Statistical Analysis Plan

NCT Number: NCT06610279

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

Study Number: TAK-951-1008

Document Version and Date: Version 3.0, 03 August 2023

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-951-1008

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

Phase 1

Version: 3.0

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Prepared by:

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Study Statistician, Takeda Pharmaceuticals.

Based on:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0	14-FEB-2022	[Not Applicable]
2.0	30-MAR-2022	Updated text in Section 6.10 for administrative reasons to remove the first IA. Update the Markedly Abnormal Values in Appendices to reflect most current safety criteria and add Appendix 9.7 Orthostatic Vital Sign Changes. Minor editorial and formatting changes.
3.0	3-AUG-2023	The following changes have been made in this version of SAP to accommodate the changes due to Amendment 1 of the Protocol dated 24Jan2023 and Amendment 2 of the Protocol dated 16Mar2023: • Change the title of the study and making the study sponsor open. • Additional subgroup analyses of AE and vital signs are planned to evaluate the impact of physical maneuver changes due to protocol amendment 2.

Approval Signatures

Electronic signature can be found on the last page of this document.

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

Approvals:

[redacted], PhD
[redacted], Statistics

Date

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ABBREVIATIONS

%CV	percent coefficient of variation
AE	adverse event
AUC	area under the concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
$AUC_{extrap\%}$	percent of AUC_∞ extrapolated
AUC_{last}	area under the TAK-951 plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_\infty = AUC_t + C_{last}/\lambda_z$
AUC_τ	area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval
BID	twice daily
BLQ	below the lower limit of quantitation
BMI	body mass index
bpm	beats per minute
BP	blood pressure
CL/F	apparent clearance after extravascular administration, calculated as = $Dose/AUC_\infty$ after a single dose and as $Dose/AUC_\tau$ after multiple dosing (at steady state).
C_{last}	Last quantifiable concentration
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
COVID-19	coronavirus disease 2019
CPAP	Clinical Pharmacology Analysis Plan
CRO	contract research organization
CSR	clinical study report
C_{trough}	observed plasma concentration at the end of a dosing interval.
CV	cardiovascular
DBP	diastolic blood pressure
eCRF	electronic case report form
ECGe	electrocardiogram
[redacted]	[redacted]
[redacted]	[redacted]
HR	heart rate
HRV	heart rate variability
IRB	institutional review board
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.
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple rising dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NOAEL	no-observed-adverse-effect level
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
QD	once daily
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
$R_{ac[AUC24]}$	accumulation ratio (based on AUC_{24}), calculated as AUC_{24} at steady state/AUC_{24} after a single dose
$R_{ac[AUC\tau]}$	accumulation ratio (based on AUC_{τ}), 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.
RBC	red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SEM	standard error of a mean
SRD	single rising dose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life calculated as $\ln(2)/\lambda_z$.
TID	3 times daily
t_{lag}	lag time to first quantifiable concentration.
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated as $(CL/F)/\lambda_z$
WBC	white blood cell

1.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

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

1.1.2 Secondary Objectives

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

- Part 1:
  - To characterize the pharmacokinetic (PK) of TAK-951 in plasma following single SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-951 following single SC doses in healthy subjects.
- Part 2:
  - To characterize the PK of TAK-951 in plasma following multiple SC doses in healthy subjects.
  - To assess the immunogenicity of TAK-951 following multiple SC doses in healthy subjects.
- Part 3:
  - To characterize the safety and tolerability of single SC rechallenge doses of TAK-951 after a washout from multiple SC dose regimens that include titration from lower doses in healthy subjects.
  - To assess the immunogenicity of TAK-951 following multiple SC dose regimens that include titration from lower doses, washout, and redosing in healthy subjects.

1.1.3 Exploratory Objectives

Exploratory objectives of this study include the following:

[redacted]

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

1.2 Endpoints

1.2.1 Primary Endpoint

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

1.2.2 Secondary Endpoints

Secondary endpoints include:

- Part 1: plasma PK parameters for TAK-951
  - Maximum observed plasma concentration (Cmax).
  - Area under the plasma concentration-time curve from time 0 to 24 hours (AUC24).
  - 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 (AUClast).
  - Time of first occurrence of Cmax (tmax).
  - Terminal disposition phase half-life (t1/2z).
  - Apparent clearance after extravascular administration (CL/F).
  - Apparent volume of distribution during the terminal disposition phase after extravascular administration (Vz/F).
- Part 2: plasma PK parameters for TAK-951 on Day 1.
  - Cmax, tmax, AUC24, and area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUCτ).

