Statistical Analysis Plan

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 1; 31 October 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.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-510-1001

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

PHASE 1

Version: **2.0 (Amendment 1)**

Date: 31 October 2022

Prepared by:

[redacted]

Manager, Statistical and Quantitative Sciences,
Takeda Development Center Americas, Inc.

Based on:

Protocol Amendment 03, Protocol Date: 21 April 2022

Statistical Analysis Plan, Original Version, Date: 09 March 2021

1.1 APPROVAL SIGNATURES

REPRESENTATIVES OF TAKEDA

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

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

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

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λ_z	terminal disposition phase rate constant
ADA	anti-drugs antibodies
AE	adverse event
AESI	adverse event of special interest
A_{et}	amount of drug excreted in urine from time 0 to time t
$A_{et1\text{-}t2}$	amount of drug excreted in urine from time 1 to time 2
$A_{e\tau}$	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 level
BMI	body mass index
BP	blood pressure
BLQ	below limit quantification
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
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
$f_{e,t}$	fraction of administered dose of drug excreted from urine from time 0 to time t
FIH	first-in-human
HR	heart rate
[redacted]	[redacted]
GLP	Good Laboratory Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities

MRD	Multiple rising dose
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
CPAP	clinical pharmacology analysis plan
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
QTcF	QT interval with Fridericia correction
Rac(AUC)	accumulation ratio based on AUCτ
Rac(C_{max})	accumulation ratio based on C_{max}
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous(ly)
SRD	single rising dose
SOC	system organ class
ULN	upper limit of normal
TEAE	treatment-emergent adverse event
TBILI	total bilirubin
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of C_{max}
TQT	thorough QT
$V_{z/F}$	apparent volume of distribution during the terminal disposition phase after extravascular

3.0 INTRODUCTION

This document describes the statistical analyses to be performed and data presentations to be produced for this randomized, double-blind, placebo-controlled, phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of TAK-510 in healthy subjects.

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of the study findings by specifying the statistical approaches to the analyses of the double-blinded data prior to database lock. This SAP was developed based on the International Conference on Harmonization (ICH) E3 and E9 Guidelines and in reference to the following document:

- Protocol TAK-510-1001 Amendment 03 dated 21 April 2022.

Any deviations during the analysis and reporting process from the current statistical analysis plan will be described and justified in the final report. Analysis issues that suggest changes to the principal features stated in the protocol will be documented in a protocol amendment. Otherwise, the statistical analysis plan will be updated through an amendment in which the changes in the analysis will be documented.

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives of this study are:

- Part 1:
  - To characterize the safety and tolerability of single SC doses of TAK-510 in healthy subjects.
- Parts 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.

4.2 Secondary Objectives

The secondary objectives of this 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.

[redacted]

- Part 3:
  - To characterize the PK of TAK-510 in plasma following multiple SC doses and dosing schedules in healthy subjects.

4.4 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.

