Statistical Analysis Plan

NCT Number: NCT04964258

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

Study Number: TAK-105-1001

Document Version and Date: Version 2.0, 15 May 2023

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-105-1001

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

Phase: 1

Version: 2.0 (Amendment 1)

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Based on:

Protocol Amendment 04, Protocol Date: 19 December 2022

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0	19 July 2021	Not Applicable
2.0	15 May 2023	To remain consistent with Protocol Amendment 04.

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ABBREVIATIONS

λ_z	terminal elimination rate constant
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
A*e*t	amount of drug excreted in urine from time 0 to time t
A*e*t1-t2	amount of drug excreted in urine from time 1 to time 2
Aeτ	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
AUClast	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUCτ	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
CLR	renal clearance
Cmax	maximum observed plasma concentration
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	observed plasma concentration at the end of a dosing interval
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
fe,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]
[redacted]	[redacted]
[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(Cmax)	accumulation ratio based on Cmax
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
t1/2z	terminal disposition phase half-life
tmax	time of first occurrence of Cmax
TQT	thorough QT
Vz/F	apparent volume of distribution during the terminal disposition phase after extravascular

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

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

1.1.2 Secondary Objective(s)

The secondary objectives of the study are:

- *Part 1:*
  - *To characterize the PK of TAK-105 in plasma following single SC dose of TAK-105-a in healthy subjects.*
  - *To assess the immunogenicity of TAK-105 following single SC dose in healthy subjects.*
  - *To characterize the PK of TAK-105 in urine following single SC dose of TAK-105-a in healthy subjects.*
- *Part 2:*
  - *To characterize the PK of TAK-105 in plasma following multiple SC doses of TAK-105-a in healthy subjects.*
  - *To assess the immunogenicity of TAK-105 following multiple SC doses in healthy subjects.*

  - *To characterize the PK of TAK-105 in urine following multiple SC doses of TAK-105-a in healthy subjects.*

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

1.1.3 Exploratory Objective(s)

[redacted]

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

1.2 Endpoints

1.2.1 Primary Endpoint(s)

The primary endpoint of the study is:

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

1.2.2 Secondary Endpoint(s)

Secondary endpoints include:

- *Parts 1, 5a, and 6: plasma PK parameters for TAK-105*
  - *Maximum observed plasma concentration (C_{max}).*
  - *Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).*
  - *Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).*
  - *Time of first occurrence of C_{max} (t_{max}).*
  - *Terminal disposition phase half-life ($t_{1/2z}$).*
  - *Apparent clearance after extravascular administration (CL/F).*
  - *Apparent volume of distribution during the terminal elimination phase after extravascular administration(V_z/F).*
- *Parts 2 and 5b: plasma PK parameters for TAK-105 on Day 1 (the first dose):*
  - *C_{max}, t_{max}, and area under the concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_{τ}).*
- *Parts 2 and 5b: plasma PK parameters for TAK-105 on Day 22 (the fourth dose):*

  AUCτ, C_{max}, t_{max}, $t_{1/2z}$, CL/F, V_z/F, observed plasma concentration at the end of a dosing interval (C_{trough}).
- *Parts 1, 2, and 5a/b include the following urine PK parameters:*
  - *Amount of drug excreted in urine from time 0 to time t (Ae_t).*
  - *Amount of drug excreted in urine from time 1 to time 2 (Ae_{t1-t2}).*
  - *Amount of drug excreted in urine during a dosing interval (τ) after last dose (Ae_{τ}).*
  - *Fraction of administered dose of drug excreted from urine from time 0 to time t ($f_{e,t}$).*
  - *Renal clearance (CL_R).*

- *All parts of the study:*
  - *Status of subject's ADA assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer).*

1.2.3 Exploratory Endpoint(s)

Exploratory endpoints will be assessed through the following parameters:

- [redacted]
- *Parts 3 and 4 include the following plasma PK parameters:*
  - AUC_{τ}.
  - AUC_{last}.
  - C_{max}.