- Part 2: plasma PK parameters for TAK-951 at steady state.
  - AUCτ, AUC24, maximum observed concentration at steady state (Cmax,ss), tmax, t1/2z, CL/F, Vz/F, observed plasma concentration at the end of a dosing interval (Ctrough), accumulation ratio based on AUCτ (Rac[AUCτ]), calculated as AUCτ at steady state/AUCτ after a single dose, and accumulation ratio based on Cmax (Rac[Cmax]), calculated as Cmax at steady state/Cmax after a single dose. PK parameters will be calculated as permitted by the data. Additional PK parameters may be computed, as needed.
- Part 3:
  - Safety and tolerability of single SC rechallenge doses after a washout from multiple SC dose regimens of TAK-951 as assessed through vital signs, ECG, laboratory assessments, and AEs.
- All parts of the study:
  - Status of subject's antidrug antibodies (ADA) assessment (i.e., ADA-negative, or ADA-positive, and low or high ADA titer).

1.2.3 Additional/Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

- All parts of the study:
  - [redacted]
  - [redacted]
  - TAK-951 metabolites.
  - PK parameters in Part 3 may be computed as permitted by data collected.

1.2.4 Separately Reported Endpoints

The analysis of the following Endpoints will not be described in this statistical analysis plan (SAP) or reported in the clinical study report (CSR), but in a separate Biomarker Analysis Plan.

- Part 2: Change from baseline (Day -2 before first dose) in wearable/digital device parameters including: electrodermal activity (EDA), heart rate (HR), heart rate variability (HRV), actigraphy, and temperature through 48 hours post last dose.
- 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.

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

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

The study will consist of 3 parts:

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

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

An overview of treatment cohorts is presented in Table 1. Schedules of assessments for Part 1, Part 2, and Part 3 of the study are presented in Appendix A of the protocol "Schedule of study procedures".

Table 1 Overview of Treatment Cohorts

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

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

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

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.0 Statistical Hypotheses

Not applicable.

3.1 Statistical Decision Rules

Not applicable.

3.2 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

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

5.0 ANALYSIS SETS

5.0 Safety Analysis Set

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

5.1 PK Analysis Set

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

5.2 Immunogenicity Analysis Set

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

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All data recorded on the case report form (CRF) for raw and derived data will be listed by Study Part, cohort, and subject number. Data from each part of the study will be analyzed separately. Unless stated otherwise, the rechallenge results from Part 3 of the study will be presented along with the Part 3 results prior to the wash-out. For each part of the study, summaries will be presented by placebo (combined across cohorts), TAK-951 dose level (for Part 1)/TAK-951 dose level and frequency (e.g., BID or TID, for Part 2)/TAK-951 dose regimen (for Part 3), and TAK-951 overall (i.e., combining all dose levels (for Part 1)/dose levels and frequencies (for Part 2)/ dose regimens (for Part 3) of TAK-951). In addition, subgroup summary of adverse event and vital signs by placebo (combined across cohorts) and TAK-951 dose level by orthostatic maneuver status (Yes: Cohorts 1 through 4 vs No: Cohorts 5 and above) will be provided separately. Note that PK summaries will not combine TAK-951 dose levels or frequencies. Some summaries may also include a Total column of results for all data (i.e., combining placebo and TAK-951). Placebo data will be pooled across cohorts within each Part of the study where appropriate. The same TAK-951 dose level (Parts 1)/dose level and frequency (Part 2)/dose regimen (Part 3) will be pooled across cohorts within each part of the study where appropriate.

For summarization of safety data, the number of observations (n) and counts will be presented as an integer (no decimal places), arithmetic mean (mean), and median values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. For categorical variables, the denominator for any proportion will be the number of subjects who provided non missing responses. For continuous variables, the number of subjects with non-missing values, mean, SD, minimum, median, and maximum values will be used in tabulations.

