max} and AUC versus dose) and by using a power model within each part of the study separately as data allow; no formal statistical comparisons will be conducted.

Sample Size Justification:

The selected sample sizes in Parts 1, 2, and 3 of the study are considered sufficient for evaluation of safety and tolerability of TAK-510 in healthy subjects. No formal statistical hypothesis testing is planned in Parts 1, 2, or 3. Therefore, no formal power calculations were performed in the determination of sample size for the study.

1.1 Protocol Amendment 3 Summary of Changes

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. Clarify maximum exposure of TAK-510.
2. Revise study design to include additional single rising dose (SRD) and multiple rising dose (MRD) cohorts.
3. Add safety measures at follow-up visits for coronavirus disease 2019 (COVID-19) monitoring.
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.	Title Page		For consistency
2.	Section 1.0 STUDY SUMMARY	Updated planned number of subjects.	To include subjects from additional single rising dose (SRD) and multiple rising dose (MRD) cohorts.
3.	Section 1.0 STUDY SUMMARY Section 6.1.2 Part 1: SRD Cohorts 1 to 12 and 21 to 25 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 and 26 to 28 Section 6.1.4 Part 3: Dose Titration and Redosing Cohorts 18 to 20	Clarified that approximate sample sizes do not account for potential replacement of subjects and updated total sample size due to the increase in number of cohorts.	To clarify the approximate sample sizes and to update total sample size to account for the increase in number of cohorts.

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***
4.	Section 1.0 STUDY SUMMARY Section 2.0 STUDY SCHEMATIC Section 3.1 Part 1 for SRD Cohorts 1 to 12 and 21 to 25 Section 3.2 Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and Early Termination Section 6.1.1 Overall Study Design Section 6.1.2 Part 1: SRD Cohorts 1 to 12 and 21 to 25 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 and 26 to 28 Section 6.3.1 Rationale of Study Design Section 6.3.2.2 FIH Proposed Dose Regimen for the SRD Cohorts	Updated study design to add SRD and MRD cohorts. Figure 2.a, Table 3.a, Table 3.b, Table 3.f, Table 3.j, and Table 6.a were updated.	To clarify the maximum exposure cap for TAK-510 and study doses that will produce concentrations in efficacious range.
6.	Section 3.1 Part 1 for SRD Cohorts 1 to 12 and 21 to 25	For Table 3.a, blood pressure (BP) and pulse assessments were added to the follow-up visits on Days 8, 14, and 29.	Correction of study procedures.
	Section 3.2.1 Overall Schedule of Study Procedures for Part 2	For Table 3.b, BP and pulse assessments were added to the follow-up visit on Day 14.	
	Section 3.2.4 Part 2 for MRD Day 5 Through Day 9 Assessments, Follow-Up, and Early Termination	For Table 3.e, BP and pulse assessments were added to the follow-up visits on Days 14, and 29.	
	Section 3.2.2 Part 2 for MRD Screening Through Day 1 Assessments Section 3.3.2 Part 3 Screening Through Day 1 Assessments	Table 3.c and Table 3.g was updated to remove footnote h "Only serum chemistry to measure electrolytes (sodium, potassium, chloride, and carbon dioxide) should be performed at the 4-hour assessment."	

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 3.3.5 Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and Early Termination	For Table 3.j, BP and pulse assessments were added to the follow-up visit on Day 29 and the "inclusion/exclusion criteria" row was removed. In addition, a footnote for BMI was added for clarification.	
7.	Section 3.1 Part 1 for SRD Cohorts 1 to 12 and 21 to 25 Section 3.2 Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and Early Termination Section 3.3 Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and Early Termination Section 9.2.4 Vital Signs Section 11.1.4.3 Vital Signs	Table 3.a, Table 3.b, Table 3.c, Table 3.d, Table 3.e, Table 3.f, Table 3.g, Table 3.h, Table 3.i, and Table 3.j were updated. Added language to define "inconsistent" BP measurements.	Text added for clarification.
8.	Section 3.1 Part 1 for SRD Cohorts 1 to 12 and 21 to 25 Section 3.2 Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and Early Termination Section 3.3 Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and Early Termination Section 9.2.10 PK, Immunogenicity, Biomarker, and DNA Samples Section 9.2.10.4.1 Blood Sample for DNA Section 9.2.10.4.2 Biological Sample Retention and Destruction	Table 3.a, Table 3.b, Table 3.e, Table 3.f, Table 3.i, Table 3.j, and Table 9.a were updated. Removed collection of buccal epithelial cell sample from the study.	Buccal sampling removed due to technical issues with the sample for the assay.

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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9.	Section 3.1 Part 1 for SRD Cohorts 1 to 12 and 21 to 25 Section 3.2 Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and Early Termination Section 3.3 Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and Early Termination	Table 3.a, Table 3.b, Table 3.c, Table 3.f, and Table 3.g were updated. Modified language in footnote for predose time-matched telemetry.	For clarification of time period for time-matched extractions.
10.	Section 1.0 STUDY SUMMARY Section 6.1.1 Overall Study Design Section 6.3.1 Rationale of Study Design	Updated wording "dose/dose regimen" to "cohort."	For consistency between Part 1 and Part 2/3.
11.	Section 3.3.5 Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and Early Termination	Table 3.j was updated to add adverse event (AE) monitoring on Days 9 to 13.	To clarify AE monitoring.
12.	Section 1.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria	Modified inclusion criterion #7 to clarify the birth control criteria for male subjects.	For clarification of birth control criteria #7 for male subjects.
		Modified language in exclusion criterion #1 to "last dose."	For correction of exclusion criterion #1 that criterion is after last dose of study drug.
		Modified language in exclusion criteria #14 and #15.	For clarification of exclusion criteria #14 and #15.
13.	Section 4.3 Benefit/Risk Profile	Myalgia was added to potential risks of TAK-510.	To include preliminary safety data from Study TAK-510-1001.
		Updated with results from embryo-fetal development study.	To include audited draft results from a definitive rat embryo-fetal development.
		"TAK-510 is a modified peptide with a lipidated conjugation" was removed.	Repetitive text was deleted

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	Location	***Description***	***Rationale***
		"*excluding women of childbearing potential*" was added to the last paragraph.	For clarification.
14.	Section 6.1.2 Part 1: SRD Cohorts 1 to 12 and 21 to 25 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 and 26 to 28 Section 6.1.4 Part 3: Dose Titration and Redosing Cohorts 18 to 20 Section 6.3.2.2 FIH Maximum Dose Consideration Section 6.3.2.2 FIH Proposed Dose Regimen for the SRD Cohorts Section 6.3.2.4 Rationale for Dosing Interval	Exposure levels, details of highest planned doses, and preliminary pharmacokinetic (PK) data were added. The maximum exposure of TAK-510 was updated to 705,000 h*ng/mL. Table 6.b was updated.	To include observed preliminary human data. To clarify the maximum exposure cap for TAK-510 and study doses that will produce concentrations in efficacious range. This range was predicted by emerging information and will allow optimal onset of response of 30 minutes and highest dose exposures of at least 2-fold the anticipated efficacious exposure. The no-observed-adverse-effect level is unchanged.
15.	Section 6.1.2 Part 1: SRD Cohorts 1 to 12 and 21 to 25 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 and 26 to 28 Section 6.1.4 Part 3: Dose Titration and Redosing Cohorts 18 to 20	Language for injection volume added.	Text edited for clarification and consistency.
16.	Section 6.1.2 Part 1: SRD Cohorts 1 to 12 and 21 to 25 Section 6.1.3 Part 2: MRD Cohorts 13 to 17 and 26 to 28 Section 6.1.4 Part 3: Dose Titration and Redosing Cohorts 18 to 20 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 to clarify that this is not an official committee. This is a dose escalation meeting and does not require a charter as would a Dose Escalation Committee.

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	Location	***Description***	***Rationale***
17.	Section 6.2.2 Criteria for Premature Termination or Suspension of the Study	a. Added language clarifying that criteria apply when related to study drug administration.	a. To clarify that criteria apply when related to study drug administration and for better consistency.
		b. Removed "vasovagal" from "vasovagal syncope." Removed greater than or equal to sign in bullet for: "Two or more subjects experience a CTCAE v5.0 Grade ≥3 event considered related to TAK-510 administration". Added bullet for Grade ≥2 injection site reaction criterion.	b. For correction.
18.	Section 6.3.2.2 (previous numbering)	Previous Section 6.3.2.2, "Other Supporting Estimated Pharmacologically Active Exposures" was removed.	Removed because determination of doses [redacted] efficacy data and observed human PK data.
19.	Section 6.3.2.3 (previous numbering)	Previous Section 6.3.2.3 "Summary of FIH Starting Dose Consideration" was merged into Section 6.3.2.1.	To remove repetitive information.
20.	Section 6.4 Procedure Modifications Permitted Within Protocol Parameters	Removed details of Section 6.4 and provided general guidance.	For correction following the guidance of other studies in the program to document changes in the study file.
21.	Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject	"AE" was updated to "TEAE."	Text updated for clarification.
22.	Section 9.2.4.1 Follow-Up Safety Monitoring (new section)	Added to describe follow-up safety monitoring procedures.	To continue safety monitoring of subjects who terminate early from the study.
23.	Section 9.2.6.1 Screening and Safety ECGs	Added "in semirecumbent position."	For clarification.
24.	Section 9.2.9.3 Urinalysis	Changed "nitrate" to "nitrite."	Correct an error.
25.	Section 9.2.10 PK, Immunogenicity, Biomarker, and DNA Samples	Footnotes added to Table 9.a. Added language for sampling windows.	Footnotes added for clarification to provide time sampling windows for protocol-specified assessments.

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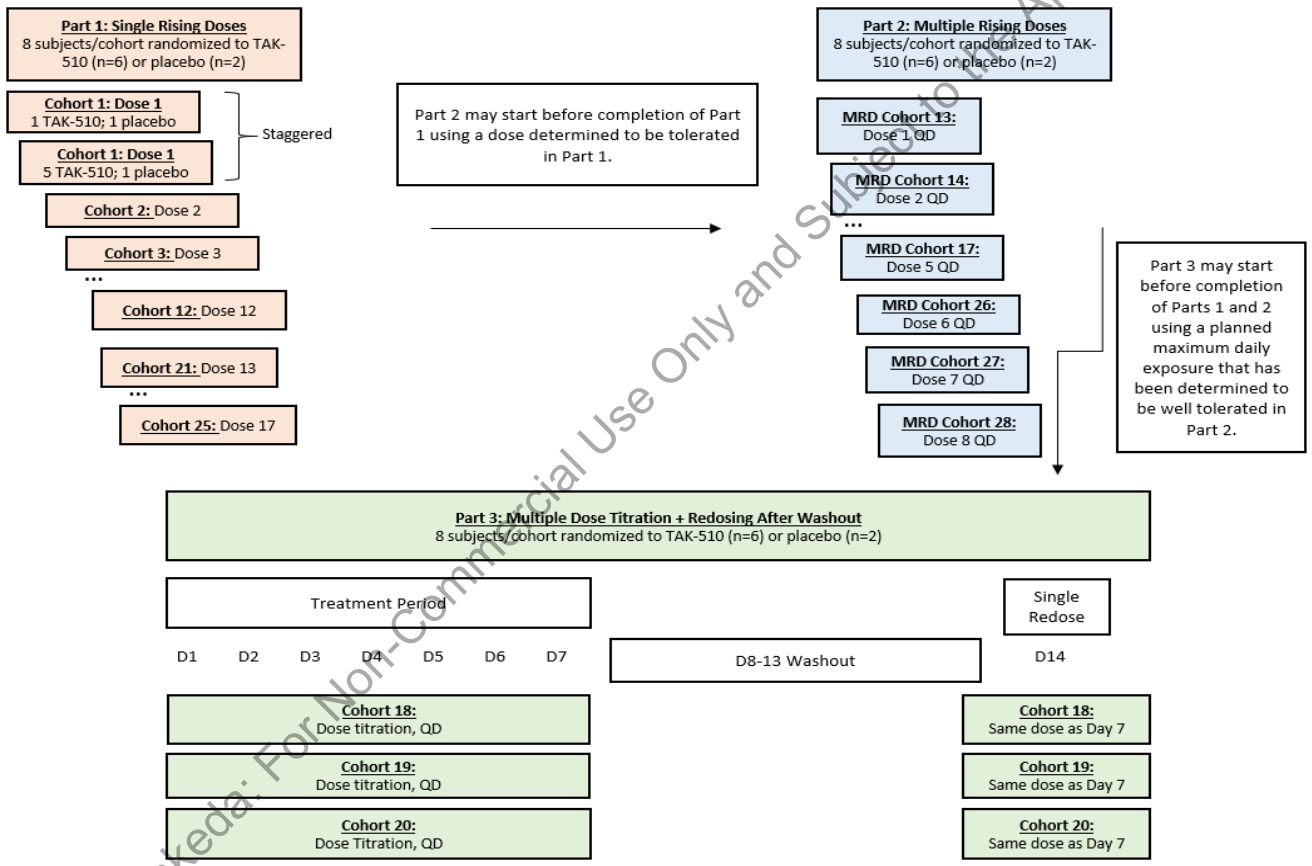
	Location	***Description***	***Rationale***
26.	Section [redacted]	[redacted]	For clarification.
27.	Section 10.2.8.3.1 SAE Follow-Up	Added "The site must use the eCRFs to report an SAE within 24 hours, and only if the eCRF is unavailable, should the site send a safety reporting form."	To clarify serious adverse event reporting.
28.	Section 10.2.8.4.3 Injection Site Reaction	Language for Grade 2 injection site reactions added.	Text edited for clarification.
29.	Section 11.2 Interim Analysis	Language for interim analysis was revised.	Add flexibility to conduct an interim analysis when a data-dependent internal decision is needed to inform the subsequent development of TAK-510 before database lock.
30.	Section 12.2 Protocol Deviations	Modified language to clarify protocol deviation.	For clarification of protocol deviation language.
31.	Section 15.1 Case Report Forms (Electronic and Paper)	Remove sentence regarding case report forms being required for each subject who signs an informed consent.	Correct an error.