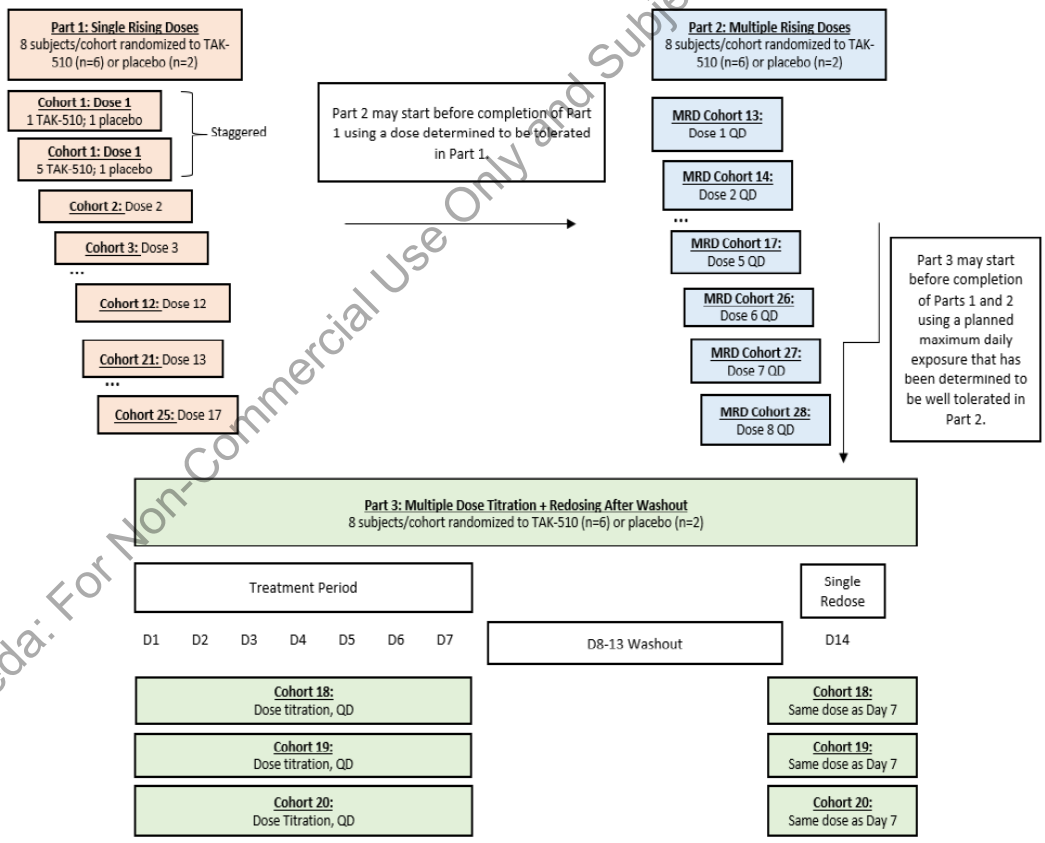
The study will consist of 3 parts (Figure 4.a):

- 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 volunteers. 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 volunteers. Up to 8 doses/dose regimens 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 volunteers. Up to 3 dose regimens 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. An overview of treatment cohorts is presented in Table 4.a.

Figure 4.a Schematic of Study Design



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.

Table 4.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.

5.0 STUDY ENDPOINTS

5.1 Primary Endpoints

- 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 AEs.

5.2 Secondary Endpoints

- 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}($R_{ac[C_{max}]}$), 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 (A_{e_t}).
  - Amount of drug excreted in urine from time 1 to time 2 ($A_{e_{t1-t2}}$).
  - Amount of drug excreted in urine during a dosing interval (τ) at steady state (A_{e_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 (i.e., ADA-negative or ADA-positive, and low or high ADA titer).

[redacted]

- Part 3 includes the following plasma PK parameters:
  - AUC_{τ}, AUC_{last}, C_{max}.

6.0 INTERIM ANALYSIS

An interim analysis may be performed for all available data from completed subjects in Parts 1 and 2 if a data-dependent internal decision is needed to inform the subsequent development of TAK-510 before database lock. A final analysis will be performed after the end of the study to report all data from all study parts. Safety, tolerability, and available PK data will be reviewed in a blinded manner after completion of each cohort and before next dose escalation stage in the study.

7.0 DETERMINATION OF SAMPLE SIZE

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

8.0 METHODS OF ANALYSIS AND PRESENTATION

8.1 General Principles

All study-related raw and derived data for randomized subjects will be presented in by-subjects listings. All available data from Study Parts (e.g., 1, 2, and/or 3) will be analyzed and presented separately.

Data listings and summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK/Immunogenicity).

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.

The following conventions will be applied to present the analyses results in this SAP, unless otherwise specified.