The level of precision and rules for rounding PK concentrations and parameters are presented in the Clinical Pharmacology Analysis Plan (CPAP).

Further data handling conventions are outlined in Section 9.2 of this SAP.

6.1.1 Handling of Treatment Misallocations

Subjects who are misallocated treatments will be analyzed per the treatment received rather than the treatment they were randomized to.

6.1.2 Conventions for Missing Data

Other than the imputation of missing or partially missing dates as given in Section 6.1.3, there will be no imputation of incomplete or missing safety data.

For the analysis of plasma concentration data and derivation of PK parameters:

1. BLQ values will be set to 0.

2. A single BLQ value that occurs between 2 quantifiable concentrations in a profile will be set to missing.
3. Additional methods for the handling of missing plasma concentrations are outlined in the CPAP.

Original values will be presented in the data listings. Deviations from this convention may be considered on a case-by-case basis as deemed appropriate or mentioned in the CPAP.

6.1.3 Conventions for Missing/Partial Dates for Adverse Event/Concomitant Medication/Procedures

The start date that is completely or partially missing will be imputed as follows:

- If month and year are known but day is missing:
    - If month and year are the same as month and year of the 1st dose date, the day of the 1st dose date will be used to impute the missing day.
    - If month and year are prior to the month and year of the 1st dose date, the last day of the month will be used to impute the missing day.
    - If month and year are after the month and year of the 1st dose date, the 1st day of the month will be used to impute the missing day.
- If year is known, but both day and month are missing:
    - If the year is same as year of the 1st dose date, the month and day of the 1st dose date will be used to impute the missing month and day, respectively.
    - If the year is prior to the year of the 1st dose date, December 31st of the year will be used to impute the missing month and day, respectively.
    - If the year is after the year of the 1st dose date, January 1st of the year will be used to impute the missing month and day, respectively.
- If all (day, month, year) are missing, the 1st dose date will be used to impute the missing year, month, and day, respectively.

Imputing missing start date is mandatory. After imputation, all imputed dates are checked against the stop dates to ensure that start dates do not occur after stop dates. If an imputed start date occurs after the stop date, then change the imputed start date to be the same as the stop date.

The stop dates that are completely or partially missing will be imputed as follows:

- If the AE is “ongoing”, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be used to impute the missing day.
- If year is known, but both day and month are missing:
    - December 31st of the year will be used to impute the missing month and day, respectively.

- If all (day, month, year) are missing, the event will be considered as ongoing.

Imputing missing stop date is not mandatory if event is considered as ongoing. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for the stop date. After imputation, all imputed dates are checked against start dates to ensure that stop dates do not occur before start dates. If an imputed stop date occurs prior to the start date, then change the imputed stop date to be the same as the start date.

6.2 Disposition of Subjects

Disposition of all randomized subjects will be tabulated (count and percentage) for each part of the study:

- All treated subjects
- Subjects who were randomized but not treated, if applicable
- Subjects who completed the study investigational products
- Subjects who prematurely discontinued study investigational products
- Subjects who completed all study visits
- Subjects who prematurely discontinued from study.

Within each part of the study, the summary statistics will be presented by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), TAK-951 overall, and Total.

Primary reasons for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. Reasons for discontinuation include adverse event, lost to follow-up, pregnancy, protocol deviation, study terminated by sponsor, withdrawal by subject, and other specify. The date of first dose, date of last dose, duration of treatment and the primary reason for premature discontinuation of study treatment will be presented for each subject in listings.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by study part for all subjects in the Safety Set.

Summary statistics will be presented for continuous variables (e.g., age, height, weight, and body mass index [BMI]. The number and percentage of subjects within each category will be presented for categorical variables (e.g., gender, race, etc.). Individual subject demographic and baseline characteristic data will be listed. Within each part of the study, the summary statistics will be presented by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and

frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), TAK-951 overall, and Total.

All demographic and baseline characteristics will be provided by Study Part, cohort, and subject listings using safety analysis set.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23 or higher) and will be presented in listings based on safety analysis set.

6.4 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped at 8 or more days prior to the first dose of study drug. Concomitant medications are recorded on the eCRF and include any medications, other than study drug, taken at any time between 7 days prior to the first dose and 2 days after discharge from the study.

