Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects Following Intravenous Administration

NCT Number: NCT04486950

SAP Approve Date: 13 May 2021

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-951-1004

A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects Following Intravenous Administration

Phase 1

Version: Final

Date: 13 May 2021

Prepared by:

PPD

Based on:

Original Protocol Dated: 07-May-2020

Protocol Amendment 1 Dated: 08-Jan-2021

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	13-MAY-2021	[Not Applicable]

Approval Signatures

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

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects Following Intravenous Administration

Approvals:

PPD

Date

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ABBREVIATIONS

ADA	anti-drug antibodies
AE	adverse event
$AUC_{extrap\%}$	percent of AUC_{∞} extrapolated
AUC_{last}	area under the TAK-951 plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{∞}	area under the TAK-951 plasma concentration-time curve from time 0 to infinity
BLQ	below the lower limit of quantitation
BP	blood pressure
C_{eoi}	TAK-951 plasma concentration at end of infusion
CFB	change from baseline
CL	total clearance after IV administration
COVID-19	coronavirus disease 2019
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CRU	clinical research unit
CV%	arithmetic percent coefficient of variation
DN	dose-normalized
ECG	electrocardiogram
FIH	first-in-human
Geom CV%	geometric percent coefficient of variation
Geom mean	geometric mean
HR	heart rate
IV	Intravenous
mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	pharmacodynamic
PK	pharmacokinetic
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
TBD	to be determined
TFL	table, figure, and listing
t_{max}	time of first occurrence of C_{eoi}
$t_{½z}$	terminal disposition phase half-life
V_z	volume of distribution during the terminal disposition phase after IV administration, calculated using the observed value of the last quantifiable concentration
λ_z	terminal disposition phase rate constant

Note: The PK parameters presented in the clinical study report and in the in-text tables will be subscripted, whereas the PK parameters presented in the end-of-text tables will not be subscripted. In addition, AUC_{∞} and λ_z will be presented as AUCinf and Lambdaz in the end-of-text tables, respectively.

1.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To evaluate the overall safety and tolerability of a single intravenous (IV) infusion of TAK-951 administered with at least 2 different infusion rates (rapid and slow) at the same dose level in healthy subjects.

1.1.2 Secondary Objectives

- *To assess the pharmacokinetics (PK) of TAK-951 following a single IV infusion of TAK-951 in healthy subjects.*
- *To assess for anti-drug antibodies (ADA) following a single IV infusion of TAK-951 in healthy subjects.*

CCI

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint

The primary endpoint of the study is safety and tolerability as assessed through adverse events (AEs), vital signs, safety electrocardiograms (ECGs)/telemetry, safety laboratory assessments, and physical examinations.

1.2.2 Secondary Endpoints

Secondary endpoints will be assessed through evaluation of the following PK parameters:

- *Area under the TAK-951 plasma concentration-time curve from time 0 to infinity (AUC_{∞})*
- *TAK-951 plasma concentration at end of infusion (C_{eoi})*
- *Area under the TAK-951 plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last})*
- *Terminal disposition phase half-life ($t_{½z}$)*
- *Terminal disposition phase rate constant (λ_z)*

Immunogenicity:

- *Anti-drug antibodies titer*

CCI

[redacted]

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of TAK-951 administered intravenously in healthy adult subjects.

At least 3 cohorts of 8 subjects each will be dosed sequentially. Subjects from each cohort will be admitted into the clinical research unit (CRU) on Day -2. On Day -1, baseline heart rate and blood pressure assessments will be taken, time-matched to the Day 1 assessments. Subjects will receive a single dose with TAK-951 or matching placebo on Day 1, according to the

randomization scheme, after a minimum of 8 hours of fasting. Subjects will be randomized to receive TAK-951 or matching placebo in a 6:2 ratio in a double-blind manner. PK samples will be taken up to 30 hours after the start of infusion. Subjects will be discharged after the completion of the study assessments on Day 2.

All subjects who received any amount of study drug (including subjects who terminate the study early) will return to the CRU 14 (±2) and 28 (±3) days after dosing for follow-up procedures, and to determine if any AE has occurred since the last study visit.

CCI

[redacted]

Two (2) additional cohorts may be enrolled (for a total of 5 cohorts), each cohort with 8 subjects, to explore additional IV dosing regimens. In total, the enrollment will be approximately 40 subjects. Dosing of the subsequent cohort will be based on the analysis of the previous cohort's data; however, the cohorts will not exceed the highest exposure observed in the first-in-human (FIH) study.