- Descriptive statistics:
  - For continuous data (study drug exposure and compliance, clinical laboratory data, vital signs, ECGs, etc.):
    - n, mean, standard deviation, median, minimum, and maximum.
  - For Pharmacokinetics and biomarkers:
    - n, arithmetic mean, standard deviation, percent coefficient of variation [%CV], geometric mean, geometric %CV, median, minimum, and maximum.
  - For categorical data:
    - frequency counts and percentages.
  - Percentages will be reported to 1 decimal place. For the calculation of summary statistics and statistical analysis, unrounded data will be used.
- By treatment arm:
  - For Pharmacokinetics:
    - by dose level (Parts 1 and 2 only)/dose regimen (Part 3 only if applicable) of TAK-510, as appropriate, within each part of the study separately.
  - For disposition, demographics and baseline characteristics, concomitant medication, AEs, and Impact due to COVID-19:
    - by placebo, each TAK-510 dose level (Parts 1 and 2 only)/dose regimen (Part 3 only if applicable), TAK-510 overall (i.e., combining all TAK-510 arms, not applicable to summary of disposition, demographics and baseline characteristics, concomitant medication), and total (i.e., combining placebo and TAK-510 arms), as appropriate, within each part of the study separately.
  - For the rest:
    - by placebo, dose level (Parts 1 and 2 only)/dose regimen (Part 3 only if applicable) of TAK-510, as appropriate, within each part of the study separately.

- Treatment arm pooling:
  - Placebo data will be pooled across cohorts within each part of the study where appropriate.
  - The same dose level (Parts 1 and 2 only)/dose regimen (Part 3 only if applicable) will be pooled across cohorts within each part of the study where appropriate.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Version 3.1.0 or higher will be utilized to ensure compliance with CDISC standards.

8.1.1 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 visit at which they are collected. Visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF). 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 will be used. In the event of 2 observations equidistant to the scheduled visit day, the later of the observations will be used. Summaries will be provided for scheduled visits only.

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

8.1.2 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

Plasma or urine concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summary of concentration values. These values will be flagged in the data listings and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

8.1.3 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.

8.2 Analysis Sets

- 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.

- 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.
- 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.

A summary of analysis sets based on all randomized subjects will be provided. Details of subject assignment to the analysis sets will be provided in a by-subject listing for all randomized subjects.

8.3 Disposition of Subjects

Disposition of all randomized subjects (denominator) will be tabulated (count and percent). The summaries of disposition will be presented by treatment arm.

Disposition of all randomized subjects will be tabulated for each part of the study:

- 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 study visits.

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, failure to meet continuation criteria, lost to follow-up, pregnancy, protocol deviation, study terminated by sponsor, withdrawal by subject, liver function test (LFT) abnormalities, and Other. The date of first dose, date of last dose, duration of treatment (last dose date – first dose date +1), number of dose received, and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

8.4 Protocol Deviations

All significant protocol deviations that occur during the study will be reviewed and finalized prior to database lock. Listing of all significant protocol deviations will be provided for all randomized subjects.

8.5 Demographic 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 (e.g., age, height, weight, and BMI) by treatment arm using safety analysis set. The number and percentage

of subjects in each class of the categorical demographic variables and baseline characteristics variables (e.g., sex, ethnicity, race) will be tabulated by treatment arm using safety analysis set.

All data will be provided in by-subject listings using safety analysis set.

8.6 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. Concurrent medical conditions include significant ongoing conditions or diseases present at signing of informed consent.

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.

8.7 Medication History and Concomitant Medications

Medication history includes all medications, other than study treatment, which was stopped at or prior to the first dose of study treatment. Concomitant medication includes all medication, other than study treatment, which was started on and after the first dose of study treatment, through the end of the safety follow-up period.

Medication history and concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODrug, March, 2020 or higher) coding system.

The summary of concomitant medication will include the number and percentage of subjects by preferred term within each Anatomical Therapeutic Chemical (ATC) class level 2 by treatment arm using safety analysis set. The summary table will be presented with ATC class sorted in alphabetical order and preferred term sorted in decreasing frequency based on the total number of subjects. A subject will be counted only once within a given ATC class and within a given preferred term, even if he/she received the same concomitant medication at different times.

All medication history and concomitant medication data will be provided in by-subject listings using safety analysis set.

8.8 Study Drug Exposure and Compliance

Treatment exposure (e.g., duration of treatment = last dose date – first dose date +1, number of dose received) will be summarized using descriptive statistics by treatment arm based on safety analysis set.