All medication history and concomitant medications will be listed by site (study center) and subject number. The listings will contain subject identifier, treatment, preferred medication name, dose, unit, frequency, route, start date, stop date, whether the medication was ongoing, and reason for use.

Medication history and concomitant medications will be coded using the WHO Drug Version 01March 2020 or higher.

6.5 Efficacy Analysis

Not Applicable.

6.6 Safety Analysis

The Safety Set will be used for all summaries of safety and tolerability assessment including AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters.

All safety data will be provided by-subject listings based on safety analysis set.

6.6.1 Adverse Events

All adverse events will be coded using MedDRA latest version. In this dictionary, each verbatim term is coded to a lower-level term, and then mapped to a preferred MedDRA term, which is then mapped to an SOC. All adverse events will be included in the data listings but only treatment emergent adverse events will be included in the summary tables.

A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened after first study drug administration and within 30 days of last dose of study drug (AE onset date – date of last dose ≤30). AEs with missing onset dates will be summarized with TEAEs regardless of toxicity grade and relationship to study medication. AEs of special interest (AESIs) for TAK-951 include injection site reactions, hypotension, orthostatic hypotension and tachycardia, and tachycardia. In addition, orthostatic hypotension is considered an identified risk based on previous clinical experience.

The summary of treatment-emergent adverse events (TEAEs) will include the number and percentage of subjects with at least 1 TEAE and be presented for each part of the study separately. Within each part of the study, the summary statistics will be presented by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), TAK-951 overall, and Total based on safety analysis set.

For Part 3 only, summary of TEAEs (after washout from multiple dose titration) will also be performed by placebo, TAK-951 single dose level (i.e., the single dose after washout from multiple dose titration), TAK-951 single dose overall (i.e., combine TAK-951 single dose), and Total (i.e., combine placebo and TAK-951 single dose).

The following summaries will be presented:

- Overview of TEAEs during the study – number and percentage of subjects, number of events.
- TEAEs by SOC and PT – number and percentage of subjects.
- Treatment-related TEAEs by SOC and PT – number and percentage of subjects.
- TEAEs by PT – number and percentage of subjects.
- Most frequent non-serious TEAEs (> 5% in any group within each part of the study) by PT – number and percentage of subjects.
- Toxicity grade of TEAEs by SOC and PT – number and percentage of subjects.
- Toxicity grade 3 or higher TEAEs by SOC and PT – number and percentage of subjects.
- Toxicity grade 3 or higher Treatment Related TEAEs by SOC and PT – number and percentage of subjects.
- Serious TEAEs by SOC and PT – number and percentage of subjects, number of events.
- Treatment Related Serious TEAEs by SOC and PT – number and percentage of subjects, number of events.
- Relationship of TEAEs by SOC and PT – number and percentage of subjects.
- TEAEs leading to permanent treatment discontinuation by SOC and PT – number and percentage of subjects.
- AESIs by SOC and PT - number and percentage of subjects, number of events.

In addition for Part 1 only, to assess the impact of orthostatic maneuver on TEAEs, the subgroup analyses by orthostatic maneuver status for all the above TEAE summaries will be provided.

When summarizing TEAE, a subject with multiple occurrences of the same PT within a SOC is counted only once in that PT within that SOC. SOCs will be sorted in alphabetical order, and within a SOC, PT will be sorted in descending order of the number of subjects with the PT in Total column for each part of the study, respectively.

For the summary of TEAEs by SOC, preferred term, and maximum toxicity grade, if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the maximum toxicity grade of the episode (preferred term). Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the maximum toxicity grade in that SOC.

TEAEs classified in the eCRF as related to the study treatment will also be summarized by preferred term and SOC. Adverse events with missing relationship will be classified as related to study treatment.

6.6.2 Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized using descriptive statistics for baseline (as defined in Section 9.2.2), postdose, and change from baseline to postdose by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall at scheduled assessment time points within each part of the study separately based on safety analysis set.

The number and percentage of subjects with at least 1 postdose value meeting the sponsor's markedly abnormal criteria (Section 9.4) for clinical laboratory parameters will be presented by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall within each part of the study separately based on safety analysis set.

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented. Clinical laboratory tests will be evaluated and presented using International System of Units (SI) units unless otherwise stated.