For Cohort 4 and 5, PK sampling and time-matched vital sign assessments scheduled relative to infusion timing will be based on emerging clinical data analysis. As such, this timing will be provided in a separate document and will not exceed 30 hours post start of infusion. The number of planned samples may be less than or equal to those in the protocol.

A staggered dosing approach will be used. The sentinel subjects will be dosed at least 24-hours before the remaining 6 subjects in each cohort. In each cohort, after dosing the first 2 subjects (the sentinel group - 1 receiving TAK-951 and 1 receiving placebo) the Investigator will review all available blinded safety and tolerability data up to 8 hours postdose. If after dosing the sentinel group, the Investigator and the Sponsor agree that there are no significant safety/tolerability concerns, then the rest of the cohort will be dosed. There will be at least 1 hour between dosing of each subject in each cohort, except for the sentinel subjects. A dose-escalation/blinded safety review meeting will be held between the Investigator and Sponsor after each cohort is completed to review the safety and available PK data from samples taken up to 1-day postdose, in order to confirm the dose level and/or infusion rate for the subsequent cohort. PK data from the first low dose cohort is required to allow dosing of the high dose for the second and third cohorts and the determination of the rate of infusion for the third cohort. The dose and infusion rate for Cohort 4 and 5 will be selected based on emerging clinical data analysis and is not expected to exceed the highest exposures seen in the FIH TAK-951-1001 study.

Sponsor is to remain blinded during the review of available safety and PK data. Once a decision is made to proceed to the next cohort, the Sponsor may be unblinded following dose escalation/safety meetings to allow additional analysis.

The dose and rate for Cohorts 4 and 5 will be determined by clinical data analysis so as not to exceed the highest exposure seen in the currently ongoing FIH study (TAK-951-1001). Cohorts 4 and 5 may run concurrently, sequentially, or be omitted.

Safety will be assessed by monitoring for AEs, vital signs, safety 12-lead ECGs/telemetry, safety laboratory assessments, and physical examinations throughout the study.

Immunogenicity will be assessed prior to dosing and approximately 14 and 28 days after dosing.

In accordance with local regulatory guidance for the coronavirus disease 2019 (COVID-19) pandemic, the clinical study unit will implement standard COVID-19 procedures as per their internal guidance documents. Subjects may be admitted earlier than Day -2 for COVID-19 testing not related to study protocol as per CRU requirements.

Note: After review of the data by the Sponsor it was decided that only one additional cohort would be added to the study.

The planned dose levels of TAK-951 to be evaluated are outlined in the table below:

Table 2.a Planned Dose Levels of TAK-951

Cohort[#]	Total Dose	Infusion Duration
Cohort 1	20 µg and matching placebo	60-minute
Cohort 2	1.0 mg and matching placebo	60-minute
Cohort 3	1.0 mg and matching placebo	120-minute
Cohort 4	1.0 mg and matching placebo	180-minute

Treatment descriptions to be evaluated are outlined in the table below:

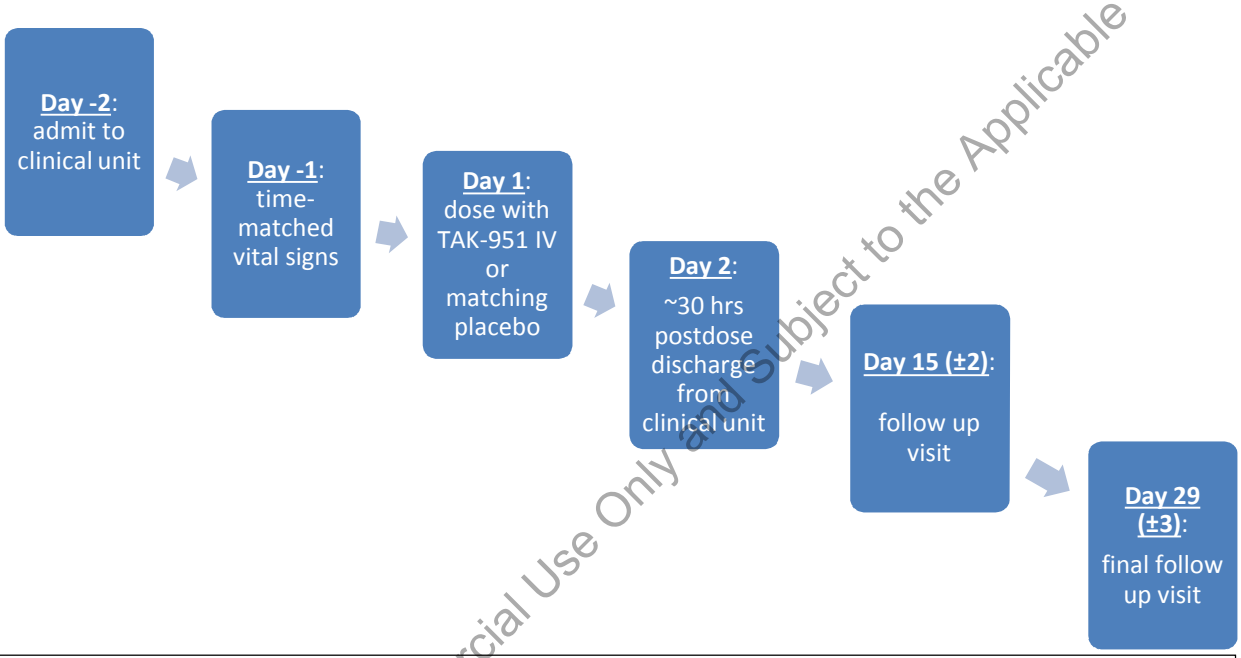
Table 2.b Treatment Descriptions

Treatment A	A single 60-minute IV infusion of 20 µg TAK-951 administered to healthy subjects on Day 1 (Cohort 1)
Treatment B	A single 60-minute IV infusion of 1.0 mg TAK-951 administered to healthy subjects on Day 1 (Cohort 2)
Treatment C	A single 120-minute IV infusion of 1.0 mg TAK-951 administered to healthy subjects on Day 1 (Cohort 3)
Treatment D	A single 180-minute IV infusion of 1.0 mg TAK-951 administered to healthy subjects on Day 1 (Cohort 4)
Treatment P1	A single 60-minute IV infusion of placebo (normal saline) administered to healthy subjects on Day 1 (Pooled)
Treatment P2	A single 120-minute IV infusion of placebo (normal saline) administered to healthy subjects on Day 1 (Pooled)
Treatment P3	A single 180-minute IV infusion of placebo (normal saline) administered to healthy subjects on Day 1 (Pooled)

* : placebo subjects will be pooled according to the length of infusion (i.e, 60, 120, or 180 minutes).

The study schematic is presented in the figure below:

Figure 2.a Study Schematic



Study schematic per cohort. Dosing of subsequent cohorts is based on dose escalation criteria. Within a cohort, sentinel subjects will be dosed at least 24 hours before the remaining subjects. There will be at least 1 hour between dosing of each subject in each cohort, except for the sentinel.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

Up to approximately 40 adult subjects (8 per cohort) are planned to be randomized. A formal sample size calculation was not performed for this study. The current sample size is deemed

appropriate to evaluate the safety, tolerability, PK, and PD of TAK-951 following IV administration. A minimum of 3 cohorts will be evaluated.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will consist of all subjects who are enrolled and received the full or partial dose of study drug or placebo.

5.2 PK Analysis Set

The PK analysis set will consist of all subjects who received the active study drug and have at least one measurable plasma concentration of TAK-951.

All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the descriptive statistics.

5.3 Immunogenicity Analysis Set

The immunogenicity analysis set will include those subjects from the safety analysis set who have a baseline and at least 1 postdose immunogenicity sample assessment.

5.4 PD Analysis Set

The PD analysis set will consist of all subjects who received the study drug or placebo and have at least one measurable time-matched Day -1 and Day 1 PD effect (semi-recumbent HR and semi-recumbent BP).

5.5 Immunogenicity/PK Analysis Set

The immunogenicity/PK analysis set will consist of all subjects in the PK set with a baseline and at least 1 postdose immunogenicity sample assessment.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonLin® Version 8.1, or higher. All statistical analyses will be conducted using SAS® Version 9.4. All data recorded on the case report form (CRF) will be listed by subject. All tables, figures, and listings (TFLs) shells and numbering list will be included and specified in the TFL Shells document.

The number of observations (n) will be presented as an integer (no decimal places), arithmetic mean (mean), median, and geometric mean (geom mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum

and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (geom CV%) will be presented to 1 decimal place.

Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero, and in the calculation of descriptive statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are obvious outliers (e.g., BLQ value between measurable values), in which case they will be treated as missing.

A subject's PK parameter data will be included in the listings but excluded from the descriptive statistics if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's maximum concentration value in that period.
- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).
- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).

The details on PK parameter calculations and TFLs will be outlined in the Clinical Pharmacology Analysis Plan (CPAP) and TFL Shell document including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other λ_z-dependent parameters.
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables.
- Concentration data file used for PK analysis.
- PK parameter WinNonlin® output file used to generate the TFLs.
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures.
- Individual concentration-time figures presented in Appendix 16.2.6.

For safety analysis only, the semi-recumbent HR and BP baseline is defined as Day 1 predose. For orthostatic HR and BP, the time-matched changes at each time point will be derived. In addition, the time-matched changes on Day 1 versus Day -1 will also be derived for semi-recumbent HR and BP as part of the PD analysis.

Placebo subjects will be pooled for summaries according to the length of infusion.

For demographic and safety data where appropriate, variables will be summarized descriptively. For the categorical variables, the count and percentage of each possible value will be tabulated, where applicable. The denominator for the proportion will be based on the number of subjects who provided non missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers.

6.1.1 Handling of Treatment Misallocations

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

6.2 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form, date of first dose, date of last dose, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets.

6.3 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized by treatment and overall active treatment. Study completion status, including reason for discontinuation, will also be listed by subject.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized descriptively by treatment and overall active treatment. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [recorded in the CRF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI recorded at screening will be used in the baseline summaries. Demographics data will also be listed as recorded on the CRF, including the date of informed consent.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing the

informed consent form (ICF). Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug(s) will be classified as an adverse event. All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.0. If appropriate, the medical history listing will include whether the event was medical or surgical, the body system or organ class involved, coded term, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

6.5 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and safety evaluation stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between time of signing the ICF through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the WHO Dictionary Version 01-Mar-2020 b3 and listed. If appropriate, the listing will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use.

6.6 Efficacy Analysis

Not applicable.

6.7 Safety Analysis

For each treatment group, safety and tolerability will be assessed through incidence, severity and type of adverse events. Safety will also be assessed through changes from baseline in subjects' vital signs, safety ECGs and clinical laboratory assessments; along with symptom-driven physical examinations. All safety data will be listed by treatment, subject, and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

6.7.1 Adverse Events

All AEs captured in the database will be listed, by treatment and subject, in data listings including; age/sex, weight, race, verbatim term, coded term, time from last dose, onset date/time, and resolution date/time. A separate listing, by treatment and subject will present frequency, severity, seriousness, outcome, action relative to study drug, relationship to study drug (related or not related), and whether AE was of special interest as recorded in the CRF. All AEs occurring during this study will be coded using MedDRA® Version 23.0. However, only

treatment-emergent adverse events (TEAEs) occurring after the start of infusion will be summarized. A TEAE is defined as any AEs newly occurring or worsening from the first dose and 14 days after last dose of study drug. A pre-treatment AE is defined as any AEs newly occurring or worsening before the first dose.

All AEs, including TEAEs, will be severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, with grading levels 1 to 5 which correspond to mild, moderate, severe or medically significant but not immediately life-threatening, life-threatening, and fatal.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summaries will be presented by treatment including placebo. Only for the overview summary of TEAEs, will AEs be summarized with both number of events and number of subjects reporting events. Summary tables for AE frequency will be presented in two forms, one to include number of subjects reporting the AE (including percent of safety analysis set), and one for number of events. TEAEs and serious adverse events will be presented in this similar way. A summary table will be generated for most commonly reported non-serious TEAEs (i.e., those events reported by >5% of all subjects in each treatment, excluding serious adverse events [SAEs]). Additional TEAE summary tables will be presented by number of subjects for severity and relationship to study drug. A separate summary will be presented for TEAEs with a severity grade 3 or higher by relationship to study drug. TEAEs leading to discontinuation, pretreatment AEs, AEs of special interest (AESIs), and all-cause mortalities will be presented separately in the listings.