All study drug exposure and compliance data will be provided in by-subject listings using safety analysis set.

8.9 Summary of the Impact due to COVID-19

The impact due to COVID-19 will be summarized using the number and percentage of subjects in each category of impact by treatment arm based on all randomized subjects:

- Subjects with at least one study visit impacted due to COVID-19.

- Subject with adjusted methods of contact used due to COVID-19 by study visit
  - Subjects with assessments done per the adjusted method of contact by study visit.

All COVID-19 impact data will be provided in by-subject listings for all randomized subjects.

8.10 Efficacy Analysis

Not applicable

8.11 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

8.11.1 Pharmacokinetic Analysis

The plasma (all parts of the study) and urine (Parts 1 and 2 only) concentrations of TAK-510 will be summarized by treatment arm using descriptive statistics, at scheduled sampling day/time within each part of the study separately, based on the PK analysis set.

The major, but not limited to, PK parameters of TAK-510 (i.e. C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_{last}, AUC_{τ}, CL/F, V_z/F, A_{e_t} , $A_{e_{t1-t2}}$, A_{e_τ}, $f_{e,t}$, CL_R, details are described in CPAP) that were determined using a non-compartmental analysis will be summarized by treatment arm using descriptive statistics based on the PK analysis set. If a PK parameter cannot be estimated from a subject's concentration data, the PK parameter will be considered as missing in the summary tables.

Individual plasma (all parts of the study) and urine (Parts 1 and 2 only) concentrations of TAK-510, and PK parameters will be presented in by-subject listings based on PK analysis set.

PK analysis and relevant details will be described in the Clinical pharmacology analysis plan (CPAP).

Dose proportionality will 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 (Parts 1 and 2 only) separately using the method below, where appropriate:

For each part of the study (Parts 1 and 2 only), the dose proportionality of AUCs 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 a given part of the study.

Dose proportionality may 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.

In addition, exploratory metabolite profiling may be conducted on plasma or urine samples to determine the metabolites of TAK-510. If conducted, the analysis plan will be documented separately, data will be reported separately and not be reported in the CSR.

8.11.2 Pharmacodynamic Analysis

Not applicable.

8.11.3 Biomarker Analysis

The concentrations of [redacted] at each time point (i.e., Day -1 0 hour and baseline [predose, Day 1]) and Overall (i.e., all available data within each part of the study) will be summarized by treatment arm using descriptive statistics based on safety analysis set. In addition, the number and percentage of subjects within each of the 4 categories defined by quartile (i.e., 0 to <Q1, Q1 to <median, median to <Q3, ≥Q3, where quartile is determined by all available data within each part of the study) of [redacted] concentrations will be presented for each time point and Overall (i.e., all available data within each part of the study) by treatment arm based on safety analysis set. The baseline, postbaseline values, and change from baseline [redacted] at scheduled time points within each part of the study will be summarized by treatment arm using descriptive statistics based on safety analysis set. All data will be provided by-subject listings.

Duplicate biomarker (i.e., more than one set of data for a particular visit) for a given time point is not expected. For continuous data, if duplicate data are received and deemed valid per data review, the results will be averaged and the average value will be used. The average value will be added to the analysis dataset.

8.12 Safety Analysis

Safety analyses will be based on the safety analysis set. No formal statistical tests or inference will be performed for safety analyses.

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

8.12.1 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 dose of the study treatment and within 30 days of last dose of study treatment (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-510 include injection site reactions, hypotension, and tachycardia.

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 treatment arm based on safety analysis set.

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

In the summary of 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 an SOC, PT will be sorted in descending order of total number of subjects with the PT for TAK-510 overall in 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.

For Part 3 only, similarly, the TEAEs that started or worsened after the single SC rechallenge dose (after 7 days of washout from multiple dose regimens of the study treatment) will be summarized by placebo and level of the single SC rechallenge dose of TAK-510, TAK-510 single SC rechallenge dose overall, and total based on safety analysis set.