2.0 STUDY SCHEMATIC

Figure 2.a Study Schematic



D: day; MRD: multiple rising dose; QD: once daily.

[a] The D8-13 washout period for Cohorts 19 and 20 is subject to change based on emerging safety, tolerability, and available pharmacokinetic data.

3.0 SCHEDULE OF STUDY PROCEDURES

3.1 Part 1 for SRD Cohorts 1 to 12 and 21 to 25

Table 3.a Part 1 for SRD Cohorts 1 to 12 and 21 to 25

	Day		Scheduled Time												Scheduled Time																Follow-up Visit	Follow-up Visit	Follow-up Visit	
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours)																			
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre-dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30	48	72	96 [c] (discharge)	Day 8 -1 day	Day 14 ±2 days	Day 29 ±3 days	ET
Administrative Procedures																																		
Informed consent	X																																	
Inclusion/exclusion criteria	X	X													X																			
Medical history/demographics	X																																	
Prior and concomitant medication review	X	X----------Continuous Review----------X																																
Clinic Procedures/Assessments																																		
Full physical examination	X	X																									X [d]				X [d]				X
Height	X																																	
Weight and BMI	X	X																																
TAK-510/placebo administration [e]																X																		
Temperature and respiratory rate	X	X													X				X		X						X							
BP and pulse [f]	X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [g]	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				X
ECG telemetry (12-lead)		X----------Continuous Monitoring [h] ----------X													X----------Continuous Monitoring----------X																				
Telemetry extraction [i]			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X							
AE monitoring	X [j]	X----------Continuous Monitoring----------X																																X
Laboratory Procedures/Assessments																																		
Safety laboratory collection (hematology and serum chemistry)	X	X													X						X [k]						X		X		X		X	X	X
Urinalysis	X	X																									X								X
Serum sample for CK [l]															X												X				X				X

Table 3.a Part 1 for SRD Cohorts 1 to 12 and 21 to 25

	Day		Scheduled Time												Scheduled Time																Follow-up Visit	Follow-up Visit	Follow-up Visit	
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours)																Day 8 -1 day	Day 14 ±2 days	Day 29 ±3 days	
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre-dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30	48	72	96 [c] (discharge)				ET
Glucose finger stick															X					X					X									
Urine drug screen	X	X																																
Alcohol breath test		X																																
Cotinine test	X	X																																
Hepatitis screen [m]	X																																	
HIV screen	X																																	
βhCG (pregnancy) test [n]	X	X																												X				X
Serum FSH test [o]	X																																	
PK Evaluations																																		
Plasma sample for TAK-510 PK															X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Urine sample for TAK-510 PK [p]															X		X				X		X			X								
Immunogenicity and Biomarker Evaluations																																		
Serum sample for immunogenicity [q]															X																X	X	X	X
Blood sample for DNA (optional) [r]																														X				X
[redacted]																																		
Other																																		
Confinement		X----------X																																

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

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

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

[c] Subjects will be confined for 96 hours after dosing (can be discharged after the 96-hour PK sample).

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

[e] Subjects will be administered a single dose of TAK-510 or matching placebo.

Table 3.a Part 1 for SRD Cohorts 1 to 12 and 21 to 25

	Day		Scheduled Time												Scheduled Time																Follow-up Visit	Follow-up Visit	Follow-up Visit	
	-28 to -3	-2 [a]	Day -1 (Hours)												Day 1 (Hours)																		
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre-dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30	48	72	96 [c] (discharge)	Day 8 -1 day	Day 14 ±2 days	Day 29 ±3 days	ET

[f] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day -1, vital signs will be time-matched (±5 minutes) to the Day 1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before dosing.

[g] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP 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] Hepatitis panel, including HBsAg and anti-HCV.

[n] Serum pregnancy test for female subjects only.

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

[p] Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-7, 7-12, and 12-24 hours.

[q] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, at ET (if applicable), and at follow-up visits on Day 8, Day 14, and Day 29. If ADAs are present, subjects may be asked to return for additional sample collection. The sampling time points will be same for all subjects dosed with either placebo or study drug.

[r] 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]

3.2 Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and Early Termination

3.2.1 Overall Schedule of Study Procedures for Part 2

Table 3.b Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and ET

	Days															
	Screening	-2 [a]	-1	Dosing						6	7	8	9 (Discharge)	Follow-up Visit Day 14 ±2 days	Follow-up Visit Day 29 ±3 days	
	-28 to -3			Pre dose	1	2	3	4	5							ET
Administrative Procedures																
Informed consent	X															
Inclusion/exclusion criteria	X	X		X												
Medical history/demographics	X															
Prior and concomitant medications	X----------Continuous review----------X															
Clinic Procedures/Assessments																
Full physical examination	X	X								X [b]			X [b]			X
Height	X															
Weight and BMI	X	X														
Vital signs [c]	X		X	X	X	X	X	X	X	X			X	X	X	X
Standing BP and pulse [d]	X		X	X	X	X	X	X	X	X						
12-Lead ECGs	X	X			X								X			
ECG telemetry (12-lead)		X [e]		X---------- Continuous ---------- X												
Telemetry extraction [f]			X	X	X	X	X	X	X	X						
TAK-510/placebo administration [g]					X	X	X	X	X							

Table 3.b Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and ET

	Days															
	Screening	**-2** [a]	**-1**	**Dosing**						**6**	**7**	**8**	**9 (Discharge)**	**Follow-up Visit Day 14 ±2 days**	**Follow-up Visit Day 29 ±3 days**	
	-28 to -3			**Pre dose**	**1**	**2**	**3**	**4**	**5**							**ET**
AE monitoring	X	X	X----------Continuous----------X													
Laboratory Procedures/Assessments																
Safety laboratory collection [h]	X		X	X	X	X		X		X			X	X	X	X
LFTs							X									
Serum sample for CK [i]				X	X								X			X
Glucose finger stick [j]				X	X	X	X	X	X							
Urine drug screen	X	X														
Alcohol breath test		X														
Cotinine test	X	X														
Hepatitis screen [k]	X															
HIV test	X															
βhCG (pregnancy) test [l]	X	X											X			X
Serum FSH test [m]	X															
PK Evaluations																
Plasma sample for TAK-510 PK				X	X	X	X	X	X	X	X	X	X			X
Plasma sample for metID				X	X	X			X	X						X
Urine sample for TAK-510 PK				X	X				X	X						
Immunogenicity and Biomarkers																
Serum sample for immunogenicity [n]				X								X		X	X	X

Table 3.b Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and ET

	Days														
	Screening	-2 [a]	-1	Dosing						6	7	8	9 (Discharge)	Follow-up Visit Day 14 ±2 days	Follow-up Visit Day 29 ±3 days	
	-28 to -3			Pre dose	1	2	3	4	5							ET
Blood sample for DNA (optional) [o]													X			X
[redacted]																
Other																
Confinement [r]		X----------													----------X	

ADA: antidrug antibodies; AE: adverse event; ALT: alanine aminotransferase; ALP: alkaline phosphatase; anti-HCV: antibodies to hepatitis C virus; AST: aspartate aminotransferase; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; GGT: gamma-glutamyl transferase; [redacted]; HBsAg: hepatitis B surface antigen; LFT: liver function test; metID: metabolite identification; MRD: multiple rising dose; PK: pharmacokinetic; MRD: multiple rising dose.

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

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

[c] Vital signs will include body temperature, BP, respiratory rate, and pulse. On Day -1 and on dosing days, vital signs will be collected as described in Table 3.c (Part 2 for MRD Screening Through Day 1 Assessments), Table 3.d (Part 2 for MRD Days 2 to 4 Assessments), and Table 3.e (Part 2 for MRD Day 5 Through Day 9 Assessments, Follow-Up, and ET).

[d] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day -1, vital signs will be time-matched (±5 minutes) to the Day 1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

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

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

[g] Dosing regimen for TAK-510/placebo will be determined based on data from Part 1.

[h] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters. During Part 2 (MRD), if a LFT (includes ALP, ALT, AST, GGT, or total bilirubin) is

Table 3.b Part 2 for MRD Cohorts 13 to 17 and 26 to 28: Screening Through Day 9, Follow-Up, and ET

	Days														
	Screening	-2 [a]	-1	Dosing						6	7	8	9 (Discharge)	Follow-up Visit Day 14 ±2 days	Follow-up Visit Day 29 ±3 days	
	-28 to -3			Pre dose	1	2	3	4	5							ET

elevated, a repeat test should be performed before the next dose of study drug is administered.

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

[j] Glucose finger stick will be performed at predose and ~1 hours postdose on each day.

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

[l] Serum pregnancy tests for female subjects only.

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

[n] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 8, at ET (if applicable), and at follow-up visits on Day 14 and Day 29. If ADAs are present, subjects may be asked to return for additional sample collections. The sampling time points will be the same for all subjects dosed with either placebo or study drug.

[o] 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]

3.2.2 Part 2 for MRD Screening Through Day 1 Assessments

Table 3.c Part 2 for MRD Screening Through Day 1 Assessments

	Day -28 to -3	Day -2 [a]	Scheduled Time																								
			Day -1 (Hours)												Day 1 (Hours)												
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24 [b]
Administrative Procedures																											
Informed consent	X																										
Inclusion/exclusion criteria	X	X													X												
Medical history/ demographics	X																										
Prior and concomitant medications		X----------Continuous review----------X																									
Clinic Procedures/Assessments																											
Full physical examination	X	X																									
Height	X																										
Weight and BMI	X	X																									
Temperature and respiratory rate	X	X													X				X		X						X
BP and pulse [c]	X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [d]	X			X		X		X		X	X			X	X		X		X		X		X	X			X
12-lead ECGs	X	X													X												X
ECG telemetry (12-lead)		X---------- Continuous monitoring [e] ---------- X													X ---------- Continuous monitoring ---------- X											
Telemetry extraction [f]			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
TAK-510/placebo administration																X												

Table 3.c Part 2 for MRD Screening Through Day 1 Assessments

	Day -28 to -3	Day -2 [a]	Scheduled Time																							
AE monitoring		X----------Continuous review----------X																								
			Day -1 (Hours)												Day 1 (Hours)											
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24 [b]
Laboratory Procedures/Assessments																											
Safety laboratory collection [g]	X							X							X						X						
Serum sample for CK [h]															X												X
Glucose finger stick															X					X							
Urine drug screen	X	X																									
Alcohol breath test		X																									
Cotinine test	X	X																									
Hepatitis screen [i]	X																										
HIV test	X																										
βhCG (pregnancy) test [j]	X	X																									
Serum FSH test [k]	X																										
PK Evaluations																											
Plasma sample for TAK-510 PK															X		X	X	X	X	X	X	X	X	X	X	X
Plasma sample for metID															X		X			X	X		X		X		X
Urine sample for TAK-510 PK [l]															X	X					X		X		X		
Immunogenicity and Biomarkers																											
Serum sample for immunogenicity															X												
[redacted]																											

Table 3.c Part 2 for MRD Screening Through Day 1 Assessments

	Day -28 to -3	Day -2 [a]	Scheduled Time
[redacted]			
Other			
Confinement [o]		X	----------X

AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; FSH: follicle-stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; LFT: liver function test; metID: metabolite identification; PK: pharmacokinetic.

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

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

[c] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day -1, vital signs will be time-matched (±5 minutes) to the Day 1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[d] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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

[g] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters. During Part 2 (MRD), if a LFT is elevated, a repeat test should be performed before the next dose of study drug is administered.

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

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

[j] Serum pregnancy tests for female subjects only.

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

[l] Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-7, 7-12, and 12-24 hours.

[redacted]

[o] Subjects will be confined.

3.2.3 Part 2 for MRD Days 2 to 4 Assessments

Table 3.d Part 2 for MRD Days 2 to 4 Assessments

	Scheduled Time												
	Days 2-4 (Hours)												
	Predose	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**7**	**10**	**12**	**16**	**24 [a]**
Administrative Procedures													
Prior and concomitant medications	X----------Continuous review----------X												
Clinic Procedures/Assessments													
Temperature and respiratory rate	X				X		X						X
BP and pulse [b]	X		X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [c]	X		X		X		X		X	X			X
TAK-510/placebo administration [d]		X											
ECG telemetry (12-lead)	X----------Continuous monitoring----------X												
Telemetry extraction	X												
AE monitoring	X----------Continuous review----------X												
Laboratory Procedures/Assessments													
Safety laboratory collection [e]	X [f]												
LFTs	X [g]												
Glucose finger stick	X					X							
PK Evaluations													
Plasma sample for TAK-510 PK	X [h]												
Other													
Confinement [i]	X----------X												

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

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

[b] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will

Table 3.d Part 2 for MRD Days 2 to 4 Assessments

	Scheduled Time												
	Days 2-4 (Hours)												
	Predose	0	0.5	1	2	3	4	5	7	10	12	16	24 [a]

be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[c] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP 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.).

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

[e] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters. During Part 2 (MRD), if a LFT is elevated, a repeat test should be performed before the next dose of study drug is administered.

[f] Safety laboratory assessments (including hematology, serum chemistry, and urinalysis parameters) will be performed on Day 2 and Day 4.

[g] Sampling for LFTs will be performed on Day 3.

[h] Blood samples for PK may be drawn 10 minutes before dosing.

[i] Subjects will be confined.