Additionally individual results of laboratory tests from serum chemistry and hematology that meet Takeda's markedly abnormal criteria (Section 9.4) will be summarized by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall within each part of the study separately based on safety analysis set.

In addition, the number and percentage of subjects within each of the following categories of liver function tests during the on-treatment period will be summarized by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall within each part of the study separately based on safety analysis set.

- ALT:
  - >3 × ULN;
  - >3 –≤ 5 × ULN;
  - >5 –≤ 8 × ULN;
  - >8 –≤ 20 × ULN;
  - >20 × ULN.
- AST:
  - 3 × ULN;
  - 3 –≤ 5 × ULN;
  - 5 –≤ 8 × ULN;
  - 8 –≤ 20 × ULN;
  - 20 × ULN.
- ALT or AST:
  - ALT > 3 × ULN or AST >3 × ULN;
  - (ALT > 3 × ULN and ALT ≤ 5 × ULN) or (AST ≥ 3 × ULN and AST ≤ 5 × ULN);
  - (ALT > 5 × ULN and ALT ≤ 8 × ULN) or (AST > 5 × ULN and AST ≤ 8 × ULN);
  - (ALT > 8 × ULN and ALT ≤ 20 × ULN) or (AST > 8 × ULN and AST ≤ 20 × ULN);
  - ALT > 20 × ULN or AST > 20 ×ULN.
- ALT/AST and Total Bilirubin:
  - ALT > 3 × ULN AND TBILI > 2 × ULN;
  - AST > 3 × ULN AND TBILI > 2 × ULN;
  - (ALT > 3 × ULN or AST > 3 × ULN) AND TBILI > 2 × ULN.

For Part 3 only, similar summary analyses of lab data (after washout from multiple dose titration) will also be performed by placebo, TAK-951 single dose level, TAK-951 single dose overall based on safety analysis set.

All clinical laboratory data will be presented in data listings. Laboratory data outside of the normal reference range will be flagged on the listing along with values meeting the markedly abnormal criteria.

6.6.3 Vital Signs

Vital sign measurements consist of body temperature, respiratory rate, BP, and HR. Orthostatic measurements for BP and HR will also be collected at screening and at the time points in Appendix A of the protocol “Schedule of study procedures”.

All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The investigator can take a third measurement if there is inconsistency between assessments. By providing the third measurement, the investigator is making a medical judgement of the presence of an inconsistency in the first two measurements. If 3 measurements are obtained, the final BP readout should be the average of the 2 more consistent assessments. The 2 more consistent assessments and final average can then be obtained by the following steps:

1. Calculate the absolute difference between two different measurements.
2. Pick the pair with smallest difference to calculate the average if no ties in the absolute difference occurs.
3. If the smallest difference is tied, pick the pair with later assessment times for calculating the average.

Vital signs (including but not limited to BP) data will be summarized using descriptive statistics for baseline, postdose, and change from baseline (as defined in Section 9.2.2) to postdose by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall at scheduled assessment time points within each part of the study separately based on safety analysis set.

Note, for all orthostatic measurements the baseline is semi-recumbent values and change from baseline is change from semi-recumbent HR and BP to standing value.

The number and percentage of subjects with at least 1 postdose value meeting the Takeda's markedly abnormal criteria (Appendix 9.5) for vital signs (including but not limited to BP) and orthostatic measurements (Appendix 9.7) will be presented by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall within each part of the study separately based on safety analysis set.

For Part 3 only, similar summary analyses of vital signs data (after washout from multiple dose titration) will be performed by placebo, TAK-951 single dose level, TAK-951 single dose overall based on safety analysis set.

In addition for Part 1 only, to assess the impact of orthostatic maneuver on vital signs, the subgroup analyses by orthostatic maneuver status for each vital sign summary will be provided.

Vital signs collected on the CRF will be presented in a by Study Part, cohort, and subject listing.

6.6.4 Electrocardiograms

ECG parameters (including but not limited to HR, QT/QTc, PR) will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) for baseline (as defined in Section 9.2.2), postdose, and change from baseline to postdose by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall at scheduled assessment time points within each part of the study separately based on safety analysis set. The number and percentage of subjects with at least 1 postdose value (Appendix 9.6) 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, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall within each part of the study separately based on safety analysis set.