8.12.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be evaluated and presented using International System of Units (SI) units unless otherwise stated. If duplicate data for a laboratory test at a given time point are received and deemed valid per data review, the results will be averaged and the average value will be used.

The clinical laboratory parameters (serum chemistry tests, urinalysis, hematology laboratory tests) will be summarized using descriptive statistics for baseline, postbaseline values, and change from baseline by treatment arm based on safety analysis set. The clinical laboratory parameters will be only summarized at the scheduled visits.

In addition, individual result for serum chemistry tests and hematology laboratory tests will be evaluated against the Takeda's predefined laboratory markedly abnormal value (MAV) criteria Appendix A). All postbaseline clinical lab results including scheduled and unscheduled measurements will be included in the MAV evaluation. For the clinical laboratory parameter of interest, the number and percentage of subjects with at least 1 postdose value meeting the Takeda's MAV criteria will be presented by treatment arm 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 treatment arm 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 (TBILI):
  - 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 if applicable, similarly, the clinical laboratory data after the single SC rechallenge dose (after 7 days of washout from multiple dose regimens of the study treatment) will be summarized by placebo and level of the single SC rechallenge dose of TAK-510, and TAK-510 single SC rechallenge dose overall based on safety analysis set.

All clinical laboratory data will be presented in the by-subject listings. Clinical laboratory data outside of the normal reference range will be flagged in the listing along with values meeting MAV criteria.

8.12.3 Vital Signs

Typically, blood pressure (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 (see Protocol 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 for each scheduled visit. If the investigator takes a third BP and pulse assessment when results are inconsistent, the average value of the 2 more consistent corresponding assessments

will be used in the summary analysis for each scheduled visit. The 2 more consistent assessments and final average can then be obtained by the following steps:

a. Calculate the absolute difference between two different measurements.

b. Pick the pair with smallest difference to calculate the average if no ties in the absolute difference occurs.

c. If the smallest difference is tied, pick the pair with later assessment times for calculating the average.

The baseline, postbaseline values, and change from baseline of vital signs (including but not limited to BP) data will be summarized using descriptive statistics by treatment arm at each study scheduled visit based on safety analysis set. Meanwhile, the time-matched difference between Day 1 and Day -1 values of vital signs will summarized using descriptive statistics by treatment arm at each nominal timepoint where appropriate based on safety analysis set.

For each orthostatic vital sign parameter (i.e., BP and Pulse), the difference between standing and semi-recumbent (i.e., standing vital sign measurement – semi-recumbent vital sign measurement) at each study scheduled visit will be summarized by treatment arm based on safety analysis set.

For visualization purpose, the line plot with error bars, with study scheduled visits as x-axis and vital sign parameter (i.e., semi-recumbent BP and pulse, standing BP and pulse, orthostatic BP and pulse) as y-axis, will be used to plot group means (± SD) of vital sign measurements that will be color coded for each treatment arm based on safety analysis set. Similar line plot with error bars will be used to plot group means (± SD) of time-matched difference between Day 1 and Day -1 values of vital signs (i.e., semi-recumbent BP and pulse, standing BP and pulse, orthostatic BP and pulse).

In addition, average result at each scheduled visit and individual result at each unscheduled visit for vital signs will be evaluated against the Takeda's predefined markedly abnormal value (MAV) criteria (Appendix B). The orthostatic hypotension will be identified by criteria for identification of markedly abnormal orthostatic changes (Appendix C). All postbaseline vital signs including both scheduled and unscheduled measurements will be included in the MAV evaluation. For each vital sign parameter or orthostatic hypotension, the number and percentage of subjects with at least 1 postbaseline value meeting the Takeda's MAV criteria will be presented by treatment arm based on safety analysis set.

For Part 3 only if applicable, similar summary analyses of vital signs after the single SC rechallenge dose (after 7 days of washout from multiple dose regimens of the study treatment) will be summarized by placebo and level of the single SC rechallenge dose of TAK-510, and TAK-510 single SC rechallenge dose overall based on safety analysis set.

All vital sign data will be presented in the by-subject listings.