2.0 STUDY DESIGN

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

The study will consist of 6 parts:

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

- *Part 6 randomized, double-blind, sponsor-open, placebo-controlled SRD design to assess the safety, immunogenicity, tolerability, and PK of a new formulation of TAK-105-b in healthy subjects. Up to 2 cohorts may be enrolled.*

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

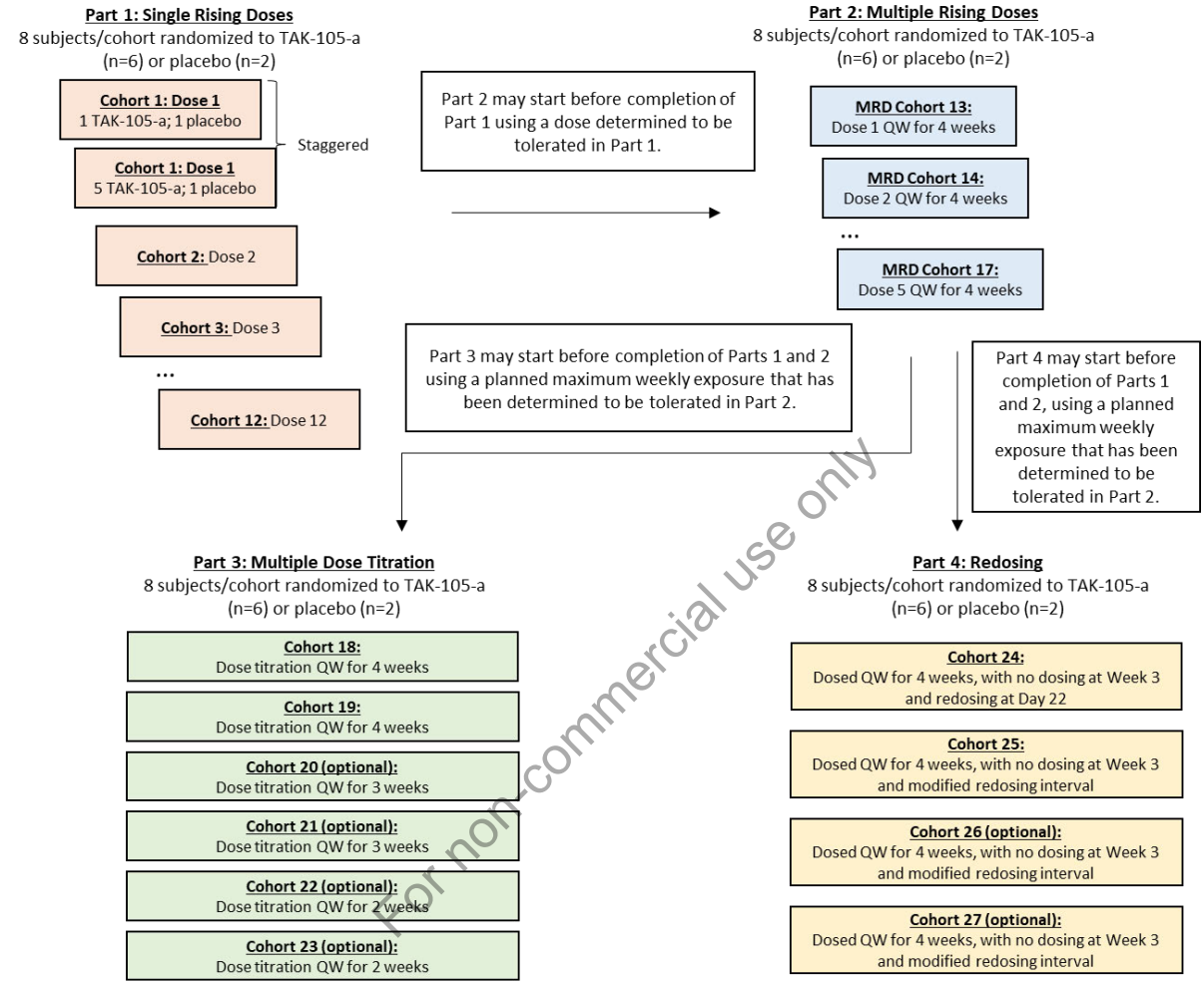
Study drug in Parts 1 to 5 is TAK-105-a (Process A formulation) or matching placebo and in Part 6 is TAK-105-b (Process B formulation) or matching placebo, which will be administered SC.