3.2.4 Part 2 for MRD Day 5 Through Day 9 Assessments, Follow-Up, and Early Termination

Table 3.e Part 2 for MRD Day 5 Through Day 9 Assessments, Follow-Up, and ET

	Scheduled Time																	
	Day 5 (Hours)												Day 6	Day 7	Day 8	Day 9 (Discharge)	Follow-up Visit Day 14 ±2 days	Follow-up Visit Day 29 ±3 days	ET
	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	48	72	96			
Prior and concomitant medications	X----------Continuous review----------X																		
Clinic Procedures/Assessments																			
Full physical examination													X [a]			X [a]			X
Temperature and respiratory rate	X				X		X						X			X			X
BP and pulse [b]	X		X	X	X	X	X	X	X	X	X	X	X			X	X	X	X
Standing BP and pulse [c]	X		X		X		X		X	X			X						X
TAK-510/placebo administration [d]		X																	
12-lead ECGs																X			
ECG telemetry (12-lead)	X----------Continuous----------X																		
Telemetry extraction	X		X	X	X	X	X	X	X	X	X	X	X						
AE monitoring	X----------Continuous----------X																		
Laboratory Procedures/Assessments																			
Safety laboratory collection [e]													X			X	X	X	X
Serum sample for CK [f]																X			X
Glucose finger stick	X					X													
βhCG (pregnancy) test [g]																X			X

Table 3.e Part 2 for MRD Day 5 Through Day 9 Assessments, Follow-Up, and ET

	Scheduled Time																		
	Day 5 (Hours)												Day 6	Day 7	Day 8	Day 9 (Discharge)	Follow-up Visit Day 14 ±2 days	Follow-up Visit Day 29 ±3 days	ET
	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	48	72	96			
PK Evaluations																			
Plasma sample for TAK-510 PK [h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Plasma sample for metID	X [h]		X			X	X		X		X		X						X
Urine sample for TAK-510 PK [i]		X					X		X		X								
Immunogenicity and Biomarkers																			
Serum sample for immunogenicity [j]															X		X	X	X
Blood sample for DNA (optional) [k]																X			X
[redacted]																			
Other																			
Confinement [m]	X----------X																		

ADA: antidrug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; metID: metabolite identification; PK: pharmacokinetic.

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

[b] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[c] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP 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.).

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

Table 3.e Part 2 for MRD Day 5 Through Day 9 Assessments, Follow-Up, and ET

	Scheduled Time																	
	Day 5 (Hours)												Day 6	Day 7	Day 8	Day 9 (Discharge)	Follow-up Visit Day 14 ±2 days	Follow-up Visit Day 29 ±3 days	ET
	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	48	72	96			

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

[f] 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.

[g] Serum pregnancy tests for female subjects only.

[h] Blood samples for PK and metID may be drawn 10 minutes before dosing.

[i] Urine PK samples will be collected at the following time intervals: predose, 0-4, 4-7, 7-12, and 12-24 hours.

[j] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 8, at ET (if applicable), and at follow-up visits on Day 14 and Day 29. If ADAs are present, subjects may be asked to return for additional sample collection. All subjects receiving either study drug or placebo will have the same collection time points.

[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]

[m] Subjects will be confined.

3.3 Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and Early Termination

3.3.1 Overall Schedule of Study Procedures for Part 3

Table 3.f Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and ET

	Days																	
	Screen			Dosing														
	-28 to -3	-2 [a]	-1	Pre dose	1	2	3	4	5	6	7	8 (Discharge)	9 to 13 Wash out [b]	Day 13 ±1 day (Confine again)	Day 14 ±1 day (Single Dose)	Day 15 ±1 day (Discharge)	Follow-up Visit Day 29 ±3 days	ET
Administrative Procedures																		
Informed consent	X																	
Inclusion/exclusion criteria	X	X		X														
Medical history/demographics	X																	
Prior and concomitant medications	X----------Continuous review----------X																	
Clinic Procedures/Assessments																		
Full physical examination	X	X										X [c]		X		X [c]	X	X
Height	X																	
Weight and BMI	X	X													X			
Vital signs [d]	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Standing BP and pulse [e]	X		X	X	X	X	X	X	X	X	X			X	X	X		
12-Lead ECGs	X	X			X							X		X		X		
ECG telemetry (12-lead)		X [f]		X ---------- Continuous ---------- X											X			
Telemetry extraction [g]			X	X	X	X	X	X	X	X	X	X			X	X		

Table 3.f Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and ET

	Days																	
	Screen			Dosing														
	-28 to -3	-2 [a]	-1	Pre dose	1	2	3	4	5	6	7	8 (Discharge)	9 to 13 Washout [b]	Day 13 ±1 day (Confine again)	Day 14 ±1 day (Single Dose)	Day 15 ±1 day (Discharge)	Follow-up Visit Day 29 ±3 days	ET
TAK-510/placebo administration [h]					X	X	X	X	X	X	X				X			
AE monitoring	X	X	X----------Continuous----------X															
Laboratory Procedures/Assessments																		
Safety laboratory collection [i]	X		X	X	X	X		X		X	X	X		X	X	X	X	X
LFTs							X		X									
Serum sample for CK [j]				X	X							X						X
Glucose finger stick [k]				X	X	X	X	X	X	X	X				X			
Urine drug screen	X	X												X				
Alcohol breath test		X												X				
Cotinine test	X	X												X				
Hepatitis screen [l]	X																	
HIV test	X																	
βhCG (pregnancy) test [m]	X	X										X		X				X
Serum FSH test [n]	X																	
PK Evaluations																		
Plasma sample for TAK-510 PK				X	X	X	X	X	X	X	X	X			X	X		X
Immunogenicity and Biomarkers																		
Serum sample for immunogenicity [o]				X								X			X		X	X

Table 3.f Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and ET

	Days																
	Screen			Dosing													
	-28 to -3	-2 [a]	-1	Pre dose	1	2	3	4	5	6	7	8 (Discharge)	9 to 13 Washout [b]	Day 13 ±1 day (Confine again)	Day 14 ±1 day (Single Dose)	Day 15 ±1 day (Discharge)	Follow-up Visit Day 29 ±3 days	ET
Blood sample for DNA (optional) [p]												X						X
[redacted]																		
[redacted]																		
Other																		
Confinement [s]		X----------X												X----------X				

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

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

[b] Based on emerging safety, tolerability, and available PK data, subjects may be confined during washout at the discretion of the investigator in consultation with the sponsor and medical monitor. Duration of washout period may be shortened or lengthened in Cohorts 19 and 20 based on emerging data, refer to Section 6.1.4 for confinement and discharge during redosing interval.

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

[d] Vital signs will include body temperature, BP, respiratory rate, and pulse. On Day -1 and on dosing days, vital signs will be collected as described in Table 3.g (Part 3 Screening Through Day 1 Assessments), Table 3.h (Part 3 Days 2 to 6 Assessments), Table 3.i (Part 3 Day 7 and Day 8 Assessments), and Table 3.j (Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and ET).

[e] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day -1, vital signs will be time-matched (±5 minutes) to the Day 1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

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

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

Table 3.f Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and ET

	Days																
	Screen			Dosing													
	-28 to -3	-2 [a]	-1	Pre dose	1	2	3	4	5	6	7	8 (Discharge)	9 to 13 Washout [b]	Day 13 ±1 day (Confine again)	Day 14 ±1 day (Single Dose)	Day 15 ±1 day (Discharge)	Follow-up Visit Day 29 ±3 days	ET

[h] Dosing regimen for TAK-510/placebo will be determined based on data from Part 1.

[i] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters. During Part 3, if an LFT is elevated, a repeat test should be performed before the next dose of study drug is administered.

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

[k] Glucose finger stick will be performed at predose and ~1 hours postdose on each day.

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

[m] Serum pregnancy tests for female subjects only.

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

[o] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 8, at ET (if applicable), predose on Day 14, and at the follow-up visit on Day 29. If ADAs are present, subjects may be asked to return for additional sample collections. All subjects receiving either study drug or placebo will have the same collection time points.

[p] 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]

3.3.2 Part 3 Screening Through Day 1 Assessments

Table 3.g Part 3 Screening Through Day 1 Assessments

	Day -28 to -3	Day -2 [a]	Scheduled Time																							
			Day -1 (Hours)												Day 1 (Hours)											
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24 [b]
Administrative Procedures																											
Informed consent	X																										
Inclusion/exclusion criteria	X	X													X												
Medical history/demographics	X																										
Previous and concomitant medications		X----------Continuous review----------X																									
Clinic Procedures/Assessments																											
Full physical examination	X	X																									
Height	X																										
Weight and BMI	X	X																									
Temperature and respiratory rate	X	X													X				X		X						X
BP and pulse [c]	X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [d]	X			X		X		X		X	X			X	X		X		X		X		X		X	X	X
12-lead ECGs	X	X													X												X
ECG telemetry (12-lead)		X ----------Continuous monitoring [e] ---------- X													X ----------Continuous monitoring ---------- X											
Telemetry extraction [f]			X				X	X	X						X					X	X	X					
TAK-510/placebo administration																X											
AE monitoring		X----------Continuous review----------X																									
Laboratory Procedures/Assessments																											
Safety laboratory collection [g]	X							X							X						X						
Serum sample for CK [h]															X												X
Glucose finger stick															X					X							
Urine drug screen	X	X																									
Alcohol breath test		X																									
Cotinine test	X	X																									

Table 3.g Part 3 Screening Through Day 1 Assessments

	Day -28 to -3	Day -2 [a]	Scheduled Time																								
			Day -1 (Hours)												Day 1 (Hours)												
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24 [b]
Hepatitis screen [i]	X																										
HIV test	X																										
βhCG (pregnancy) test [j]	X	X																									
Serum FSH test [k]	X																										
PK Evaluations																											
Plasma sample for TAK-510 PK															X					X	X	X					
Immunogenicity and Biomarkers																											
Serum sample for immunogenicity															X												
[redacted]																											
Other																											
Confinement [n]		X----------X																									

AE: adverse event; anti-HCV: antibodies to hepatitis C virus; βhCG: beta-human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; FSH: follicle-stimulating hormone; [redacted]; HBsAg: hepatitis B surface antigen; LFT: liver function test.

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

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

[c] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. On Day -1, vital signs will be time-matched (±5 minutes) to the Day 1 clock time (ie, time-matched baseline). At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before blood sampling.

[d] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

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

Table 3.g Part 3 Screening Through Day 1 Assessments

	Day -28 to -3	Day -2 [a]	Scheduled Time																							
			Day -1 (Hours)												Day 1 (Hours)											
	Screening		0	0.5	1	2	3	4	5	7	10	12	16	24 [b]	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24 [b]

[g] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters. During Part 3, if a LFT is elevated, a repeat test should be performed before the next dose of study drug is administered.

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

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

[j] Serum pregnancy tests for female subjects only.

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

[redacted]

Subjects will be confined.

3.3.3 Part 3 Days 2 to 6 Assessments

Table 3.h Part 3 Days 2 to 6 Assessments

	Scheduled Time												
	Days 2-6 (Hours)												
	Pre dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**7**	**10**	**12**	**16**	**24 [a]**
Administrative Procedures													
Previous and concomitant medications	X----------Continuous review----------X												
Clinic Procedures/Assessments													
Temperature and respiratory rate	X				X		X						X
BP and pulse [b]	X		X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [c]	X		X		X		X		X	X			X
TAK-510/placebo administration [d]		X											
ECG telemetry (12-lead)	X----------Continuous monitoring----------X												
Telemetry extraction	X					X [e]	X [e]	X [e]					
AE monitoring	X----------Continuous review----------X												
Laboratory Procedures/Assessments													
Safety laboratory collection [f]	X [g]												
LFTs	X [h]												
Glucose finger stick	X					X							
PK Evaluations													
Plasma sample for TAK-510 PK	X [i]					X [j]	X [j]	X [j]					
Other													
Confinement [k]	X----------X												

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

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

[b] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured

Table 3.h Part 3 Days 2 to 6 Assessments

	Scheduled Time												
	Days 2-6 (Hours)												
	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24 [a]

within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[c] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP 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.).

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

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

[f] Safety laboratory will include hematology, serum chemistry, and urinalysis parameters. During Part 3, if a LFT is elevated, a repeat test should be performed before the next dose of study drug is administered.

[g] Safety laboratory assessments (including hematology, serum chemistry, and urinalysis parameters) will be performed on Day 2, Day 4, and Day 6.

[h] Samples for LFTs will be performed on Day 3 and Day 5.

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

[j] Samples will be collected only on day(s) when the dose has changed from the previous day. Sampling times may change based on emerging data from Part 1.

[k] Subjects will be confined.

3.3.4 Part 3 Day 7 and Day 8 Assessments

Table 3.i Part 3 Day 7 and Day 8 Assessments

	Scheduled Time													
	Day 7 (Hours)													Day 8 (Discharge)
	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30
Previous and concomitant medications	X----------Continuous review----------X													
Clinic Procedures/Assessments														
Full physical examination														X [a]
Temperature and respiratory rate	X				X		X						X	X
BP and pulse [b]	X		X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [c]	X		X		X		X		X	X			X	
TAK-510/placebo administration [d]		X												
12-lead ECG														X
ECG telemetry (12-lead)	X----------Continuous----------X													
Telemetry extraction	X					X	X	X					X	X
AE monitoring	X----------Continuous----------X													
Laboratory Procedures/Assessments														
Safety laboratory collection [e]	X													X
Serum sample for CK [f]														X
Glucose finger stick	X					X								
βhCG (pregnancy) test [g]														X
PK Evaluations														
Plasma sample for TAK-510 PK	X [h]					X	X	X					X	X
Immunogenicity and Biomarkers														
Serum sample for immunogenicity [i]														X
Blood sample for DNA (optional) [j]														X

Table 3.i Part 3 Day 7 and Day 8 Assessments

	Scheduled Time													
	Day 7 (Hours)													Day 8 (Discharge)
	Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30
[redacted]														
Other														
Confinement [1]	X----------													----------X

AE: adverse event; βhCG: beta human chorionic gonadotropin; BP: blood pressure; CK: creatine kinase; ECG: electrocardiogram; ET: early termination; PK: pharmacokinetic.

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

[b] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[c] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP 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.).

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

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

[f] 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.

[g] Serum pregnancy tests for female subjects only.

[h] Plasma sample for TAK-510 PK may be drawn 10 minutes before dosing.

[i] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 8, at ET (if applicable), predose on Day 14, and at the follow-up visit on Day 29. If ADAs are present, subjects may be asked to return for additional sample collections. All subjects receiving either study drug or placebo will have the same collection time points.

[j] If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected at any time on Day 8 (discharge) or at ET (if applicable; see Table 3.j).

[redacted]

[l] Subjects will be confined.