For Part 3 only, similar summary analyses of ECG parameters (after washout from multiple dose titration) will be performed by placebo, TAK-951 single dose level, TAK-951 single dose overall based on safety analysis set.

ECG data will be listed by Study Part, cohort, and subject for each part of the study.

6.6.5 Physical Examination

Physical examination will be performed at screening. Symptom-driven physical exams may be performed at other times at the discretion of the PI. Physical exam findings will be presented in the data listings by Study Part, cohort, and subject.

6.6.6 Other Safety Analysis (if applicable)

Holter ECG and telemetry monitoring will be performed but the data will not be presented in the CSR.

6.6.7 Study Drug Exposure and Compliance

Study drug exposure (e.g., duration of treatment = last dose date – first dose date +1, number of dose received) will be summarized using descriptive statistics by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall within each part of the study separately based on safety analysis set. All study drug exposure and compliance data will be provided in by-subject listings using safety analysis set.

6.7 Immunogenicity Analysis

ADA positive is defined as subjects who have confirmed positive ADA status in at least 1 postbaseline assessments. ADA negative is defined as subjects who do not have a confirmed positive ADA status in any postbaseline assessment.

Pre-existing ADA response is defined as the patients who have ADA response in the baseline samples (before the treatment) or have ADA response in both baseline and postbaseline samples but the titer of the postbaseline ADA does not significantly increase (not ≥3 times the baseline titer value).

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

Immunogenicity will be summarized using the number and percentage of subjects in the following categories: ADA status (ADA negative, ADA positive), ADA titer (low or high) at baseline (prior and closest to a subject's first dose) and postbaseline visits by placebo, TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only)/TAK-951 dose regimen (for Part 3 only), and TAK-951 overall within each part of the study separately based on safety analysis set.

The summary of TEAE by PT and immunogenicity categories (ADA status (ADA negative, ADA positive), ADA titer (low or high)) and treatment arm based on immunogenicity analysis set may be provided to explore the relationship between immunogenicity status and safety, if deemed necessary.

The summary of PK parameters by immunogenicity categories (ADA status (ADA negative, ADA positive), ADA titer (low or high)) and treatment arm based on immunogenicity analysis set will be provided to explore the relationship between immunogenicity status and PK, if appropriate.

All immunogenicity data will be provided in by study part, cohort and subject listings based on immunogenicity analysis set.

6.8 Pharmacokinetic Analysis

All PK summaries and analyses (Parts 1 and 2 only) will be based on the PK Analysis Set and all concentration data listed by Study Part, cohort, and subject. The plasma concentrations of TAK-951 will be summarized by TAK-951 dose level (for Part 1 only)/TAK-951 dose level and frequency (for Part 2 only) at each scheduled sampling day/time within each part of the study using descriptive statistics (n, mean, standard deviation, percent coefficient of variation [%CV], median, minimum, and maximum).

PK parameters of TAK-951 will be derived using non-compartmental analysis methods. The PK parameters of TAK-951 will be determined from the concentration-time data for all subjects receiving TAK-951. Actual sampling times, rather than scheduled sampling times, will be used in all computations.

The following plasma PK parameters will be included in the PK summaries and analyses:

- Part 1: plasma PK parameters for TAK-951
  C_{max}, AUC_{24}, AUC_{∞}, AUC_{last}, t_{max}, $t_{1/2z}$, CL/F, V_z/F

- Part 2: plasma PK parameters for TAK-951 on Day 1
  C_{max}, t_{max}, AUC_{24}, and $AUC\tau$

- Part 2: plasma PK parameters for TAK-951 at steady state
  AUC_{τ}, AUC_{24}, $C_{max,ss}$, t_{max}, $t_{1/2z}$, CL/F, V_z/F, observed plasma concentration at the end of a dosing interval (C_{trough}), $R_{ac[AUC\tau]}$, and $R_{ac[Cmax]}$.

Additional PK parameters may be calculated as appropriate. PK parameters in Part 3 may be computed as permitted by data collected. Additional details will be provided in the Clinical Pharmacology Analysis Plan (CPAP).