While Parts 1 (SRD) and 2 (MRD) of TAK-105-1001 are intended to be completed as planned, subsequent parts of the study (ie, Parts 3 or 4) may not be conducted at the discretion of the sponsor. Parts 1 and 2 will be initiated in advance of Parts 3 and 4. Parts 3 and 4 will be conducted at the discretion of the sponsor based on a review of the available safety and PK data from Parts 1 and 2. At the discretion of the sponsor, Parts 3 and 4 may be initiated before completion of all cohorts in Parts 1 and 2 as otherwise permissible in the protocol. Parts 5 may be performed in parallel with Parts 1 and 2 based on the review of safety and PK data at the matching dose from the previous parts. Part 6 with the new drug formulation of TAK-105 (TAK-105-b) may be performed in parallel with Part 1 provided that the new formulation is available and after Part 1 SRD data are available.

Safety will be assessed by monitoring for adverse events (AEs), vital signs including orthostatic assessments, 12-lead electrocardiograms (ECGs), telemetry, safety laboratory assessments after each dose, and immunogenicity. PK sampling times may vary based on emerging safety, tolerability and PK data, but the maximal number of samples will not change. Subjects may not participate in more than 1 part or more than 1 dosing cohort of the study.

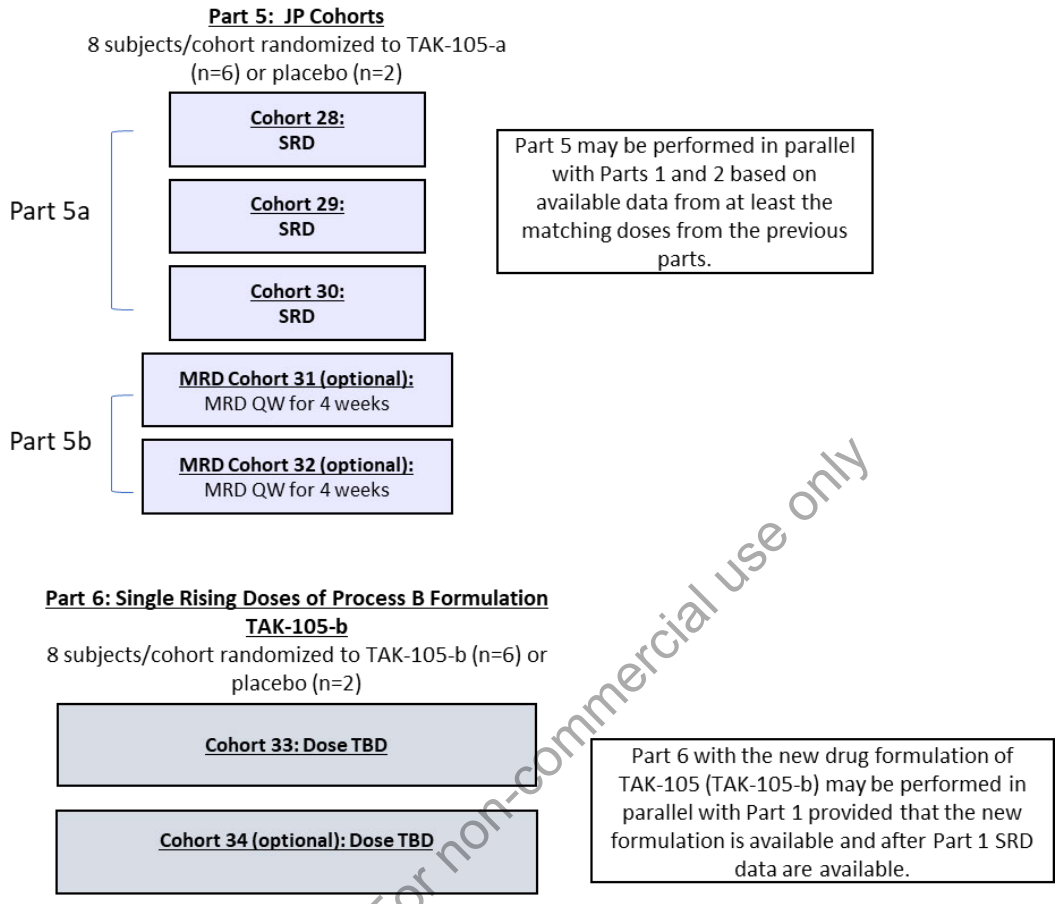
A scheme of the overall study design is presented in Figure 2.a (Parts 1 to 4) and Figure 2.b (Parts 5a/b and 6). An overview of treatment cohorts is presented in Table 2.a.