3.3.5 Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and Early Termination

Table 3.j Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and ET

	Days 9 to 13	Day 13	Scheduled Time															
			Day 14 (Hours)														Follow-up Visit Day 29 ±3 days	ET
	Washout [a]		Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30 (Discharge) (Day 15)		
Administrative Procedures																		
Previous and concomitant medications	X	X----------Continuous review----------X																
Clinic Procedures/Assessments																		
Full physical examination		X														X [b]	X	X
Weight and BMI [c]		X																
Temperature and respiratory rate		X	X				X		X						X			
BP and pulse [c]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP and pulse [d]		X	X		X		X		X		X	X			X	X		
12-lead ECGs		X														X		X
ECG telemetry (12-lead)			X----------Continuous monitoring----------X															
Telemetry extraction			X			X		X	X	X			X		X	X		
TAK-510/placebo administration				X														
AE monitoring	X	X----------Continuous review----------X																X
Laboratory Procedures/Assessments																		
Safety laboratory collection [e]		X	X												X	X	X	X
Serum sample for CK [f]																		X
Glucose finger stick			X					X										
Urine drug screen		X																
Alcohol breath test		X																
Cotinine test		X																
βhCG (pregnancy) test [g]		X																X

Table 3.j Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and ET

	Days 9 to 13	Day 13	Scheduled Time														
			Day 14 (Hours)													Follow-up Visit Day 29 ±3 days	ET
	Washout [a]		Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30 (Discharge) (Day 15)	
PK Evaluations																	
Plasma sample for TAK-510 PK			X			X		X	X	X			X		X	X		X
Immunogenicity and Biomarkers																	
Serum sample for immunogenicity [h]			X														X	X
[redacted]																		
Other																		
Confinement [k]			X----------													----------X		

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

[a] Based on emerging safety, tolerability, and available PK data, subjects may be confined during washout at the discretion of the investigator in consultation with the sponsor and medical monitor. Duration of washout period may be shortened or lengthened in Cohorts 19 and 20 based on emerging data.

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

[c] For BMI, any assessment on Days 13 through 15 will be acceptable as noted also in Table 3.f. All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency (ie, a difference >10 beats per minute in heart rate or a difference >10 mm Hg in systolic or diastolic BP) between assessments (see Section 9.2.4 for details). If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. At predose, vital signs will be measured within approximately 1 hour before the first dose. All BP and pulse assessments must be completed before PK blood sampling.

[d] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP is <85 mm Hg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision). Day 1 time points will be time-matched (±5 minutes) to the Day -1 clock time (ie, time-matched baseline).

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

[f] 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.

[g] Serum pregnancy tests for female subjects only.

Table 3.j Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and ET

	Days 9 to 13	Day 13	Scheduled Time														
			Day 14 (Hours)													Follow-up Visit Day 29 ±3 days	ET
	Washout [a]		Pre dose	0	0.5	1	2	3	4	5	7	10	12	16	24	30 (Discharge) (Day 15)	

[h] Immunogenicity serum samples for ADA testing will be taken at predose on Day 1, on Day 8, at ET (if applicable), predose on Day 14, and at the follow-up visit on Day 29. If ADAs are present, subjects may be asked to return for additional sample collections. All subjects receiving either study drug or placebo will have the same collection time points.

[i] If subjects have provided consent for the optional DNA collection, blood samples should be collected and can be collected on Day 8 (discharge; see Table 3.i) or at ET (if applicable).

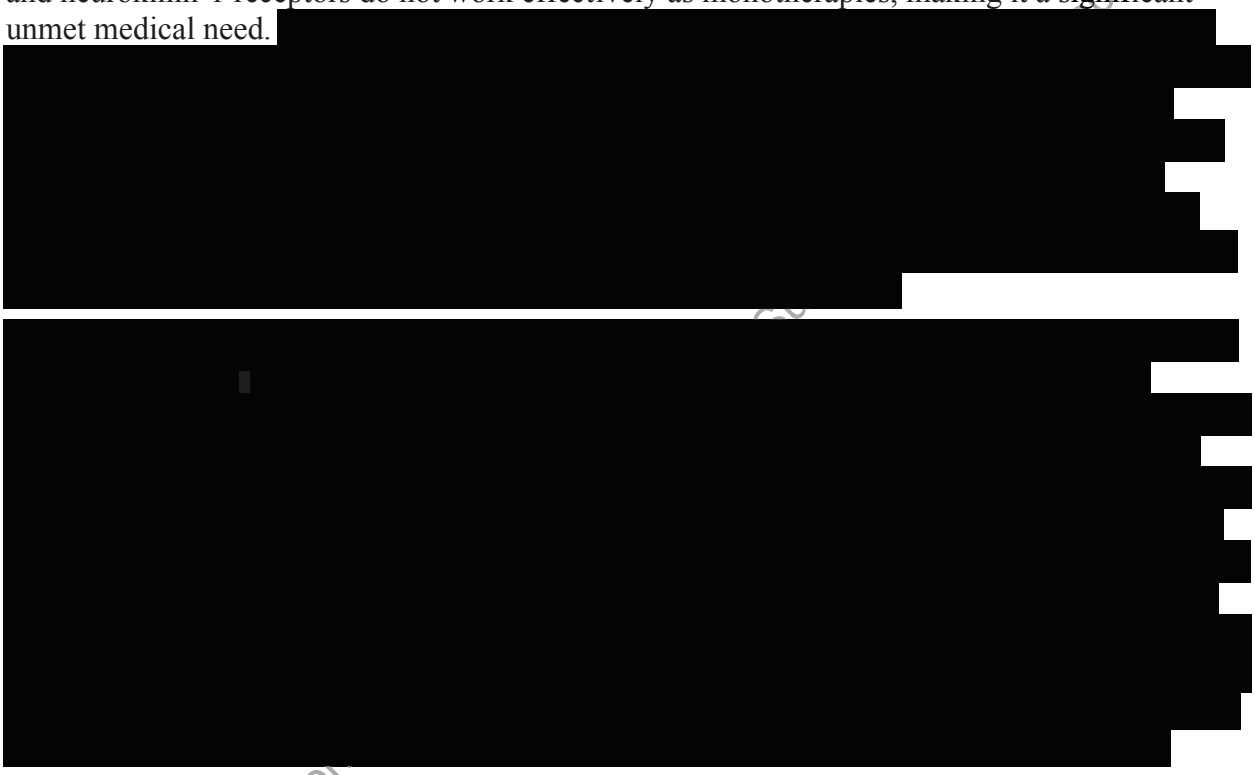
[redacted]

[k] Subjects will be confined.

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 serotonin 3 (5-HT3) and neurokinin-1 receptors do not work effectively as monotherapies, making it a significant unmet medical need.



4.2 Rationale for the Proposed Study

The purpose of this first-in-human (FIH) study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-510 in healthy subjects to support further development of TAK-510. The study will be conducted in 3 parts: SRD via SC administration will be assessed in Part 1, and repeat-dose SC administration will be assessed in Part 2 (MRD) and Part 3 (dose titration and redosing after washout).

4.3 Benefit/Risk Profile

This study represents the first study in humans with TAK-510.

The main objective of this study is to assess the safety and tolerability of TAK-510 in healthy subjects; as such, no clinical benefit is expected for study participants.

The potential risks of TAK-510 include HR increase, decreased BP, body weight loss, renal effects (proximal tubule vacuolation), elevated liver enzymes, injection site reaction, hypersensitivity, immunogenicity, postural hypotension, and myalgia. These potential risks are based on safety observations from the Good Laboratory Practice (GLP)-compliant nonclinical safety pharmacology and repeat-dose toxicity studies conducted with TAK-510, and clinical experience with TAK-510 [redacted] (refer to the TAK-510 Investigator's Brochure for additional details).

In nonclinical safety studies, the magnitude and duration of HR and BP changes in dogs were equivalent [redacted] at predicted therapeutic doses (sponsor data on file). Safety results from the [redacted] FIH study demonstrated a transient increase in HR within the first hour of [redacted] dosing as well as decreases in systolic BP and diastolic BP that were more prominent with postural changes (orthostatic) in some individuals within the first 2 hours postdosing ([redacted]; refer to the TAK-510 Investigator's Brochure for additional details). Postural hypotension is an identified risk [redacted] Given the findings of decreased BP and increased HR [redacted], it is hypothesized that TAK-510 causes vasodilation which leads to decreased BP and increased HR.

Audited draft results from a definitive rat embryo-fetal development study indicate fetal malformations were observed in a single fetus at each of the mid and high dose [redacted]; the no-observed-adverse-effect level (NOAEL) for embryo-fetal development [redacted] (refer to investigator's brochure, Section 4.3.6 for additional details).

[redacted] All of these factors could contribute to the risk of immunogenicity and thus an assessment of antidrug antibodies (ADA) in all parts of the study 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-510 formulation or with a history of significant multiple and/or severe allergies are excluded from this study. Subjects will be evaluated for the development of ADA as part of the study. The potential risks related to HR increase, decreased BP, body weight loss, renal effects (proximal tubule vacuolation), 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.

In addition to the potential risks associated with study drug administration, there is minimal risk associated with study procedures, including scheduled periodic phlebotomy (limited to <575 mL). Total blood sampling volumes will not exceed approximately 319 mL (over 7 days of confinement) in Part 1, approximately 505 mL (over 11 days of confinement) in Part 2, and approximately 573 mL (over 10 days of confinement followed by 3 days of confinement after washout) in Part 3. The maximum volume of blood sampling on any single day is approximately 117 mL in Part 1, approximately 147 mL in Part 2, and approximately 82 mL in Part 3.

To minimize the risks to the subjects in this study, the sponsor considers the following measures to be appropriate: selecting TAK-510 doses with appropriate safety margins based on nonclinical study data; managing study eligibility criteria; excluding women of childbearing potential; 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. Overall, the proposed risk mitigation plan is adequate to monitor subjects enrolled in the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Study Primary Objective

The primary objective of the study is:

- Part 1:
  - To characterize the safety and tolerability of single SC doses of TAK-510 in healthy subjects.
- Part 2:
  - To characterize the safety and tolerability of multiple SC doses of TAK-510 in healthy subjects.
- Part 3:
  - To characterize the safety and tolerability of multiple SC dose regimens of TAK-510 that include titration from lower doses in healthy subjects.

5.1.2 Study Secondary Objectives

The secondary objectives of the study are:

- Part 1:
  - To characterize the PK of TAK-510 in plasma following single SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-510 following single SC doses in healthy subjects.
  - To characterize the PK of TAK-510 in urine following single SC doses in healthy subjects.
- Part 2:
  - To characterize the PK of TAK-510 in plasma following multiple SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-510 following multiple SC doses in healthy subjects.
  - To characterize the PK of TAK-510 in urine following multiple SC doses in healthy subjects.
- Part 3:
  - To characterize the safety and tolerability of single SC rechallenge doses of TAK-510 after a washout from multiple SC dose regimens that include titration from lower doses in healthy subjects.
  - To assess the immunogenicity of TAK-510 following multiple SC dose regimens that include titration from lower doses, washout, and redosing in healthy subjects.

5.1.3 Study Exploratory Objectives

Exploratory endpoints of this study include:

[redacted]

  - To characterize the PK of TAK-510 in plasma following multiple SC doses and dosing schedules in healthy subjects.

5.2 Endpoints

5.2.1 Primary Endpoint

- All parts of the study:
  - The primary safety 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:

- Part 1: plasma PK parameters for TAK-510
  - Maximum observed plasma concentration (C_{max}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Terminal disposition phase half-life ($t_{1/2z}$).
  - Apparent clearance after extravascular administration (CL/F).
  - Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Part 2: plasma PK parameters for TAK-510 on Day 1
  - C_{max}, t_{max}, and area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_{τ}).
- Part 2: plasma PK parameters for TAK-510 at steady state
  - 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}), accumulation ratio based on AUC_{τ} ($R_{ac[AUC]}$), calculated as AUC_{τ} at steady state/AUC_{τ} after a single dose, and accumulation ratio based on C_{max} ($R_{ac[Cmax]}$), calculated as C_{max} at steady state/C_{max} after a single dose.
- Parts 1 and 2: urine PK parameters for TAK-510
  - 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) at steady state (Ae_{τ}).
  - Fraction of administered dose of drug excreted from urine from time 0 to time t ($f_{e,t}$).
  - Renal clearance (CL_R).

- Part 3:
  - Safety and tolerability of single SC rechallenge doses after a washout from multiple SC dose regimens of TAK-510 as assessed through vital signs, ECG, laboratory assessments, and AEs.
- All parts of the study:
  - Status of subject's ADA assessment (ie, ADA-negative or ADA-positive, and low or high ADA titer).

5.2.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

[redacted]

- Part 3 includes 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, tolerability, and PK of TAK-510 in healthy subjects.

The study will consist of 3 parts:

- Part 1 is a FIH, randomized, double-blind, placebo-controlled, SRD design to assess the safety, immunogenicity, tolerability, and PK of TAK-510 in healthy subjects. Up to 17 cohorts may be enrolled.
- Part 2 is a randomized, double-blind, placebo-controlled, MRD design to assess the safety, immunogenicity, tolerability, and PK of TAK-510 in healthy subjects. Up to 8 cohorts may be tested in independent subject cohorts.
- Part 3 is a randomized, double-blind, placebo-controlled, multiple-dose, dose titration and redosing design to assess the safety, immunogenicity, tolerability, and PK of TAK-510 in healthy subjects. Up to 3 cohorts may be tested in independent subject cohorts using a dose titration design, followed by redosing with a single dose of study drug after a 7-day washout (168 hours after the previous dose).

TAK-510 and matching placebo will be administered SC. Safety will be assessed by monitoring for AEs, vital signs, ECG/telemetry, safety laboratory assessments after each dose, and

immunogenicity. PK sampling times and scheme may vary based on emerging safety, tolerability and PK data, but the maximal number of samples or the maximum time point will not change. Subjects may not participate in more than 1 part or dosing cohort of the study.

An overview of treatment cohorts is outlined in Table 6.a. A schematic of the study design is presented in Section 2.0. The schedule of study procedures is presented in Section 3.0.