8.12.4 12-Lead ECGs

ECG parameters (i.e., heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (Fridericia's)) will be summarized using descriptive statistics for baseline, postbaseline value, and change from baseline by treatment arm based on safety analysis set. The ECG parameters will be only summarized at the scheduled visits.

In addition, individual result for ECG parameters (heart rate, PR interval, QRS interval, and QTc interval) will be evaluated against the Takeda's predefined markedly abnormal value (MAV) criteria (Appendix D). All postbaseline ECG data including scheduled and unscheduled measurements will be included in the MAV evaluation. For the ECG parameter of interest, the number and percentage of subjects with at least 1 postdose value meeting Takeda's MAV criteria for ECG parameters will be presented by treatment arm based on safety analysis set.

The investigator's ECG interpretation (Normal, Abnormal but not clinically significant, or Abnormal and clinically significant, Not evaluable) will summarized using a shift table as cross-tabulations (baseline versus each scheduled postbaseline visit) of numbers and percentage of subjects in each of appropriate categories by treatment arm based on safety analysis set.

For Part 3 only, similar summary analyses of ECG data after the single SC rechallenge dose (after 7 days of washout from multiple dose regimens of the study treatment) will be summarized by placebo and level of the single SC rechallenge dose of TAK-510, and TAK-510 single SC rechallenge dose overall based on safety analysis set.

All ECG data along with values meeting MAV criteria will be presented in the by-subject listings based on safety analysis set.

8.12.5 Analysis of Other Safety Parameters

Physical examination findings will only be presented in by-subject listings based on safety analysis set.

8.13 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.

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 and postbaseline visits by treatment arm based on immunogenicity 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 plasma concentration and PK parameters (including but not limited to C_{max} , AUCs and CL/F where appropriate) by 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 PK, if deemed necessary.

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

8.14 Interim Analysis

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

Two scenarios where the data-dependent internal decision will activate an interim analysis and associated analyses are detailed below:

1. A decision about whether to complete Part 3 has not been made.
2. Study will end after completion of Parts 1 and 2 (IA will become final analysis).

In the event of scenario 1, the interim analyses of PK (per method in Section 8.11.1), Safety (per method in Section 8.12), and immunogenicity (per method in Section 8.13) endpoints, based on the data cut prespecified by the study team, will be performed.

In the event of scenario 2 where the study ends after completion of Parts 1 and 2, all relevant analysis described in this SAP for Parts 1 and 2 will be completed.

9.0 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.

10.0 CHANGES IN THE STATISTICAL ANALYSIS PLAN

10.1 Changes to Protocol Planned Analyses

Not applicable.

10.2 Revision History

Version	Approval Date	Primary Rationale for Revision
1.0	09 March 2021	Not Applicable
2.0	31 October 2022	Updated the texts in Section 4.4 Study Design, Section 6.0 Interim Analysis, Section 8.14 Interim Analysis, Figure 4.a, and Table 4.a to reflect the updates in Protocol Amendment 03. Added summary for TEAE with toxicity grade 3 or higher in Section 8.12.1. Added the statistical algorithm in Section 8.12.3 (previous Section 8.13.3) to calculate the average value if a second or a third measurement has been made per protocol specified procedure for vital signs assessment. Clarified the MAV evaluation for values at scheduled and unscheduled visits in Section 8.12.3 and updated the tables in Appendix B and Appendix C.

11.0 APPENDIX

Appendix A Criteria for Identification of Markedly Abnormal Laboratory

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 × ULN
Platelet Count	SI	$<75 \times 10^9$/L	$>600 \times 10^9$/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	--	>3 × ULN
AST	SI	--	>3 × 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	>1.2 × 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.

Appendix B 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	^{o}C	<35.6	>37.7
	^{o}F	<96.1	>99.9
Pulse rate	bpm	<50	>120
Respiratory Rate	breath per minute	<12	>16

Appendix C Criteria for Identification of Markedly Abnormal Orthostatic Changes

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

Note: Orthostatic measurement = standing vital measurement – semi-recumbent vital measurement.

Appendix D 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	01-Nov-2022 20:13 UTC