Figure 2.a Schematic of Study Design: Parts 1 to 4



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

Figure 2.b Schematic of Study Design: Parts 5 and 6



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

Table 2.a Overview of Treatment Cohorts

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

Table 2.a Overview of Treatment Cohorts

Cohort	Regimen	TAK-105 formulation	Treatment	
			TAK-105	Placebo
9			6	2
10			6	2
11			6	2
12			6	2
Part 2				
13	MRD	TAK-105-a	6	2
14			6	2
15			6	2
16			6	2
17			6	2
Part 3				
18	Dose Titration	TAK-105-a	6	2
19			6	2
20 (optional)			6	2
21 (optional)			6	2
22 (optional)			6	2
23 (optional)			6	2
Part 4				
24	Redosing	TAK-105-a	6	2
25			6	2
26 (optional)			6	2
27 (optional)			6	2
Part 5a (Japanese subjects)				
28	SRD	TAK-105-a	6	2
29			6	2
30			6	2

Table 2.a Overview of Treatment Cohorts

Cohort	Regimen	TAK-105 formulation	Treatment	
			TAK-105	Placebo
Part 5b (Japanese subjects) [a]				
31 (optional)	MRD	TAK-105-a	6	2
32 (optional)			6	2
Part 6				
33	SRD	TAK-105-b	6	2
34 (optional)			6	2

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

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

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

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

No formal statistical hypothesis testing is planned in this study.

3.2 Statistical Decision Rules

No formal statistical decisions are planned in this study.

3.3 Multiplicity Adjustment

Not Applicable

4.0 SAMPLE-SIZE DETERMINATION

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

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set consists of all subjects who are randomized and receive at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment actually received.

5.2 Pharmacokinetic Analysis Set

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

5.3 Immunogenicity Analysis Set

The immunogenicity analysis set consists of all subjects who receive at least 1 dose of study treatment and have the baseline sample and at least 1 postbaseline sample antidrug antibodies (ADA) assessment.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All data for randomized subjects will be presented in by-subjects listings. All available data from Study Parts (eg, 1, 2, 3, 4, 5, and/or 6) will be analyzed separately. In particular, data from Parts 5a (SRD) and 5b (MRD) will be analyzed separately, as data allows.

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

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

- Descriptive statistics:
  - For continuous data (study drug exposure and compliance, clinical laboratory data, vital signs, ECGs, etc.):
    - n, mean, standard deviation, median, minimum, and maximum.
  - For PK and biomarkers:
    - n, arithmetic mean, standard deviation, percent coefficient of variation [%CV], geometric mean, geometric %CV, median, minimum, and maximum.
  - For categorical data:
    - frequency counts and percentages.
  - Percentages will be reported to 1 decimal place. For the calculation of summary statistics and statistical analysis, unrounded data will be used.
- By treatment arm:
  - For PK:
    - by dose level (Parts 1, 2, 5, and 6 only)/dose regimen (Parts 3 and 4 only) of TAK-105, as appropriate, within each part of the study separately.

  - For disposition, demographics and baseline characteristics, and concomitant medication:
    - by placebo, each TAK-105 dose level (Parts 1, 2, 5, and 6)/dose regimen (Parts 3 and 4 only), and total (ie, combining placebo and TAK-105 arms), as appropriate, within each part of the study separately.
  - For AEs and impact due to COVID-19:
    - by placebo, each TAK-105 dose level (Parts 1, 2, 5, and 6)/dose regimen (Parts 3 and 4 only), TAK-105 overall (ie, combining all TAK-105 arms), and total (ie, combining placebo and TAK-105 arms), as appropriate, within each part of the study separately.
  - For immunogenicity and biomarker:
    - by placebo, each TAK-105 dose level (Parts 1, 2, 5, and 6)/dose regimen (Parts 3 and 4 only), and TAK-105 overall (ie, combining all TAK-105 arms, as appropriate, within each part of the study separately.
  - For all other analyses:
    - by placebo, dose level (Parts 1, 2, 5, and 6)/dose regimen (Parts 3 and 4 only) of TAK-105, as appropriate, within each part of the study separately.
- Treatment arm pooling:
  - Placebo will be pooled across cohorts within each part of the study where appropriate.
  - The same dose level (Parts 1, 2, 5, and 6)/dose regimen (Parts 3 and 4 only) of TAK-105 will be pooled across cohorts within each part of the study separately 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 2.1.0 or higher will be utilized to ensure compliance with CDISC standards.

6.1.1 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.

6.1.2 Handling of Treatment Misallocations

Subjects will be analyzed as treated.