Table 6.a Overview of Treatment Cohorts

Cohort	Regimen	Treatment	
Part 1			
		TAK-510	**Placebo**
1	SRD [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
21		6	2
22		6	2
23		6	2
24		6	2
25		6	2
Part 2			
		TAK-510	**Placebo**
13	MRD	6	2
14		6	2
15		6	2
16		6	2
17		6	2
26		6	2
27		6	2
28		6	2
Part 3			
		TAK-510	**Placebo**
18	Dose Titration, Washout, Redosing	6	2
19		6	2
20		6	2

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

[a] Up to 17 doses may be explored with a maximum escalation factor between cohorts of 5-fold at lower exposures and 2-fold at high exposures.

6.1.2 Part 1: SRD Cohorts 1 to 12 and 21 to 25

Part 1 will consist of up to 17 sequential cohorts with 8 healthy subjects per cohort. Subjects in each cohort will be randomly assigned to receive a single dose of TAK-510 or matching placebo via SC administration in a 3:1 ratio in a double-blind manner. Up to approximately 136 healthy subjects will be randomized in Part 1 (approximate value do 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. Baseline HR and BP assessments, including postural measurements, will be taken on Day -1, and Day -1 HR and BP assessments will be time-matched to the Day 1 assessments. Subjects will be dosed with TAK-510 or matching placebo on Day 1 after a minimum of 8 hours of fasting. Subjects will be confined for 96 hours after dosing (ie, they can be discharged after the 96-hour PK sample). Assessments of postural hypotension will be measured predose and at 0.5, 2, 4, 7, 10, 24, 48, 72, and 96 hours after the dose on Day 1, as well as at time-matched time points on Day -1. Blood samples for assessment of TAK-510 plasma concentrations will be collected up to 96 hours postdose. Urine will be collected up to 24 hours postdose. [redacted] Optional DNA samples will also be collected from subjects that provide consent for collection through a separate procedure. DNA samples can be collected at any time on the day of discharge or at early termination (if applicable). Samples for immunogenicity will be collected at discharge and at follow-up visits on Days 14 and 29.

Cohort 1 will use a staggered dosing scheme. After dosing the first 2 subjects (1 receiving TAK-510 and 1 receiving placebo), the investigator will review all available safety and tolerability data up to 24 hours postdose before dosing the remaining subjects in the cohort. A staggered dosing approach may be used for subsequent cohorts in Part 1 (if decided in the dose escalation meeting). Except the starting dose, doses may be modified based on emerging safety and available PK data during the study, but will have a corresponding dose that does not exceed the maximal defined exposure.

The exposure levels (AUC_{∞}) of TAK-510 range [redacted] with a planned maximum dose escalation factor of 5-fold between lower exposures and 2-fold at high exposures. [redacted] Doses may change 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 who drop out of the study may be replaced at the discretion of the sponsor after discussion with the investigator.

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

analyzed in the dose escalation meeting (composed of representatives from the sponsor and site study teams).

The blind may be broken for select sponsor representatives before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety considerations based on the prospectively prepared unblinding plan. Following each blinded dose cohort review and after dose escalation decisions have been made, the sponsor may be unblinded using the prospectively prepared unblinding plan, to enable further data review to inform later parts of the study.

Study Drug Administration

[redacted] The single SC dose of TAK-510 should be administered in the abdomen (at least 2 cm away from the umbilicus) followed by upper arms, then thigh, as alternative sites. In all cases, care should be taken to avoid areas of scars, moles, tattoos, or other irritated skin (eg, vitiligo, eczema, etc). TAK-510 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 pulse measurements. For additional information on study drug administration, please refer to the study pharmacy manual.

6.1.3 Part 2: MRD Cohorts 13 to 17 and 26 to 28

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 based on predicted exposure to be below that observed at the highest completed cohort in Part 1. The daily maximum exposure anticipated at steady state 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 8 ascending cohorts of healthy subjects. In each cohort, 8 healthy subjects will be randomly assigned to receive TAK-510 or matching placebo in a 3:1 ratio in a double-blind manner. Up to approximately 64 healthy subjects may be randomized in Part 2 (approximate value do not account for potential replacement of subjects who withdraw for nonsafety reasons).

Subjects will be admitted to the study unit on Day -2. Baseline HR and BP assessments will be taken on Day -1, and Day -1 HR and BP assessments will be time-matched to the Day 1 assessments. Subjects will be dosed on Day 1 in each cohort/period after a minimum of 8 hours of fasting. Subjects will be confined until Day 9, 96 hours after the Day 5 dose, to assess safety, tolerability, immunogenicity, and PK. Assessments of postural hypotension will be measured predose and at 0.5, 2, 4, 7, 10, and 24 hours after each dose, as well as at time-matched time points on Day -1. Blood samples for assessment of TAK-510 plasma concentrations will be collected up to 96 hours after the last dose. [redacted] Optional DNA samples will also be collected from subjects that provide consent for

collection through a separate procedure. DNA samples can be collected at any time on the day of discharge or at early termination (if applicable). Subjects will return after discharge for additional immunogenicity and other assessments at follow-up visits on Days 14 and 29.

In Part 2, up to 8 tolerated doses from Part 1 up to the current planned maximum exposure (AUC_∞) of 705,000 h*ng/mL will be studied in an ascending manner. The daily 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 once daily. Based on safety, tolerability, and emerging PK data from Part 1 and any available PK data from Part 2, reductions in dose and in repeat dosing duration may be implemented.

After completion of each dosing cohort, and before selecting the next dose, a blinded assessment of the safety and tolerability, laboratory results of at least 24 hours after the last dose in the cohort, and available PK data will be analyzed in the dose escalation meeting (composed of representatives from the sponsor and site study teams). At the dose escalation meeting, the starting dose in Part 2 will be decided based on emerging safety, tolerability, and available PK data from Part 1.

The blind may be broken for select sponsor representatives before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns based on the prospectively prepared unblinding plan. Following each blinded dose cohort review and after dose escalation decisions have been made, the sponsor may be unblinded using the prospectively prepared unblinding plan, to enable further data review to inform later parts of the study.

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

Study Drug Administration

In Part 2, when administering TAK-510, injection sites must be rotated. [redacted] The single SC dose of TAK-510 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 TAK-510 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 TAK-510 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 pulse measurements. For additional information on study drug administration, please refer to the study pharmacy manual.

6.1.4 Part 3: Dose Titration and Redosing Cohorts 18 to 20

The overall purpose of Part 3 is to characterize the safety and tolerability of multiple SC dose regimens of TAK-510 involving dose titration over 7 days of treatment. The intent of this study part is to enable a descriptive comparison (ie, without hypothesis testing) of tolerability findings between Part 3 cohorts and cohorts in Parts 1 and 2 with comparable exposures, to determine whether dose titration results in different tolerability. The redosing component of Part 3 is intended to provide an evaluation to assess the effects of a single rechallenge dose (after 7 days [168 hours] of washout following the 7-day treatment period) on the safety and tolerability profile (vital signs, adverse events, and other safety parameters).

Part 3 may start before the completion of Parts 1 and 2. If Part 3 is started before the completion of Part 2, the maximum daily exposure in Part 3 will be at a total daily exposure level below or at the highest completed cohort in Part 2 that has been determined to be well tolerated. Similar to Part 1 and Part 2, a staggered dosing approach may be used for cohorts in Part 3. Part 3 consists of up to 3 sequential cohorts of healthy subjects. In each cohort, 8 healthy subjects will be randomly assigned to receive TAK-510 or matching placebo in a 3:1 ratio in a double-blind manner. Up to approximately 24 healthy subjects may be randomized in Part 3 (approximate value do not account for potential replacement of subjects who withdraw for nonsafety reasons).

Subjects will be admitted to the study unit on Day -2. Baseline HR and BP assessments will be taken on Day -1, and Day -1 HR and BP assessments will be time-matched to the Day 1 assessments. Subjects will be dosed on Day 1 in each cohort/period after a minimum of 8 hours of fasting. Subjects will be confined until Day 8, 30 hours after the Day 7 dose, to assess safety, tolerability, immunogenicity, and PK. Assessments of postural hypotension will be measured predose and at 0.5, 2, 4, 7, 10, and 24 hours after each dose, as well as at time-matched time points on Day -1. Blood samples for assessment of TAK-510 plasma concentrations will be collected on Days 1 to 7 and on Day 14, at predose and at select postdose time points to capture the predicted C_{max}, as well as at 30 hours after the Day 7 and Day 14 doses. [redacted] Optional DNA samples will also be collected from subjects that provide consent for collection through a separate procedure. DNA samples can be collected at any time on the day of discharge (Day 8) or at early termination (if applicable). Subjects will be discharged on Day 8 and will be readmitted the evening prior to redosing. After a 7-day washout (168 hours after the last dose of the 7-day treatment period), subjects will be dosed with a single dose of study drug (ie, at the same dose and double-blind treatment assignment as their highest daily dose during the 7-day treatment period). The duration of washout may be subject to change based on emerging safety, tolerability, and available PK data. Subjects will be confined the evening prior to redosing and for at least 30 hours after their redosing, while not being confined for the entire washout period. Subjects will return after discharge for additional immunogenicity and other assessments at follow-up visits on Day 29. Based on emerging safety, tolerability, and available PK data, subjects may be confined during washout at the discretion of the investigator in consultation with the sponsor and medical monitor.

In Part 3, up to 3 cohorts may be dosed sequentially for 7 days using a dose titration design of 1 to 5 days at lower doses followed by 2 to 6 days at the highest dose for that cohort, which will not exceed the dose studied in the highest completed dose cohort in Part 2. Cohorts 18 and 19 may be started in parallel. The proposed dose titration designs for the 3 cohorts are as follows:

Cohort 18: Single doses that escalate on a daily basis will be given on the first 2 to 5 days of the 7-day dosing period, followed by a maximum daily dose on the remaining days of the 7-day dosing period.

Cohort 19: A lower starting dose will be given on the first 2 to 3 days of the 7-day dosing period, followed by a maximum daily dose for the remaining days of the 7-day dosing period. The lower starting dose is to be determined based on Cohort 18.

Cohort 20: The initial daily dose(s) are to be determined by Cohorts 18 and 19 and will be given on the first 1 to 3 days, followed by the maximum daily dose for the remaining days of the 7-day dosing period. The maximum daily dose will be the same as that Cohorts 18 and 19, or higher as supported by safety, tolerability, and PK data from at least the same daily dose (or higher) in Part 2 MRD cohorts.

Dose regimens up to the current planned maximum exposure level (AUC_∞) of 705,000 h*ng/mL will be studied as determined by the prior dosing regimen in Part 2. The daily exposure will not exceed an exposure established as well tolerated in Part 2. Doses in Part 3 are planned to be administered SC once daily. Based on emerging PK data from Parts 1 and 2, and PK data from prior cohorts in Part 3, adjustments to dose and to repeat dosing duration may be implemented.

The dose escalation meeting will determine the doses and dose schedule of Cohort 18 and 19 based on safety, tolerability and available PK data from Parts 1 and 2. After completion of Cohort 18 and 19, and before selecting the next dose schedule, a blinded assessment of the safety and tolerability, laboratory results of at least 24 hours after the last dose in the cohort, and available PK data will be analyzed in the dose escalation meeting (composed of representatives from the sponsor and site study teams).

The blind may be broken for select sponsor representatives before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns based on the prospectively prepared unblinding plan. Following each blinded dose cohort review and after dose escalation decisions have been made, the sponsor may be unblinded using the prospectively prepared unblinding plan.

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

Study Drug Administration

In Part 3, when administering TAK-510, injection sites must be rotated. [redacted]. The single SC dose of TAK-510 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 TAK-510 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 TAK-510 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 pulse measurements. For additional information on study drug administration, please refer to the study pharmacy manual.

6.2 Stopping Rules

6.2.1 Stopping Criteria for Individual Subjects

Subjects will permanently discontinue study drug for any study drug-related adverse events that are rated Grade ≥3 in severity on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale (v5.0).

6.2.2 Criteria for Premature Termination or Suspension of the Study

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

- Any subject experiences a Hy's Law reaction (defined as alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 × the upper limit of normal [ULN] in conjunction with elevated total bilirubin >2 × ULN without findings of cholestasis or other alternate etiology).
- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk profile for TAK-510, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- The sponsor elects to terminate or suspend the study for administrative reasons including plans to modify, suspend, or discontinue development of the study drug.

In addition, the study may be interrupted for review of the safety data during Parts 1, 2, or 3 if one of the below criteria is met:

- 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-510, or
- Two or more subjects experience a CTCAE v5.0 Grade ≥3 hypotension (ie, requiring medical intervention) and considered related to TAK-510, or
- One subject experiences a CTCAE v5.0 Grade ≥3 syncope (fainting or orthostatic collapse) and considered related to TAK-510, or

- Two or more subjects experience a CTCAE v5.0 Grade 3 event considered related to TAK-510 administration, or
- One subject experience a CTCAE v5.0 Grade 4 event considered related to TAK-510 administration, or
- One subject with ALT or AST >5 × ULN after TAK-510 administration, or
- One subject with ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), or
- One subject with increases in creatinine >1.5 × ULN after TAK-510 administration, or
- One subject with a serious adverse event (SAE) considered related to TAK-510 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).

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 the event is considered unlikely to be related to treatment with study drug by the investigator and sponsor.

During Study Drug Dosing in Part 2 (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 may continue provided it is at a lower daily dose than in Part 1 than that at which the event was observed, and the sponsor and investigator agree after careful review of the totality of the available blinded data.

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

If the criteria for pausing occurs in MRD Part 2 or SRD Part 1 at a higher level than is being dosed in Part 3 (ie, higher level than the maximal dose during titration or Day 14), dosing in Part 3 may continue provided it is at a lower daily dose than in Parts 1 or 2 than that at which the event was observed, and the sponsor and investigator agree after careful review of the totality of the available blinded data.

6.3 Rationale for Study Design, Dose, and Endpoints

6.3.1 Rationale of Study Design

A randomized, double-blind, placebo-controlled design for Part 1 is considered adequate to characterize the safety, tolerability, and PK of single doses of TAK-510.

Part 2 of the study is a randomized, double-blind, placebo-controlled, sequential panel MRD study where up to 8 cohorts may be studied under repeat-dose conditions.