For each part of the study (Parts 1 and 2 only), dose proportionality (for Part 1, dose proportionality is evaluated based on TAK-951 dose level; for Part 2 only, dose proportionality is evaluated based on TAK-951 dose level and frequency) will be assessed graphically (log-

transformed dose-normalized C_{max} and AUC versus dose) and by using a power model where appropriate. Dose proportionality of AUC_{∞}, AUC_{last} and C_{max} will be evaluated using a power model [1] with the form:

$$Y = \exp(\alpha) * (\text{dose})^{\beta} * \exp(\text{error})$$

where Y is the PK parameter of interest, $\exp(\alpha)$ and β are the coefficient and exponent of the power equation, respectively. Equivalently, by taking the natural logarithm (ln), the power model can be analyzed using linear regression model with the form:

$$\ln(Y) = \alpha + \beta * \ln(\text{dose}) + \text{error}$$

where α is the intercept, and β is the slope, and ln(dose) is the dose for each subject. Estimates of slope and intercept along with their 90% confidence intervals (CIs) will be reported.

A minimum of 3 values per dose must be available for a given parameter to assess the dose proportionality using the power model. In particular, dose proportionality is indicated if the 90% CI of the slope β of power model falling within the limits [1]:

$$\left(1 + \frac{\ln(.8)}{\ln(r)}, 1 + \frac{\ln(1.25)}{\ln(r)}\right)$$

where r is the ratio of the highest and the lowest dose in each Part of the study.

Dose proportionality may also be assessed graphically using scatter plots with regression lines presented and ln(dose) as the x-axis versus the ln(PK parameter) as the y-axis.

The assessment of linearity may also be determined visually from plots by the Pharmacokineticist. This assessment may override the statistical assessment; where this occurs; it will be detailed in the CSR.

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

Specific descriptions of the analyte and PK parameter summary tables and figures for the CSR are provided in the CPAP.

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

6.8.1 Biomarker Analysis

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

[redacted]

Details on the analysis of data from the wearable device (embrace Plus) will be provided in a separate document (Biomarker Analysis Plan) and not reported in the CSR. [redacted]

6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable

6.10 Interim Analysis

An interim analysis (IA) may be planned to support internal decision making regarding further development of [redacted] TAK-951. In case an IA is deemed necessary by the sponsor, it will take place during the double-blind portion of the study.

Takeda personnel will be unblinded to review the data and results of IA to inform later parts of the study and support internal decision making, while the site personnel and study subjects will remain blinded to study treatment assignment. The details of IA data access and distribution will be described in a separate document (i.e., data access management plan).

The statistical methodologies to be used in the IA are as described in this SAP. In particular,

- All available data at the data cut of the IA will be included in the IA.
- The deliverables for IA will focus on data below:
    - Subject disposition, demographic and baseline characteristics.
    - Key safety data including but not limited to TEAEs, lab, vital signs, ECG.
    - TAK-951 plasma concentrations and PK parameters.

6.11 Additional Analysis Related to COVID

Depending on the prevalence of coronavirus disease (COVID) infections and illness in regions where the study is conducted, additional analysis may be performed to evaluate the impact of COVID on the safety of all participating subjects:

- A separate data listing of adverse event information from all subjects with COVID-19 related AEs, including but not limited to the preferred terms that contains "COVID-19", "SARS-CoV-2", and "Coronavirus".
- Data listing of all subjects affected by COVID-19 related study disruption, including subject ID, site ID, and which visits, and assessments were impacted and any alternative method of subject contact due to COVID-19.

7.0 REFERENCES

1. Jurgen Hummel, Sue McKendrick, Charlie Brindley and Raymond French. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. *Pharmaceut. Statist.* 2009; 8: 38–49.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

At the signing of this document there are no changes to the analyses as outlined in the protocol.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

SAP Version	Date	Revision History
1.0	14Feb2021	NA
2.0	30Mar2022	The following changes have been made in this version of SAP per the Protocol dated 23Nov2021: • Updated text in Section 6.10 for administrative reasons to remove the first IA. • Updated the Markedly Abnormal Values in Appendices to reflect the most recent safety criteria and add Appendix 9.7 Orthostatic Vital Sign Changes The following additional changes were also made in this version of SAP to ensure agreement with the methods being used in the CPAP: • Corrected the typo in the section number for immunogenicity analysis by changing it from Section 6.7.1 to Section 6.7 • The geometric mean will not be calculated for the plasma concentrations.
3.0	3Aug2023	The following changes have been made in this version of the SAP to accommodate the changes due to Amendment 1 of the Protocol dated 24Jan2023