6.1.3 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. Deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

6.1.4 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 (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 planned 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.

All significant protocol deviations that occur during the study will be reviewed and finalized prior to database lock. Significant protocol deviations will be summarized by treatment arm within each part of the study separately. Listing of all significant protocol deviations will be provided for all randomized subjects.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Baseline Characteristics

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for continuous demographic variables and baseline characteristics variables (eg, age, height, weight, and BMI) by treatment arm in Parts1, 2, 3, 4, 5 and 6 separately. In particular, data from Part 5a (SRD) and 5b (MRD) will be analyzed separately, as data allows. The count and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (eg, sex, ethnicity, race) will be tabulated by treatment arm in Parts 1, 2, 3, 4, 5 and 6 separately. In particular, data from Part 5a (SRD) and 5b (MRD) will be analyzed separately, as data allows. The safety analysis set will be used to summarize the demographics and baseline characteristics.

All data will be provided in by-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. 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.

6.4 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 continued taking or started 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.

6.5 Efficacy Analysis

Not Applicable.

6.6 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.

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 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-105 include injection site reactions, hypotension, tachycardia and postural hypotension

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, number of events.
- Treatment-related TEAEs by SOC and PT - number and percentage of subjects, number of events.
- TEAEs by PT - number and percentage of subjects, number of events.
- Most frequent non-serious TEAEs (>5% in any treatment arm within each part of the study) by PT - number and percentage of subjects, number of events.
- Treatment-related TEAEs by PT - number and percentage of subjects, number of events.
- Toxicity grade of TEAEs by SOC and PT - number and percentage of subjects, number of events.
- 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, number of events.

- TEAEs with Toxicity Grade >=3 by PT - number and percentage of subjects, number of events.
- Treatment-related TEAEs with Toxicity Grade >=3 by PT - number and percentage of subjects, number of events.
- Serious TEAEs leading to permanent treatment discontinuation by SOC and PT - number and percentage of subjects, number of events.
- Most frequent TEAEs (≥ 5% in total subjects within each part of the study) by PT - number and percentage of subjects, number of events.

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-105 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 4 only, as data allows, similarly, the TEAEs that started or worsened after the single SC rechallenge dose (after a modified period of withholding study treatment after second dose) will be summarized by placebo and level of the single SC rechallenge dose of TAK-105-a, TAK-105-a single SC rechallenge dose overall, and total based on safety analysis set.

6.6.2 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 Section 9.4). 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 × upper limit of normal (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 4 only, as data allows, similarly, the clinical laboratory data after the single SC rechallenge dose (after a modified period of withholding study treatment after second dose) will be summarized by placebo and level of the single SC rechallenge dose of TAK-105-a, and TAK-105-a 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.

6.6.3 Vital Signs

Typically, blood pressure (BP) and heart rate (HR) assessments are made in duplicate with an interval of approximately 2 minutes between the 2 assessments. The investigator can take a third BP and HR assessment if results are inconsistent (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 HR 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 be summarized using descriptive statistics by treatment arm at each nominal timepoint where appropriate based on safety analysis set.

For each orthostatic vital sign parameter (ie, BP and HR), the difference between standing and semi-recumbent (ie, 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 (ie, semi-recumbent BP and HR, standing BP and HR, orthostatic BP and HR) 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 sign parameter (ie, semi-recumbent BP and HR, standing BP and HR, orthostatic BP and HR).

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 (Section 9.5). Orthostatic hypotension and orthostatic tachycardia will be identified by criteria for identification of markedly abnormal orthostatic changes (Section 9.6). 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 or orthostatic tachycardia, 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 4 only, as data allows, similarly, the vital signs parameters after the single SC rechallenge dose (after a modified period of withholding study treatment after second dose) will be summarized by placebo and level of the single SC rechallenge dose of TAK-105-a, and TAK-105-a single SC rechallenge dose overall based on safety analysis set.

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

6.6.4 12-Lead ECGs

ECG parameters (ie, 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 (ie, heart rate, PR interval, QRS interval, and QTc interval) will be evaluated against the Takeda's predefined MAV criteria (Section 9.7). 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 be 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 4 only, as data allows, similarly, the ECG data after the single SC rechallenge dose (after a modified period of withholding study treatment after second dose) will be summarized by placebo and level of the single SC rechallenge dose of TAK-105-a, and TAK-105-a 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.

6.6.5 Physical Examinations

Physical examination findings may be presented in by-subject listings based on safety analysis set, as data allows.