The intention with the dose titration part of Part 3 is to provide an exploratory evaluation to assess the safety and tolerability profile of dose titration at the start of the 7-day treatment period. This comparison will be descriptive (ie, without hypothesis testing) versus tolerability findings in Parts 1 and 2 with comparable exposures to determine whether dose titration results in different tolerability. The redosing part of Part 3 is intended to provide an exploratory evaluation to assess the effects of a single dose (after 7 days [168 hours] of washout following the 7-day treatment period) on vital signs, adverse events, and other safety parameters.

6.3.2 Rationale for Dose

The starting dose for this FIH study is 5 µg. 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 [10].
2. Nonclinical cardiovascular safety pharmacology data for TAK-510.
3. Benchmarking to [redacted] cardiovascular findings.
4. Lowest projected antiemetic effect and insulin secretion effect as demonstrated in nonclinical species.

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

The principle of the FDA Guidance "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" [10] 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-510, NOAELs were identified in the 2-week 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 60 mg/kg (highest dose investigated); minimal body weight loss and dose-dependent minimal to moderate vacuolation of the proximal convoluted tubule of the kidney (without degeneration/necrosis or changes in clinical pathology) were considered nonadverse. The NOAEL in the dog was 15 mg/kg; body weight loss and associated clinical observations were considered adverse at 50 mg/kg. [redacted]

[redacted]

However, cardiovascular effects in dogs were the principal finding in the safety pharmacology studies. In this study, the lowest dose of [redacted] TAK-510 produced a transient increase in HR and a transient decrease in BP, and a NOEL was not identified.

Given the reversible nature of the cardiovascular changes, and the lack of other significant safety findings at this dose level, the [redacted] TAK-510 dose is not anticipated to result in any clinically significant effects or significant safety risk. [redacted] Incretin effects were as expected with transient, glucose-dependent increases in both insulin and glucagon reported. Cardiovascular effects were consistent across studies with an increase in HR and decrease in BP reported during the 2 to 4 hours of infusion. [redacted]

Additionally, the lowest dose tested [redacted] in the first-in-human clinical study of [redacted] resulted in changes in BP (diastolic BP changes at 30 minutes) that were not considered clinically significant. [redacted] Refer to the current edition of the TAK-510 Investigator's Brochure for additional details of FIH study findings [redacted].

The selected FIH dose [redacted] and derived from a combination of nonclinical and clinical cardiovascular profiles in which submaximal or minimal cardiovascular changes, respectively, were reported. [redacted]

[redacted]

[redacted]

In summary, given the totality of these findings from nonclinical safety, published literature, and nonclinical pharmacology, the proposed starting dose is 5 µg.

6.3.2.2 FIH Maximum Dose Consideration

No adverse toxicological findings were observed in 2-week repeat dose GLP-compliant toxicology study in rats at doses up to 60 mg/kg; however; body weight loss and associated clinical observations were considered adverse in dogs at 50 mg/kg. The NOAEL was determined to be the mid-dose of 15 mg/kg/day in dogs, which produced an AUC (705,000 h*ng/mL) that was less than half the rat NOAEL AUC (2,470,000 h*ng/mL); the dog was considered to be the most sensitive species. As per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)" [13], for situations where only one species demonstrates adverse toxicities, the maximum clinical dose will be limited to AUC exposure at the NOAEL in the species showing toxicity or half the AUC at the NOAEL in the species without toxicity. Thus, the AUC of TAK-510 in the clinic will not exceed 705,000 h*ng/mL, which is the dog NOAEL AUC.

Preliminary data from other studies recently analyzed have helped refine [redacted] The doses that are predicted to maintain concentration in the efficacious range and allow for optimal onset of response within 30 minutes are planned to be evaluated.

Given the available formulation [redacted] and feasibility limitation of maximum administered volume of 1 mL per SC injection, [redacted] is the highest planned dose predicted to be evaluated in Part 1. The predicted exposure [redacted] will be [redacted] below the dog NOAEL (most sensitive species; AUC_{∞} = 705,000 h*ng/mL).

6.3.2.3 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 Human Dose-Related Concentrations and Exposures for Select Proposed Doses in Part 1

Dose [a] (µg)	C_{max} (ng/mL)	AUC_{∞} (h*ng/mL)	Safety Margin NOAEL Exposure
5	[redacted]		

AUC: area under the plasma concentration-time curve; AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinity; C_{max}: maximum observed plasma concentration; NOAEL: no-observed-adverse-effect level; PK: pharmacokinetic.
Exposure at NOAEL in dog 705,000 h*ng/mL (AUC).
Values represent geometric mean.
[a] Single dose administered.
[b] Preliminary observed PK parameters.
[c] Predicted assuming linear PK from observed [redacted] preliminary human PK data from this ongoing study.

It is planned that up to 17 doses may be explored with a maximum escalation factor between cohorts [redacted] at lower exposures and [redacted] at high exposures.

Dose levels may be adjusted based on emerging safety 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.

6.3.2.4 Rationale for Dosing Interval

Multiple dose cohorts (Part 2) will be administered TAK-510 once daily. [redacted]

The dosing regimens selected for Parts 2 and 3 will have a projected AUC_{∞} that will not exceed an AUC_{∞} of 705,000 h*ng/mL or the highest AUC_{∞} determined to be tolerated in Part 1.

6.3.2.5 Rationale for Dose Titration and Redosing After Washout

Part 3 of the study is intended to evaluate whether dose titration can result in a different tolerability, particularly with regard to cardiovascular effects, and whether redosing after a 7-day washout results in cardiovascular effects (ie, loss of potential attenuation of cardiovascular effects with dose titration and multiple dosing). GLP-compliant and non–GLP-compliant cardiovascular safety studies in telemetered dogs with TAK-510 have demonstrated: (1) a dose-response of cardiovascular effects, where the lowest dose tested [redacted] results in an ~ED_{50} (median effective dose) of maximal heart rate and blood pressure effects observed in dogs; (2) repeat-dosing at therapeutic doses results in a significant attenuation of cardiovascular effects following administration of the second daily dose. These data demonstrate that sub-therapeutic

doses can elicit minimal cardiovascular effects and that repeat dosing may elicit tachyphylaxis. 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 cardiovascular effects at therapeutic doses.

6.3.3 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.

6.3.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the following procedures are critical:

Parts 1, 2, and 3:

- 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.

6.4 Procedure Modifications Permitted Within Protocol Parameters

This is a phase 1 study of TAK-510 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, for example, 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 informed consent form update if the changes do not impact the burden of subjects or safety monitoring.

6.5 Study Beginning and End/Completion

6.5.1 Definition of Beginning of the Study

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

6.5.2 Definition of End of the Study

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

6.5.3 Definition of Study Discontinuation

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

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

Study discontinuation because of safety reasons:

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

6.5.4 Criteria for Premature Termination or Suspension of the Study

6.5.4.1 Criteria for Premature Termination or Suspension of Study

See Section 6.2 for study-specific stopping rules and additional criteria for premature termination or suspension of the study.

6.5.4.2 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 early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.5.5 Criteria for Premature Termination or Suspension of a Site

6.5.5.1 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 Good Clinical Practices (GCP), protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.5.5.2 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 early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

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

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be a healthy man or woman of nonchildbearing potential 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 dosing and throughout the study.
5. Have a body mass index (BMI) ≥18 and ≤30.0 (kg/m^2) at the screening visit.
6. Be judged to be in good health (eg, no evidence of psychiatric, hepatic, renal, pulmonary, or cardiovascular disease) by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug or invasive procedure.
7. 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 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.

7.2 Exclusion Criteria

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

1. The subject has participated in another investigational study within 4 weeks (or based on local regulations) or within 5 half-lives 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-510.
5. The subject has a positive pregnancy test or is lactating or breastfeeding.
6. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody/antigen, at the screening visit.
7. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.
8. The subject is unable to refrain from or anticipates using all medications including herbal medicines beginning approximately 7 days before administration of the first dose of study drug, throughout the study until 2 days after discharge.
9. The subject is unable to refrain from or anticipates using marijuana or cannabis-containing products beginning approximately 7 days before administration of the first dose of study drug, throughout the study until after the last PK dose.
10. The subject has a history or presence of alcoholism or drug abuse within the past 2 years prior to dosing, or frequent or heavy use (ie, near-daily) of medical or recreational cannabis in the past 3 months before screening.
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 has had a previous major psychotic disorder.

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

the above criterion, the subject will not be eligible. A confirmed orthostatic increase of >30 bpm, but <40 bpm, on 1 or more Day -1 assessments may not be considered exclusionary if not considered clinically significant by the investigator and the medical monitor. Such assessments must be discussed with the medical monitor prior to determination that the subject is eligible to proceed.

19. The subject has a known or suspected current COVID-19 infection or is at risk of COVID-19 infection as assessed by the investigator.

7.3 Excluded and Allowed Concomitant Medications, Supplements, and Dietary Products

7.3.1 Concomitant Medications

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

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

7.3.2 Fruit Juice

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

7.3.3 Alcohol

Subjects will refrain from consuming alcohol, 24 hours before admission until the final PK sample has been collected. Subjects may undergo an alcohol 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 the PK blood sample at 30 hours after dosing in each cohort. At all other times in Part 1 and in Parts 2 and 3, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit = 120 mg of caffeine).

7.3.5 Smoking

Subjects will abstain from the use of tobacco- or nicotine-containing products from screening until discharge after the last scheduled dose.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

7.4.1.1 Part 1

On Day -1 of each cohort, subjects will fast overnight (at least 8 hours) and will continue to fast for 4 hours after Hour 0 for the collection of baseline time-matched 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 telemetry recording extractions and/or safety ECG.

Normal fluid intake of water is permitted and encouraged, and decaffeinated coffee or tea with nothing added are also permitted. Standard meals will be administered at approximately 4 (lunch), 7 (snack), 10 (dinner), and 13 (snack) hours postdose on Day 1. Standardized meals will be served on all other confinement days.

7.4.1.2 Part 2 and 3

On Day -1 of each cohort, subjects will fast overnight (at least 8 hours) and will continue to fast for 4 hours after Hour 0 for the collection of baseline time-matched HR and BP assessments. On Days 1 and 5 in Part 2, and Days 1, 7, and 14 in Part 3, subjects will fast overnight (at least 8 hours) before the dose and will continue to fast for an additional 4 hours (after Hour 0) postdose.

Normal fluid intake of water is permitted and encouraged, and decaffeinated coffee or tea with nothing added are also permitted. Standard meals will be administered at approximately 4 (lunch), 7 (snack), 10 (dinner), and 13 (snack) hours postdose on dosing days. All meals should be served at approximately the same time each day.

7.4.2 Activity

Subjects will avoid strenuous physical activity (eg, weight lifting, running, bicycling) from 72 hours before admission to the study site, throughout the study (including the washout interval in Part 3), and until after discharge after the last scheduled dose.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

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

- Pretreatment event or TEAE. The subject has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pretreatment event or AE.

- Liver function test (LFT) abnormalities.
  - 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, 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 early termination visit.

7.7 Subject Replacement

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

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

TAK-510 will be supplied to the study site by the sponsor [redacted] for injection. The matching placebo is normal saline.

TAK-510 and placebo will be prepared for injection by licensed pharmacy staff at the clinical research unit according to the procedures outlined in the pharmacy manual.

Details regarding the dosage form description and strengths, or composition for the extemporaneous 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.

TAK-510 will be provided in a labeled glass vial and packaged in an appropriately labeled carton with a single-panel label that will contain, but will not be limited to, the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, caution statement, and storage conditions.

8.1.2 Clinical Study Drug Inventory and Storage

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

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

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-510 must be stored at -25°C to -15°C (-13°F to 5°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 study; the investigator and subjects are blinded to treatment assignment. An unblinded study drug supply will be provided to an unblinded pharmacist or other qualified personnel at the study site who will blind the study supplies. Treatment identity (name and strength or potency) will be included on the study drug container label. Randomization code/disclosure envelopes or lists will be provided per the standard operating procedures of the study site.

After completion of each dosing cohort, and before selecting the next dose, a blinded assessment of the safety and tolerability, laboratory results of at least 24 hours after the last dose in the cohort, and available PK data will be performed in the dose escalation meeting (composed of representatives from the sponsor and site study teams).

The blind may be broken for select sponsor representatives before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns based on the prospectively prepared unblinding plan. Following each blinded dose cohort review and after dose escalation decisions have been made, the sponsor may be unblinded using the prospectively prepared unblinding plan, to enable further data review to inform later parts of the study.

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.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

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

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator and investigator's designated site pharmacy must ensure that the sponsor- or contract research organization (CRO)-supplied drug is used in accordance with the protocol and pharmacy manual and is dispensed only to subjects enrolled in the study. To document appropriate use of the sponsor-supplied drug, the investigator pharmacy/site must maintain records of drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

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

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

- Monitoring expiration dates.

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

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

8.2 Ancillary Supplies

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

9.0 STUDY PROCEDURES

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

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.1.1 Assignment of Screening and Randomization Numbers

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

9.1.1.2 Study Drug Assignment

On Day 1, subjects will be assigned a randomization number in ascending numerical order at the clinical site. The randomization number encodes the subject assignment to either TAK-510 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

9.2.1 Full Physical Examination

Qualified site personnel will conduct full or symptom-driven physical examinations as indicated in the Schedule of Study Procedures (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 -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, and first dose in Part 3) should be consistent with the vital sign criteria as defined in Section 7.2 (exclusion criteria). If vital sign criteria are outside of the specified range defined in Section 7.2 for any dose after the first dose in Parts 2 and 3, the investigator may exercise discretion related to appropriateness of the subject's ongoing study participation on the basis of assessment of clinical significance of vital signs and any ongoing AEs. The investigator will regularly update the Takeda medical monitor of vital sign findings outside of the ranges described in Section 7.2 and ongoing AEs. No protocol deviation will be issued for dosing that may be delayed for up to 1 hour due to an ongoing AE (Part 2 and Part 3) or vital sign criteria defined in Section 7.2. Should dosing be delayed in Parts 2 or 3 of the study, adjustment should be made on subsequent days to administer the dose as close as possible to the originally planned TAK-510 dosing time based on Day 1 dosing.