The following guidelines will be applied for the summary of AEs:

- AEs with missing or unknown intensity will be considered as severe (or Grade 3).
- AEs with missing or unknown relationship to study drug will be counted as related.
- A subject with 2 or more AEs within the same level of the MedDRA term will be counted only once in that level.
- SOCs will be sorted in alphabetical order. Within an SOC, adverse events will be sorted in descending order of total number of subjects with the preferred term among all the treatment groups.
- For the summary of TEAEs by SOC and PT and intensity (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.
- For the summary of TEAEs by SOC and PT and relationship to study drug, if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the closest relationship to the study drug 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 closest relationship to study drug in that SOC.

6.7.2 Adverse Events of Special Interest (if applicable)

AESIs for TAK-951 include injection site reactions, hypotension, hypersensitivity, and sinus tachycardia of CTCAE grade 2 or higher. AESIs include those indicated by the PI on the CRF and those derived from the MedDRA terms below. AESIs will be listed.

AESIs	MedDRA Terms or definitions
Injection site reaction	Injection Site Reaction (HLT)
Hypotension	Hypotension (PT)
Hypersensitivity	Hypersensitivity reaction (SMQ)
Sinus Tachycardia	Tachycardia (PT)

6.7.3 Clinical Laboratory Assessments

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -2), Day 1 (after infusion), Day 2, and early termination (if applicable). Urine drug screening will be carried out at screening and check-in (Day-2) only. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment (including placebo), and assessment time points. Data will be summarized from baseline (check-in) and presented along with the change from baseline. Baseline is defined as the last assessment including rechecks taken prior to the start of infusion (generally Day -2). All clinical laboratory listings and tables will be presented in conventional units, except for the markedly abnormal value analysis which will be presented in SI units.

For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Additionally individual results of laboratory tests from serum chemistry and hematology that meet Takeda's markedly abnormal criteria (see Appendix A) will be summarized.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a laboratory clinically significant (CS) range. If the value falls within the CS range, it will be noted as "N" for not clinical significant. If the value fails the CS range, it will be flagged with a "Y" which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. Additionally, the PI will provide a 4th flag when the 3rd flag indicates "R" or "^". This 4th flag is intended to capture final CS (+)/NCS (-) when the 3rd flag does not document significance. All clinically significant laboratory tests, as indicated by the PI, and the corresponding values

will be listed by subject. All clinical laboratory data will be presented in by-subject data listings. CS results will also be presented as part of the listings.

6.7.4 Vital Signs

Vital sign measurements consist of body temperature, respiratory rate, BP, and HR. Temperature and respiratory rate will be collected at screening only. Orthostatic measurements for BP and HR will also be collected at screening and at the time points detailed below. HR and BP, for the different study cohorts, will be collected at the time points (and early termination if applicable) outlined in the table below:

Table 6.a Vital Signs Collection (Cohorts 1 and 2)

Assessment	Days	Scheduled Time (Hours)*
HR^	Day -1 and Day 1	0.083, 0.17 0.25, 1 (EOI), 1.25, 1.5, 12, 30[$]
BP^	Day -1 and Day 1	0.25, 1 (EOI), 1.25, 1.5, 12, and 30[$]
Orthostatic VS[&]	Day -1 and Day 1	predose and 0.5, 2, 4, 8, and 24[$]

Table 6.b Vital Signs Collection (Cohort 3)

Assessment	Days	Scheduled Time (Hours)*
HR^	Day -1 and Day 1	0.25, 0.5, 1.5, 2 (EOI), 2.083, 2.25, 12, 30[$]
BP^	Day -1 and Day 1	0.25, 0.5, 1.5, 2 (EOI), 2.25, 12, 30[$]
Orthostatic VS[&]	Day -1 and Day 1	predose and 1, 2.5, 3, 5, 8, 24[$]

Table 6.c Vital Signs Collection (Cohort 4)

Assessment	Days	Scheduled Time (Hours)*
HR^	Day -1 and Day 1	0.25, 0.5, 1.5, 2.5, 3 (EOI), 3.25, 12, 30[$]
BP^	Day -1 and Day 1	0.25, 0.5, 1.5, 2.5, 3 (EOI), 12, 30[$]
Orthostatic VS[&]	Day -1 and Day 1	predose and 1, 2, 3.5, 4, 7, 24[$]

[*]: The actual date and time of sample collection will be recorded on the source document in the case report form.
^: When scheduled after the start of infusion, vital signs will be performed within approximately 15 minutes of the scheduled time point.
[$]: Day 1 only.
[&]: Orthostatic VS include semi-recumbent and standing BP and HR measurements.

BP and HR measurements (excluding orthostatic VS) will be performed in duplicate and then an average taken which will be used for the final result of both.