6.6.6 Extent of Exposure and Compliance

Treatment exposure (eg, duration of treatment = last dose date – first dose date +1, number of doses 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

6.7 Immunogenicity Analysis

The number and percentage of subjects within each of the following categories for ADA status and ADA titer of immunogenicity at scheduled visits will be summarized by treatment arm based on immunogenicity analysis set within each part of the study separately. In particular, the summary of immunogenicity for Parts 5a (SRD) and 5b (MRD) will be provided separately, as data allows.

ADA status will be summarized in the following categories:

- ADA negative, defined as subject who does not have a confirmed positive ADA status in any Baseline and postbaseline assessments.
- Pre-existing ADA positive, defined as subjects who has a confirmed positive ADA status in the Baseline assessment, and
  - Does not have a confirmed positive ADA status in any postbaseline assessment, **or**
  - Has confirmed positive ADA status in at least 1 postbaseline assessments, and the maximum titer value among the postbaseline assessments is <4 times the Baseline titer value.
- Treatment-boosted ADA positive, defined as subject who has a confirmed positive ADA status in the Baseline assessment and in at least 1 postbaseline assessments, and the maximum titer value among the postbaseline assessments is ≥4 times the Baseline titer value.
- Treatment-induced ADA positive, defined as subject who does not have a confirmed positive ADA status in the Baseline assessment, and has confirmed positive ADA status in at least 1 postbaseline assessments.
- In addition, treatment-induced and treatment-boosted ADA positive will further be summarized in the following categories:
  - Transiently ADA positive, defined as subject who has 1 or 2 confirmed positive ADA status in postbaseline assessments.
  - Persistently ADA positive, defined as subject who has >2 confirmed positive ADA status in postbaseline assessments.

For ADA positive (if any pre-existing, treatment-boosted, and treatment-induced ADA positive) only, ADA titer will be summarized in the following categories:

- High ADA titer, defined as subject who has at least 1 Baseline and/or postbaseline ADA titer >16.
- Low ADA titer, defined as subject whose Baseline and postbaseline ADA titers are all ≤16.

The summary of TEAE by PT and immunogenicity categories (ie, ADA negative and ADA positive, if any pre-existing, treatment-boosted, and treatment-induced ADA positive; for ADA positive only, ADA high titer and ADA low titer) 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 study drug concentration and PK parameters (including but not limited to C_{max} , AUCs and CL/F where appropriate) by immunogenicity categories (ie, ADA negative and ADA positive, if any pre-existing, treatment-boosted, and treatment-induced ADA positive; for ADA positive only, ADA high titer and ADA low titer) 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.

6.8 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.8.1 Pharmacokinetic Analysis

The plasma (all parts of the study) and urine (Parts 1, 2, and 5a/b only) concentrations of TAK-105 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. In particular, the summary of plasma and urine concentration of TAK-105 for Parts 5a (SRD) and 5b (MRD) will be provided separately, as data allows.

PK parameters of TAK-105, but not limited to (ie, C_{max}, t_{max}, $t_{1/2z}$, AUC_{∞}, AUC_{last}, AUC_{τ}, CL/F, Vz/F, A_{e_t} , $A_{e_{t1-t2}}$, A_{e_τ}, $f_{e,t}$, CL_R,) 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, 2, and 5a/b only) concentrations of TAK-105, and PK parameters will be presented in by-subject listings based on PK analysis set.

Details of the pharmacokinetics analysis will be described in clinical pharmacology analysis plan (CPAP).

Dose proportionality will be assessed graphically and by using a power model within each part of the study (Parts 1, 2, and 5a/b only) and days (Parts 2 and 5b only) separately using the method below, where appropriate:

For each part of the study (Parts 1, 2, and 5a/b only), as data allows, the dose proportionality of AUCs and Cmax 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 will 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.

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.

6.8.2 Pharmacodynamic Analysis

Not Applicable.

6.8.3 Biomarker Analysis

The concentrations of [redacted] at each time point (ie, Day-1 0 hour and baseline [predose, Day 1]) 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 (ie, 0 to <Q1, Q1 to < median, median to <Q3, ≥Q3, where quartile is determined by all available data at specified time point within each part of the study) of [redacted] concentrations will be presented for each time point by treatment arm based on safety analysis set. The baseline, postbaseline values, and change from baseline in the [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 (ie, 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.