Subjects should rest in a semirecumbent position for at least 3 minutes before vital signs are measured. Vital signs will include pulse rate (bpm), respiratory rate, and systolic and diastolic BP in all parts of the study. BP and pulse assessments should be made in duplicate with an interval of approximately 2 minutes between the 2 assessments. The investigator can take a third BP and pulse assessment if results are inconsistent (ie, a difference >10 bpm in HR or a difference >10 mm Hg in SBP or DBP between assessments). If 3 measurements are obtained, the final BP and pulse readout should be the average of the 2 more consistent assessments. 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 prior to dosing or Hour 0. When scheduled after the dose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

Orthostatic BP and pulse assessment will be performed with the subject standing after the semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment.

- 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 systolic BP ≥20 mm Hg or a decrease in diastolic BP ≥10 mm Hg after approximately 3 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 systolic BP 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 after 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.

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

9.2.4.1 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 study site.

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 the study site per policy, or if a subject should leave the study site due to unforeseen circumstances, the sponsor will be consulted immediately to discuss the following:

- If the subject is asymptomatic in relation to cardiovascular symptoms but **without** telemetry observations during the postdose period, the subject could be discharged home after discussion with the sponsor, but with adequate 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 cardiovascular 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 cardiovascular symptoms **with or without** telemetry observations during the postdose period, the recommendation is to discuss disposition with the sponsor and potentially discharge to the emergency department.

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

9.2.5 Glucose

Blood glucose will be monitored using finger-stick blood samples in Parts 1, 2, and 3 and will also be monitored using safety laboratory testing.

9.2.6 ECG Procedure

9.2.6.1 Screening and Safety ECGs

A 12-lead ECG will be collected at the time points specified in the Schedule of Study Procedures (see 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 (in semirecumbent position), or experiences hypotension with systolic BP <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, pulse, 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

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

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 9.2.4.1 for details).

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 in Parts 1, 2, and 3 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 thorough QT (TQT) analysis as described below. For all postdose ECG collections, three 10-second ECGs will be extracted at each extraction window time point.

ECG extraction time points will occur before PK blood draws. Accordingly, subjects will be supervised and quietly resting semirecumbent beginning a minimum of 5 minutes before each actual ECG extraction window of 5 minutes if possible. The rest period 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 concentration-QT analysis unless a safety signal is detected and additional information is required for proper interpretation of the findings. eCRF data for telemetry extractions will only include date and start and stop time and whether assessment was performed.

Collected ECG data from 12-lead telemetry may also be used to explore the relationship with TAK-510 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-510 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 the upper limit of normal, total bilirubin will be fractionated
Protein (total)	Creatine kinase

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and international normalized ratio) should be performed 24 hours after the abnormality was noted, and the medical monitor should be contacted. In Parts 2 and 3, if subjects experience ALT or AST >3 × ULN or total bilirubin >2 × ULN, laboratory tests for ALT and AST should be repeated before the next scheduled dose.

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

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

9.2.9.3 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.

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 and/or serum samples collected will be assayed for evaluation of PK will be determined by the sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). 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-510 PK	Blood	Plasma	PK analysis	Mandatory
Plasma sample for metID	Blood	Plasma	metID analysis	Mandatory
Urine sample for TAK-510 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-510 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be involved in all computations involving sampling times.

Exploratory metabolite profiling may be conducted on blood samples to determine the metabolites of TAK-510. If conducted, these data will be reported separately and not be reported in the CSR.

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

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

The following urine PK parameters of TAK-510 will be determined after SC administration in Parts 1 and 2:

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

Plasma samples for PK analysis of TAK-510 will be collected into chilled blood collection tubes (vacutainer) containing the anticoagulant K2EDTA. The collected blood or resultant plasma samples may be archived for exploratory characterization of potential circulating metabolites. If

conducted, these data will be reported separately and not be reported in the CSR. A full description of PK sample collection, handling, storage, and shipping can be found in the laboratory manual.

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

[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 [14]. 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.

9.2.10.1.2 Urine for PK Measurements

Urine concentrations of TAK-510 will be measured by a validated high-performance liquid chromatography with tandem mass spectrometry assay. 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-510 levels for exploratory characterization of potential urinary metabolites.

9.2.10.2 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), on Day 1, predose, at Day 8, and at the follow-up visits. 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-510 in this study as well as the regulatory request if it is applied.

[redacted]

9.2.10.4 DNA Measurements

9.2.10.4.1 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.

9.2.10.4.2 Biological Sample Retention and Destruction

In this study, sample of blood for DNA analysis will be collected as described in Section 9.2.10.4.1. 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 Part 1 (SRD)

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic for 96 hours postdose (Day 5). At the discretion of the investigator, subjects may be requested to remain in the clinical site longer.

9.3.2 Part 2 (MRD)

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until discharge on Day 9 (96 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 and Redosing)

Subjects will report to the clinical site on Day -2. Subjects will remain in the clinic until discharge on Day 8, 30 hours after last dose of study drug. Based on emerging safety, tolerability, and available PK data, subjects may be confined during washout at the discretion of the investigator in consultation with the sponsor and medical monitor. Subjects will report to the clinical site for readmission on the evening before the scheduled day of study drug redosing (Day 13). Subjects will remain in the clinic until discharge on Day 15, 30 hours after the single dose of study drug on Day 14. 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 will be excluded from this study.

9.4.1.1 Definition of Women of Childbearing Potential

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

9.4.2 Women of Nonchildbearing Potential

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

- Postmenopausal: At least 12 months of spontaneous amenorrhea and an FSH concentration >40 mIU/mL.
- Surgically sterile by hysterectomy, bilateral salpingectomy, 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 Women of Nonchildbearing Potential

No contraception is required for women of nonchildbearing potential.

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 may be 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 retest 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 in the Dosing section 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 eCRF(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-510 include injection site reactions, hypotension, and tachycardia. In addition, orthostatic hypotension is considered as a potential risk based on clinical experience [redacted]

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 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.

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 Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

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

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."

- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, AESIs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, AESIs, and abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until approximately 30 days after the last dose of investigational product. For subjects who discontinue 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).
- Action taken with study drug.

- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

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

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

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

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

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

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.
[a] Symptoms may include dizziness, light headedness, chest pain, chest heaviness, palpitations, and shortness of breath.

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

10.2.8.4.2 Low BP

If a subject develops symptoms suggestive of hypotension or postural hypotension, BP should be assessed for evidence of hypotension, which should be managed as per local guidelines, and the medical monitor should be contacted. TAK-510 administration will be discontinued on occurrence of an event of CTCAE v5.0 Grade ≥3 hypotension (ie, requiring medical intervention).

If systolic BP is <85 mm Hg or if the subject is experiencing symptoms suggestive of postural hypotension after standing, the subject should be advised to lie flat, and BP and HR should be rechecked in that position. If systolic BP 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-510, provide immediate treatment, and contact the medical monitor. Any injection site reaction assessed as a CTCAE v5.0 Grade 2 (ie, pain, lipodystrophy, edema, phlebitis) should be managed according to standard of care. Symptomatic treatment should be administered, and the investigator should contact the medical monitor.

10.2.8.4.4 Hypersensitivity

If anaphylaxis or other serious allergic reactions occur, TAK-510 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. 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 and/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 and/or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB and/or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

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

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

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

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-510 and have at least 1 measurable postdose plasma or urine concentration for TAK-510.

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) for placebo, each TAK-510 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-510 overall in Parts 1, 2, and 3 separately. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (eg, gender, ethnicity, race) will be tabulated for placebo, each TAK-510 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-510 overall in Parts 1, 2, and 3 separately. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2)/dose regimen (Part 3) will be pooled across cohorts within each part of the study where appropriate. The safety analysis set will be used to summarize the demographics and baseline characteristics. All data will be provided in by-subject listings.

11.1.3 PK Analysis

The plasma (all parts of the study) and urine (Parts 1 and 2 only) concentrations of TAK-510 will be summarized by dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) at each scheduled sampling day/time within each part of the study separately, using descriptive statistics (n, mean, standard deviation, geometric mean, percent coefficient of variation [%CV], median, minimum, and maximum) based on the PK analysis set. The PK parameters of TAK-510 determined using a noncompartmental analysis approach will be summarized by dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) of TAK-510, as appropriate, within each part of the study separately, using descriptive statistics (n, mean, standard deviation, geometric mean, %CV, median, minimum, and maximum) based on the PK analysis set. Dose proportionality may be assessed graphically (log-transformed dose-normalized C_{max} and AUC versus dose) and by using a power model within each part of the study separately as data allow; no formal statistical comparisons will be conducted. The same dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) may be pooled across cohorts within each part of the study where appropriate. All data will be provided in by subject listings.

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

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 placebo, TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. In particular, the number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for BP and HR will be provided. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) will be pooled across cohorts within each part of the study where appropriate. For Part 3 only, similar safety summary analyses (excluding ADA assessments) will be performed for the single dose after washout from multiple dose regimens of TAK-510 by placebo, TAK-510 single dose level after washout, and TAK-510 single dose overall after washout. 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 MedDRA System Organ Class and Preferred Term and by placebo, each TAK-510 dose level (Parts 1 and 2)/dose regimen (Part 3), and TAK-510 overall within each part of the study separately. Similar summary analyses will be provided for treatment-related TEAEs, SAEs, AESIs, and AEs leading to permanent treatment discontinuation as well. will be For Part 3 only, similar summary analyses of TEAEs will be performed for the single dose after 7 days of washout from multiple dose regimens of TAK-510 by placebo, TAK-510 single dose level after washout, and TAK-510 single dose overall after washout.

11.1.4.2 Clinical Laboratory Evaluations

Clinical laboratory parameters will be summarized using descriptive statistics for baseline, postdose, and change from baseline to postdose by placebo, each TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for clinical laboratory parameters will be presented by placebo, each TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. For Part 3 only, similar summary analyses of clinical laboratory data will be performed for the single dose after 7 days of washout from multiple dose regimens of TAK-510 by placebo, TAK-510 single dose level after washout, and TAK-510 single dose overall after washout.

11.1.4.3 Vital Signs

Typically, BP and pulse assessments are made in duplicate with an interval of approximately 2 minutes between the 2 assessments. The investigator can take a third BP and pulse 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 pulse assessment when results are inconsistent, the average value of the 2 more consistent corresponding assessments (details will be provided in the statistical analysis plan) 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 placebo, each TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for vital signs (including by not limited to BP) will be presented by placebo, each TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. For Part 3 only, similar summary analyses of vital signs data will be performed for the single dose after 7 days of washout from multiple dose regimens of TAK-510 by placebo, TAK-510 single dose level after washout, and TAK-510 single dose overall after washout.

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

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 placebo, each TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria for ECG parameters (including but not limited to HR, QT/QTc, and increase from baseline in QT/QTc) will be presented by placebo, each TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall within each part of the study separately. For Part 3 only, similar summary analyses of ECG data will be performed for the single dose after 7 days of washout from multiple dose regimens of TAK-510 by placebo, TAK-510 single dose level after washout, and TAK-510 single dose overall after washout.

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

11.1.4.5 Other Safety Parameters

Physical examination findings will only 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 ADA-positive, and low or high ADA titer) will be tabulated by placebo, TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall at scheduled time points within each part of the study separately. The relationship between immunogenicity status (ADA-negative or ADA-positive, and low or high ADA titer) and PK, and safety will be analyzed

if they are applicable. Placebo data will be pooled across cohorts within each part of the study. The same dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) will be pooled across cohorts within each part of the study where appropriate. All data will be provided in by subject listings.

11.1.6 Biomarker Analysis

Biomarker measurements will be summarized using the safety analysis set. The concentrations [redacted] at each time point (ie, Day -1 and baseline [predose, Day 1]) will be summarized using descriptive statistics (n, mean, standard deviation, geometric mean, %CV, median, minimum, and maximum) by placebo, TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) 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 placebo, TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only) within each part of the study separately. The change from baseline [redacted] will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by placebo, TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only), and TAK-510 overall at scheduled time points within each part of the study separately. Placebo data will be pooled across cohorts within each part of the study. The same dose level will be pooled across cohorts within each part of the study where appropriate. All data will be provided in by subject listings.

11.2 Interim Analysis

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

If a data-dependent internal decision is needed to inform the subsequent development of TAK-510 before 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 statistical analysis plan.

11.3 Determination of Sample Size

The selected sample sizes in Parts 1, 2, and 3 of the study are considered sufficient for evaluation of safety and tolerability of TAK-510 in healthy subjects. No formal statistical hypothesis testing is planned in Parts 1, 2, or 3. Therefore, no formal power calculations were performed in the determination of the sample size for this study.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records.

The investigator and study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB and/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 patient safety.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that have a deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB and/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 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/or 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 and/or IEC. If any member of the IRB and/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 and/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 and/or IEC for approval. The IRB's and/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 and/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 study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB and/or IEC. This may include notification to the IRB and/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 and/or IEC, and submission of the investigator's final status report to IRB and/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 and/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 and/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 and/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 and/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.

Informed consent for optional DNA sample collection and analysis will be collected in a separate section of the study informed consent form. Subjects who consented and provided a DNA sample can withdraw their consent for DNA sample analysis 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, 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 Study Registration Policy

13.4.1 Publication and Disclosure

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

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

13.4.2 Clinical Study Registration

In order to ensure that information on clinical studies reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical studies it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda

contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting study information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the sponsor.

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

13.4.3 Clinical Study Results Disclosure

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

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

14.1.2 INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

ADA	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
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
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	observed plasma concentration at the end of a dosing interval
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
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 of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
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
$R_{ac(AUC)}$	accumulation ratio based on AUC_{τ}
$R_{ac(Cmax)}$	accumulation ratio based on C_{max}
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous(ly)
SRD	single rising dose
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of C_{max}
TQT	thorough QT
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
WBC	white blood cell

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 Case Report Forms (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]

2. Wang S, Oestricker LZ, Wallendorf MJ, Sterl K, Dunai J, Kilpatrick CR, et al. Cholinergic signaling mediates the effects of xenin-25 on secretion of pancreatic polypeptide but not insulin or glucagon in humans with impaired glucose tolerance. PLoS One 2018;13(2):e0192441.