The following safety vital sign parameters will be evaluated in this study:

- Absolute semi-recumbent HR.

- Absolute semi-recumbent BP.
- Change from baseline semi-recumbent HR.
- Change from baseline semi-recumbent BP.

Absolute semi-recumbent HR and semi-recumbent BP will be listed and summarized descriptively by treatment and collection time using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, and maximum. Change from baseline for semi-recumbent HR and semi-recumbent BP will be also be summarized descriptively by treatment and collection time. Baseline will be defined as the Day 1 predose value. Excluded data will be presented and footnoted as such in the table listings, and those values will be excluded from the descriptive statistics. Any negative change from baseline values will be left as is.

The arithmetic mean absolute values and change from baseline profiles for semi-recumbent HR and semi-recumbent BP will be presented by treatment on linear scale with and without SD.

Additionally, counts and percentages of orthostatic vital signs will be summarized according to the following reporting thresholds for postdose Day 1 data only:

Table 6.d Reporting Thresholds for Orthostatic Vital Signs on Day 1

Change in HR (bpm)	Change in Systolic BP (mmHg)	Change in Diastolic BP (mmHg)
≥30	≤-20	≤-10

Individual vital signs results that meet Takeda's markedly abnormal criteria (see Appendix B) will be summarized. All vital sign collected as per the CRF will be presented in a by-subject listing.

6.7.5 Electrocardiograms

12-lead ECGs will be collected at screening, Day -1, Day 1 (predose) and Day 2 (also at early termination if applicable). ECGs will be measured in triplicate with an average taken as the final result. Additional unscheduled ECGs may be recorded at other times if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by treatment (including placebo) and time point of collection. Baseline is defined as the last assessment including rechecks taken prior to dosing. Baseline, postdose, and change from baseline will be summarized. ECG data will also be displayed in a data listing by subject.

6.7.6 Physical Examination

Physical examination will be performed at screening. Symptom-driven physical exams may be performed at other times at the discretion of the PI. Physical exam findings will be presented in the data listings by subject. Reproductive system findings will also be listed by subject.

6.7.7 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented as AEs.

6.7.8 Other Safety Analysis (if applicable)

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

Any additional safety analysis not addressed within this SAP will be considered out of scope and must be described in the CSR.

6.7.9 Extent of Exposure and Compliance

The date, time, treatment will be listed by subject.

6.7.10 Immunogenicity Analysis

The ADA data will be assessed with the baseline sample and the post baseline samples. The formation of ADAs such as IgM can occur 7 to 14 days after study drug administration. In this study we will be evaluating anti-drug antibodies at 14 (±2) and 28 (±3) days postdose administration to assess potential immunogenicity.

All immunogenicity data will be listed and summarized by treatment and point of collection using the immunogenicity analysis set.

Definitions of ADA negative and positive are as follows:

- ADA Negative: defined as a sample that was evaluated as negative in the ADA screening assay. Samples that were determined to be positive in the ADA screening assay but the result was not confirmed in the ADA confirmatory assay were considered negative.
- ADA Positive: defined as a sample that was evaluated as positive in both the ADA screening and confirmatory assays.

Subject ADA status will be grouped into 3 categories as follows:

- Negative: defined as subjects who did not have confirmed ADA results.
- Positive: defined as subjects who had at least 1 positive ADA result.
  - Note: the cut off value for high/low positive ADA titer will be determined based on the ADA data, if applicable.

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6.8 Pharmacokinetic and Pharmacodynamic Analyses

6.8.1 Pharmacokinetic Analysis

Blood samples for the assessment of plasma TAK-951 concentrations will be collected as outlined in the tables below for each cohort:

Table 6.e Collection of Blood Samples for Pharmacokinetic Analysis (Cohorts 1 and 2)

Analyte	Matrix	Scheduled Time (Hours)*
TAK-951	Plasma	Predose, and 0.083, 0.17, 0.25, 0.5, 1, 1.25, 1.5, 2, 4, 8, 12, 24, and 30 hours postdose.

*The actual date and time of sample collection will be recorded on the source document in the case report form. The collection time points listed in this table are collected after the start of infusion.

Note: A sample will be obtained at the end of infusion for each cohort. For Cohorts 1 and 2, end of infusion time point will be at 1 hour (60 minutes).