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

Not Applicable

6.10 Summary of 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.

6.11 Interim Analyses

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

In case a data-dependent internal decision is needed to inform the subsequent development of TAK-105 prior to database lock, an interim analysis may be deemed necessary.

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

1. A decision about whether to complete Parts 3 and 4 has not been made.
2. Dose selection for the development of phase 2 studies.
3. Study may end after completion of Parts 1 and 2 (IA will become final analysis).

In the event of scenarios 1 and 2, the interim analyses of the endpoints below, based on the data cut prespecified by the study team, will be presented to the study team for review for internal decision making.

- PK Analysis
  - PK concentration per method in Section 6.8.1.
  - PK parameters per method in Section 6.8.1.
  - Dose proportionality assessment per method in Section 6.8.1.
- Treatment-emergent adverse event (TEAE) per method in Section 6.6.1.
  - Overview of TEAEs.
  - Treatment-related TEAEs.
  - TEAEs by maximum severity.
  - TEAEs Grade 3 or Higher.
  - Treatment-related TEAEs Grade 3 or Higher.
  - SAE.
  - SAE leading to study drug discontinuation.

  - AESI.

- Vital Signs per method in Section 6.6.3.
- Lab data per method in Section 6.6.2.
- ECG Data per method in Section 6.6.4.
- Immunogenicity per method in Section 6.7.

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.

The interim analysis will be performed by a separate set of unblinded statisticians and programmers at the contract research organization (CRO) who are not involved in the daily activities of the study. To maintain the blind of TAK-105-1001 and to ensure the unbiased study conduct, results of the interim analyses may only be distributed within a limited team from Takeda. The subjects and investigators (including site staff) will remain blinded.

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.
2. Immunogenicity testing of therapeutic protein products–developing and validating assays for anti-drug antibody detection. US FDA, 2019.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Additional analysis on pre-existing ADA positive, treatment-boosted ADA positive, and treatment-induced ADA positive for immunogenicity data were added to follow the FDA Guidance on Immunogenicity Testing of Therapeutic Protein Products [2].

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

SAP Section	Change	Rationale for Change
Study Title 1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS 2.0 STUDY DESIGN	Added the language of sponsor-open.	To be consistent with Protocol Amendment 04.
1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS 2.0 STUDY DESIGN 4.0 SAMPLE-SIZE	Added additional parts and cohorts for Japanese subjects and new formulation of TAK-105, TAK-105-b.	To be consistent with Protocol Amendment 04.

SAP Section	Change	Rationale for Change
DETERMINATION 6.1 General Considerations 6.3.1 Demographics and Baseline Characteristics 6.8.1 Pharmacokinetic Analysis		
6.2 Disposition of Subjects	Added language for protocol deviation analysis.	To be consistent with standard analysis plan for protocol deviation.
6.6 Safety Analysis	Specified analysis plan for Part 4 redosing cohorts on each safety parameter.	To support safety and tolerability assessment for redosing cohorts.
6.6.1 Adverse Events	Added additional summary for TEAEs.	To support safety and tolerability assessment for TAK-105.
6.6.3 Vital Signs	Added statistical algorithm to calculate the average value if a second or a third measurement on vital signs has been made per protocol specified procedure. Updated MAV evaluation plan for orthostatic hypotension and orthostatic tachycardia based on the scheduled standing measurement only.	To be consistent with Protocol amendment 04. To support safety and tolerability assessment for TAK-105 on the orthostatic vital signs.
6.7 Immunogenicity Analysis	Added the definition of pre-existing ADA positive, treatment-boosted ADA positive, treatment-induced ADA positive, transiently ADA positive, and persistently ADA positive.	To be consistent with Protocol amendment 04 and FDA Guidance on Immunogenicity Testing of Therapeutic Protein Products.
6.11 Interim Analyses	Revised the interim analyses parameters.	To be consistent with the proposed IA output for the study.
9.5 Criteria for Identification of Markedly Abnormal Values for Vital Signs	Added MAV for Body Temperature in °F and MAV for Respiratory Rate.	To be consistent with Takeda [redacted] MAV plan.

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 based on 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.

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

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 x 10^9/L	>600 × 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.

9.5 Criteria for Identification of Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse Rate	bpm	<50	>120
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
Respiratory Rate	Breath per minute	<12	>16

9.6 Criteria for Identification of 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 of >30 bpm or HR >120 bpm on standing

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

9.7 Criteria for Identification of 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

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