[redacted]

[redacted]

10. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 06 July 2005. Publication No. 5541.

[redacted]

13. ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 11 June 2009. Publication No. M3(R2).
14. 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). March 2020 Revision 2.
15. Abdullah N, Beg M, Soares D, Dittman JS, McGraw TE. Downregulation of a GPCR by beta-Arrestin2-mediated switch from an endosomal to a TGN recycling pathway. Cell Rep 2016;17(11):2966-78.

[redacted]

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to 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 patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

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

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

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

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

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

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, 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 high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those aged <45 years) 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.

** No restrictions are required for a vasectomized male subject provided the subject is at least 1 year after bilateral vasectomy. 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.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly)". In this study, where medications and devices containing hormones are included/excluded, the only acceptable methods of contraception are:
   - Non-Hormonal Methods:
     - IUD (Intrauterine device).
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the study 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.

- 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, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

5. During the course of the study, regular serum hCG (human chorionic gonadotropin) pregnancy tests will be performed for female subjects, and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   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 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
21 April 2022	Amendment 3	Substantial	Global
02 September 2021	Amendment 2	Substantial	Global
19 May 2021	Amendment 1	Substantial	Global
02 December 2020	Initial protocol	Not applicable	Global

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 serum sampling for measurement of creatine kinase levels.
2. Add at least 24 hours of continuous telemetry monitoring before the first dose.
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 study parts.

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 Part 1 for SRD Cohorts 1 to Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 3.3.2 Part 3 Screening Through Day 1 Assessments Section 9.2.6.2 Telemetry	Table 3.a, Table 3.b, Table 3.c, Table 3.f, Table 3.g Added at least 24 hours of continuous telemetry monitoring before the first dose of TAK-510 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 to approximately 24 hours postdose" to "at least 24 hours before dosing and at least 24 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.

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***
2.	Section 3.1 Part 1 for SRD Cohorts 1 to Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.2.3 Part 2 Days 2 to 4 Assessments Section 3.2.4 Part 2 Day 5 Through Day 9 Assessments, Follow-Up, and Early Termination Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 3.3.2 Part 3 Screening Through Day 1 Assessments Section 3.3.3 Part 3 Days 2 to 6 Assessments Section 3.3.4 Part 3 Day 7 and Day 8 Assessments Section 3.3.5 Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and Early Termination Section 9.2.6.2 Telemetry	Table 3.a, Table 3.b, Table 3.c, Table 3.d, Table 3.e, Table 3.f, Table 3.g, Table 3.h, Table 3.i, Table 3.j Clarified that telemetry is electrocardiogram 12-lead telemetry.	Clarification
3.	Section 3.1 Part 1 for SRD Cohorts 1 to	Table 3.a Removed X indicating telemetry extraction from the Day 1 Hour 0 time point in Part 1.	To remove an extraction time point that is redundant with the predose extraction on Day 1.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	Section 3.1 Part 1 for SRD Cohorts 1 to Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.2.4 Part 2 Day 5 Through Day 9 Assessments, Follow-Up, and Early Termination Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 3.3.2 Part 3 Screening Through Day 1 Assessments Section 3.3.4 Part 3 Day 7 and Day 8 Assessments Section 3.3.5 Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and Early Termination Section 9.2.9.2 Chemistry	Table 3.a, Table 3.b, Table 3.c, Table 3.e, Table 3.f, Table 3.g, Table 3.i, Table 3.j Added serum sample collection of creatine kinase (CK) at pre- and postdose time points on Day 1, at discharge, and at early termination. 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 after TAK-510 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***
5.	Section 3.1 Part 1 for SRD Cohorts 1 to 12 Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.2.4 Part 2 Day 5 Through Day 9 Assessments, Follow-Up, and Early Termination Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 3.3.4 Part 3 Day 7 and Day 8 Assessments Section 3.3.5 Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and Early Termination 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 and Redosing Cohorts 18 to 20 Table 9.a Primary Specimen Collections Section 9.2.10.4 DNA Measurements	Table 3.a, Table 3.b, Table 3.e, Table 3.f, Table 3.i, Table 3.j Added collection of optional blood samples for DNA at discharge or at early termination in all study parts. Revised text to indicate that if subjects have provided consent for the optional DNA collection, both buccal swabs and blood samples should be collected. Table 3.f Removed statement that only 1 DNA sample will be collected per subject from the footnote.	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 Part 1 for SRD Cohorts 1 to 12 Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 3.3.2 Part 3 Screening Through Day 1 Assessments 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 and Redosing Cohorts 18 to 20 Section 9.3.1 Part 1 (SRD) Section 9.3.2 Part 2 (MRD) Section 9.3.3 Part 3 (Dose Titration and Redosing)	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.
7.	Section 3.1 Part 1 for SRD Cohorts 1 to 12 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.3.2 Part 3 Screening Through Day 1 Assessments	Table 3.a, Table 3.c, Table 3.g Revised footnote for safety laboratory assessments at the 4-hour time points 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 the 4-hour time points and removing the list of excluded measurements.
8.	Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.2.3 Part 2 Days 2 to 4 Assessments	Table 3.c, Table 3.d Removed footnote for samples for pharmacokinetics and metabolite identification stating that the 24-hour sample on Day 1 is the same as the predose sample on Day 2.	To remove redundancy with the footnote for the 24-hour columns.
9.	Section 4.3 Benefit/Risk Profile	Updated blood sampling volume totals for each study part.	To reflect the increase in blood sampling volume with the addition of sampling for DNA and CK.

Protocol Amendment 2			
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10.	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 and Redosing Cohorts 18 to 20 Section 1.0 STUDY SUMMARY	Removed the phrase "due to reasons unrelated to safety" in statement that the approximate subject number accounts for potential replacement of subjects who withdraw. Removed "for reasons unrelated to safety" from the statement describing replacement of subjects at the discretion of the sponsor after discussion with investigator.	To align with language with Section 7.7, Subject Replacement, allowing replacement of subjects as appropriate following discussion between the investigator and sponsor.
11.	Section 6.2.2 Criteria for Premature Termination or Suspension of the Study	Added language "at rest while semirecumbent."	To clarify the stopping criterion related to sinus tachycardia.
12.	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.
13.	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 dosing on subsequent dosing days and to provide a window for discussion on a case-by-case basis between the investigator and the medical monitor.
14.	Section 9.2.10.4.1 Buccal Epithelial Cells Sample and Blood Sample for DNA	Added statement that DNA sequencing analysis will not be reported in the clinical study report.	To clarify the planned reporting approach for DNA analysis.
15.	Section 12.1 Study-Site Monitoring Visits	Added a statement that alternative monitoring approaches may be used 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. Modify exclusion criteria for vital signs (including orthostatic assessments of heart rate [HR] and blood pressure [BP]). In particular, more specific criteria are implemented to account for intrasubject variability with multiple Day -1 assessments that impact subject eligibility for randomization.
2. Revise vital sign assessment and monitoring procedures (including orthostatic assessments of HR and BP).
3. Update the schedule of assessment tables to correct discrepancies.
4. Provide clarification for some of the protocol language.
5. Provide language in case the study is affected by the coronavirus disease 2019 (COVID-19) pandemic.

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 2.0 STUDY SCHEMATIC Section 3.3.1 Overall Schedule of Study Procedures for Part 3	Figure 2.a Updated schematic to add a footnote for washout period. Table 3.f, Table 3.j Added text to footnote b (Table 3.f) and footnote a (Table 3.j) indicating that the duration of washout period may be shortened or lengthened in Cohorts 19 and 20.	Added a footnote to reflect the flexibility of the washout period in Part 3 as previously detailed in the body of the protocol.
2	Section 3.1 Part 1 for SRD Cohorts 1 to 12 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.3.2 Part 3 Screening Through Day 1 Assessments	Tables 3.a, 3.c, 3.g Added a footnote to indicate that the 24-hour sample on a given day is the same as the predose sample on the next day.	To clarify that the 24-hour measurements are the same as the next day predose measurements for vital signs.

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***
3	Section 3.1 Part 1 for SRD Cohorts 1 to 12 Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 3.3.2 Part 3 Screening Through Day 1 Assessments 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 and Redosing Cohorts 18 to 20 [redacted] Section 11.1.6 Biomarker Analysis	Table 3.a, 3.b, 3.c, 3.f, 3.g For plasma sample for glucose-dependent insulinotropic polypeptide moved from collection at screening to collection at Day -1 Time 0 and updated the corresponding footnote and text accordingly.	Modify timing of sample from screening to Day -1 for administrative and feasibility purposes.
4	Section 3.2 Part 2 for MRD Cohorts 13 to 17: Screening Through Day 9, Follow-Up, and Early Termination Section 3.3 Part 3 for Dose Titration and Redosing Cohorts 18 to 20: Screening Through Day 15, Follow-Up, and Early Termination	Added a level 3 heading (Section 3.2.1 and 3.3.1) to denote that Table 3.b is the overall schedule of events for Part 2 cohorts and Table 3.f is the overall schedule of events for Part 3.	To clarify that day-by-day schedules of events is preceded by an overall assessment table for Parts 2 and 3.
5	Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 3.3.2 Part 3 Screening Through Day 1 Assessments	Table 3.b, Table 3.c, Table 3.f, Table 3.g Removed X at Day -2 for BP and pulse (vital signs) and for standing BP and pulse.	For consistency with tables in Part 1 SRD.
6	Section 3.2.1 Overall Schedule of Study Procedures for Part 2 Section 3.3.1 Overall Schedule of Study Procedures for Part 3	Table 3.b, 3.f, Changed individual "X"s to "X---continuous---X" as electrocardiogram (ECG) telemetry is a continuous reading.	For consistency with ECG telemetry measurements with other tables.

Protocol Amendment 1			
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7	Section 3.2.1 Overall Schedule of Study Procedures for Part 2	Table 3.b Shifted urine sample for pharmacokinetic (PK) from Day 7 to Days 5 and 6.	For consistency between overall schedule of assessments (SOA) for Part 2 and the SOA detailing the individual day.
8	Section 3.2.2 Part 2 Screening Through Day 1 Assessments Section 3.3.2 Part 3 Screening Through Day 1 Assessments	Table 3.c, 3.g Changed ECG telemetry spanning from Day -1 through Day 1, to only Day 1.	For consistency with other tables and telemetry procedure outlined in protocol.
9	Section 3.3.1 Overall Schedule of Study Procedures for Part 3 Section 6.1.4 Part 3: Dose Titration and Redosing Cohorts 18 to 20	Table 3.f Shifted Day 15 DNA sample to Day 8 (discharge) and modified footnote 'm' indicating that only 1 DNA sample will be collected per subject.	For consistency with other tables.
10	Section 3.3.2 Part 3 Screening Through Day 1 Assessments Section 3.3.5 Part 3 Day 9 Through Day 15 Assessments, Follow-Up, and Early Termination	Table 3.c, 3.g, 3.j Removed glucose finger stick at Day -2 and Day -1 Hour 3; and Day 13.	Corrected errors on glucose finger sticks on Day -2 and Day -1 in this SOA. Now is consistent with other tables in the study.
11	Section 3.3.4 Part 3 Day 7 and Day 8 Assessments	Table 3.i Added row for 12-lead ECG at Day 8 (discharge).	Corrected error.
12	Section 7.1 Inclusion Criteria Section 9.4.2 Women of Nonchildbearing Potential Appendix D Pregnancy and Contraception	Added bilateral tubal ligation and bilateral salpingectomy to Inclusion Criteria 7.	To include history of bilateral tubal ligation and bilateral salpingectomy as meeting criterion for surgical sterility for eligibility of female subjects.
13	Section 7.2 Exclusion Criteria Section 1.0 STUDY SUMMARY	Modified exclusion criteria (#15-18) for semirecumbent blood pressure, heart rate, orthostatic hypotension, and orthostatic tachycardia.	To control for intrasubject variability observed in vital signs in healthy subjects, in particular with multiple Day -1 time-matched assessments. Repeat measurements and flexibility for borderline values now detailed for orthostatic vital signs to account for variability while maintaining vital sign criteria for eligibility and dosing.

Protocol Amendment 1			
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14	Section 7.2 Exclusion Criteria Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject Section 11.1 Statistical and Analytical Plans	Added Exclusion Criteria 19 for subjects who are excluded due to current coronavirus disease 2019 (COVID-19) infection. Added language for subject withdrawal for reasons related to COVID-19 pandemic. Added language in case of impact in analysis due to COVID-19.	Due to the COVID-19 pandemic, language was added to exclusion criteria, subject withdrawal, and analysis sections.
15	Section 9.2.4 Vital Signs Section 3.0 SCHEDULE OF STUDY PROCEDURES	Modified vital signs procedures and updated relevant footnotes in SOAs for consistency.	Modified to include procedures for repeat vital sign measurements detailed in exclusion criteria and how to report the repeat measurements.
16	Section 9.2.6 ECG Procedure	Modified semirecumbent time from 10 minutes to 5 minutes.	Required rest period before ECG extractions shortened for feasibility while maintaining quality of extractions.
17	Section 11.1.3 PK Analysis	Added language for population PK analysis.	To better clarify possible additional PK analyses.
18	Section 10.2.8.4.1 Sinus Tachycardia	Modified language in sinus tachycardia management procedures.	To clarify the language for management of a subject with symptoms suggestive of arrhythmia. Removed language referring to management of grade 2 sinus tachycardia from this paragraph because the management of grade 2 sinus tachycardia is detailed in the existing table in Section 10.2.8.4.1.
19	Appendix D Pregnancy and Contraception	Remove bullet for “true sexual abstinence” as a method of contraception.	Removed language to fix discrepancy as sexual abstinence is not an acceptable method of contraception in this study.

Protocol Amendment 1			
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20	Appendix D Pregnancy and Contraception	Remove urine hCG test.	Serum samples will be collected for hCG to align with the schedule of assessments.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	22-Apr-2022 17:08 UTC
	Biostatistics Approval	22-Apr-2022 17:47 UTC
	Pharmacovigilance Approval	22-Apr-2022 19:06 UTC
	Clinical Science Approval	25-Apr-2022 13:08 UTC