SAP Version	Date	Revision History
		and Amendment 2 of the Protocol dated 16Mar2023: • Change the title of the study and making the study sponsor open. • Additional subgroup analyses of AE and vital signs are planned to evaluate the impact of physical maneuver changes due to protocol amendment 2.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

9.2.2 Definition of Baseline

Baseline is defined as the most recent non-missing value of each assessment prior to the subject's first dose of study treatment, unless otherwise stated. Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using appropriate SAS® procedures such as Proc Univariate.

9.2.3 Definition of Study Day and Study Visit Windows

Study day will be calculated relative to the date of the first dose of the study drug in each study part. Study days prior to the first dose of study drug in each study part will be calculated as: (date of assessment/event - date of first dose of study drug in that study part). Study days on or after the first dose of study drug in each study part will be calculated as: (date of assessment/event - date of first dose of study drug in that study part +1).

All data will be categorized on the basis of the actual visit day or time of visit day at which they are collected. Visit day and visit times are predefined values that appear in Appendix A of the protocol "Schedule of study procedures". The midpoint between visits will be used as the dividing point to assign data to a visit day or visit time. Data occurring on the midpoint will be assigned to the latter of the two visit days or visit times. More than 1 result for a parameter may be obtained in a visit window. In such an event, the result with the date closest to the scheduled visit day or time of day will be used. In the event of 2 observations are equidistant to the scheduled visit day or time of day, the latter of the observations will be used. Summaries will be provided for scheduled visits only. If the actual date and/or time are not provided the nominal visit can be used to assign the visit and time.

The study window convention will not be applied to the CRF data listings. The data listings for CRF data will display the raw data as collected and entered in the CRF.

9.3 Analysis Software

SAS® version 9.4 or higher will be used for all statistical analyses provided in the CSR.

9.4 Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	SI	<0.8 × LLN	>1.2 × ULN
Hematocrit	SI	<0.8 × LLN	>1.2 × ULN
RBC count	SI	<0.8 × LLN	>1.2 × ULN
WBC count	SI	<0.5 x LLN	>1.5 x ULN
Platelet Count	SI	<75 x 10^9/L	>600 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	SI	--	>3x ULN
AST	SI	--	>3x ULN
GGT	SI	--	>3*ULN, if baseline is normal; >2*baseline, if baseline is high abnormal
Alkaline phosphatase	SI	--	>3*ULN, if baseline is normal; >2*baseline, if baseline is high abnormal
Total Bilirubin	SI	--	>1.5*ULN, if baseline is normal; >1.5*baseline, if baseline is high abnormal
Albumin	SI	<25 g/L	--
Total protein	SI	<0.8x LLN	>1.2x ULN
Creatinine	SI		>177 μmol/L
Blood urea nitrogen	SI		>10.7 mmol/L
Sodium	SI	<130 mmol/L	>150 mmol/L
Potassium	SI	<3.0 mmol/L	>5.5 mmol/L
Glucose	SI	<3 mmol/L	>10 mmol/L
Chloride	SI	<75 mmol/L	>126 mmol/L
Calcium	SI	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	
Bicarbonate	SI	<8.0 mmol/L	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

9.5 Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	ºC	<35.6	>37.7
	ºF	<96.1	>99.9
Pulse	bpm	<50	>120
Respiratory Rate	breath per minute	<12	>16

9.6 Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	<=80 milliseconds	>=200 milliseconds
QTcF Interval		≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	<=80 milliseconds	>=120 milliseconds

9.7 Criteria for Markedly Abnormal Orthostatic Changes

Parameter	Criteria
Orthostatic Hypotension	Decrease in SBP ≥20 mm Hg OR a decrease in DBP ≥10 mm Hg on standing.
Orthostatic Tachycardia	Defined as an increase in HR of >30 bpm or HR >120 bpm on standing

Note: Orthostatic measurement = standing vital measurement – supine vital measurement.