Table 6.f Collection of Blood Samples for Pharmacokinetic Analysis (Cohort 3)

Analyte	Matrix	Scheduled Time (Hours)*
TAK-951	Plasma	Predose, and 0.25, 0.5, 1, 1.5, 2, 2.083, 2.25, 2.5, 3, 5, 8, 12, 24, and 30 hours postdose.

*The actual date and time of sample collection will be recorded on the source document in the case report form. The collection time points listed in this table are collected after the start of infusion.

Note: A sample will be obtained at the end of infusion for each cohort. For Cohort 3, the end of infusion time point will be at 2 hours (120 minutes).

Table 6.g Collection of Blood Samples for Pharmacokinetic Analysis (Cohort 4)

Analyte	Matrix	Scheduled Time (Hours)*
TAK-951	Plasma	Predose, and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.25, 3.5, 4, 7, 12, 24, and 30 hours postdose.

*The actual date and time of sample collection will be recorded on the source document in the case report form. The collection time points listed in this table are collected after the start of infusion.

Note: A sample will be obtained at the end of infusion for each cohort. For Cohort 4, the end of infusion time point will be at 3 hours (180 minutes).

Concentrations of TAK-951 will be listed and summarized descriptively by treatment (i.e., TAK-951 dose and infusion rate) and PK sampling time using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, and maximum. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive statistics.

Individual subject concentration-time curves will be plotted by treatment on linear and semi-log scales. The arithmetic mean profiles of the concentration-time data will be plotted by treatment

on linear (with and without SD) and semi-log scales. For summary statistics and arithmetic mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

The PK parameters will be calculated from TAK-951 concentration-time profiles using non-compartmental analysis methods where all calculations will be based on actual sampling times after the start of infusion, wherever possible. The PK parameters will be summarized by treatment (i.e., TAK-951 dose and infusion rate) using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, geom mean, and geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

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

Not applicable

6.10 Preliminary Analysis

A preliminary PK analysis will be completed after database lock as described in the CPAP and Section 6.8.1 of the SAP, with the following changes: 1) unblinded QCed data will be used (unless the QAed data is available, in which case the QAed data will be used); 2) nominal times will be used for the calculation of PK parameters (not actual sampling times); 3) tables and figures will be created using Phoenix® WinNonlin® Version 8.1 or higher.

6.11 Interim Analysis

No formal interim analysis is planned for this study.

6.12 Data Monitoring Committee/Internal Review Committee

A dose-escalation/blinded safety review meeting will be held between the Investigator and Sponsor after each cohort is completed to review the safety and available PK data from samples taken up to 1-day post dose, in order to confirm the dose level and/or infusion rate for the subsequent cohort.

6.13 Additional Analysis Related to COVID

Depending on the prevalence of coronavirus disease (COVID) infections and illness in regions where the study is conducted, additional analysis may be performed to evaluate the impact of COVID on the safety of all participating subjects. This analysis will be agreed between the Sponsor and Celerion prior to database lock and may include but not limited to the following:

- COVID related discontinuation, including discontinuation due to adverse events in light of COVID infection and discontinuation due to COVID-related reasons other than COVID-infection (eg, travel limitation, reduced site staff, etc.).
- COVID related AEs, including preferred term of "COVID-19 infection".
- All SAEs in COVID infected subjects.
- All protocol deviations related to COVID.
- Data listing of all subjects affected by COVID-19 related study disruption, including subject ID, site ID, and description of how individual's participation was altered.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The following analyses are not outlined in the protocol but are described in this SAP:

- Addition of absolute baseline definition for orthostatic vital signs
- Summary and change from baseline tables for orthostatic vital signs.
- Figure plots for summarization for orthostatic vital signs.
- COVID-19 related analysis.

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9.0 APPENDIX

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

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

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

Serum Chemistry—Criteria for Markedly Abnormal Values

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

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

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Systolic blood pressure	mm Hg	<85	>140
Diastolic blood pressure	mm Hg	<50	>90
Body temperature	^{o}C	<35.6	>37.7
	^{o}F	<96.1	>99.9
Heart rate (revised clinical guideline)	bpm	<50	>90
Heart rate (traditional clinical consensus)	bpm	<60	>100
Respiratory Rate	breath per minute	<12	>16
BMI		<18.5	>25.0 • Class 1: BMI of 30 to <35 • Class 2: BMI of 35 to <40 • Class 3: BMI of 40 or higher.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	18-May-2021 15:31 UTC