Statistical Analysis Plan

NCT Number: NCT06935266

Title: A Phase 1, Open-Label, Within-Dose-Level Randomized Trial to Assess the Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous 20% (Human) with Recombinant Human Hyaluronidase (TAK-881) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Participants

Study Number: TAK-881-1003

Document Version and Date: Final version, 10 Apr 2025

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STATISTICAL ANALYSIS PLAN

Trial Number: TAK-881-1003

Celerion Trial Number: CA45894

A Phase 1, Open-Label, Within-Dose-Level Randomized Trial to Assess the Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous 20% (Human) with Recombinant Human Hyaluronidase (TAK-881) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Participants

Phase: 1

Version: Final

Date: 10 April 2025

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Based on:

Protocol Version: Original

Protocol Date: 20 February 2025

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	10 April 2025	Not Applicable

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APPROVAL SIGNATURE

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Trial Title: A Phase 1, Open-Label, Within-Dose-Level Randomized Trial to Assess the Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous 20% (Human) with Recombinant Human Hyaluronidase (TAK-881) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Participants

Approval:

Signature: [redacted]

[redacted] Plasma Derived Therapies Statistics, Baxalta Innovations GmbH, part of Takeda

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ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
BLQ	below the lower limit of quantitation
BP	blood pressure
CI	confidence interval
C_{max}	maximum observed concentration after dose administration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CTR	clinical trial report
C_{trough}	observed concentration at the end of a dosing interval
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
EOT	end of trial
ET	early termination
Geom Mean	geometric mean
GMR	geometric least-squares mean ratio
HV	healthy volunteer(s)
ICF	informed consent form
IgG	immunoglobulin G
IGSC	immune globulin subcutaneous
IP	investigational product
LLOQ	lower limit of quantitation
LSM	least-squares mean
MAV	markedly abnormal values
mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
N	number of participants
n	number of observations
N/A	not applicable
PK	pharmacokinetic(s)
PRO	patient reported outcomes
PT	preferred term
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	statistical analysis plan

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SAS	Statistical Analysis System
SC	subcutaneous(ly)
SD	standard deviation
SEM	standard error of the mean
SOC	System Organ Class
TDL	target dose level
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time of first occurrence of C_{max}
WHO	World Health Organization

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1.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

1.1 Objectives + Associated Endpoints

1.1.1 Primary Objective + Associated Endpoint

Table 1.a Primary Objective + Associated Endpoint

Primary objective	*Primary endpoint*
To assess the tolerability of TAK-881 with and without ramp-up dosing in healthy adult participants.	• *Occurrence of tolerable infusions of TAK-881. Definition: A tolerable infusion is considered to have occurred if an infusion is completed without interruption (discontinuing the infusion, or infusion rate reduction) due to any TEAE related to TAK-881.*

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1.1.2 Secondary Objective + Associated Endpoints

Table 1.b Secondary Objective + Associated Endpoints

Secondary objective	*Secondary endpoints*
To assess the safety and immunogenicity of TAK-881 with and without ramp-up dosing in healthy adult participants.	• *Occurrence of TEAEs.* • *Clinical laboratory parameters.* • *Vital signs.* • *Occurrence of positive binding (defined as titer ≥1:160) antibodies to rHuPH20.* • *Occurrence of neutralizing antibodies to rHuPH20.*

1.1.3 Exploratory Objective + Associated Endpoints

Table 1.c Exploratory Objective + Associated Endpoints

Exploratory objective	*Exploratory endpoints*
To characterize the PK of total IgG in serum after SC administrations of TAK-881 in healthy adult participants.	*The following baseline-uncorrected and baseline-corrected PK parameters for TAK-881 based on serum total IgG level:* • *Maximum observed concentration after dose administration (C_{max}) at Week 8 (Schedules A and B)/Week 9 (Schedule C)* • *Time to C_{max} (t_{max}) at Week 8 (Schedules A and B)/Week 9 (Schedule C).* • *Observed concentration before dosing (C_{trough}).*

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1.2 Estimand

Not applicable.

2.0 TRIAL DESIGN

This trial is a phase 1, open-label, within-dose-level randomized, single-center trial to assess the tolerability, safety, and PK of TAK-881 (IGSC 20% with rHuPH20) in healthy adult participants.

TAK-881 will be administered via the SC route of administration using a SC needle set. The rHuPH20 solution will be administered first and then followed by IGSC, 20% using the same needle set at the same location.

A cohort of 16 participants (Cohort 1) and two cohorts of 24 participants each (Cohort 2 and Cohort 3) are planned for evaluation. Cohort 1 will evaluate either ramp-up Schedule B or no ramp-up Schedule C at a TDL of 0.6 g/kg. Cohort 2 (TDL of 1.0 g/kg) and Cohort 3 (TDL of 2.0 g/kg) will each evaluate 2 ramp-up dosing schedules (Schedules A and B) and a no ramp-up dosing schedule (Schedule C).

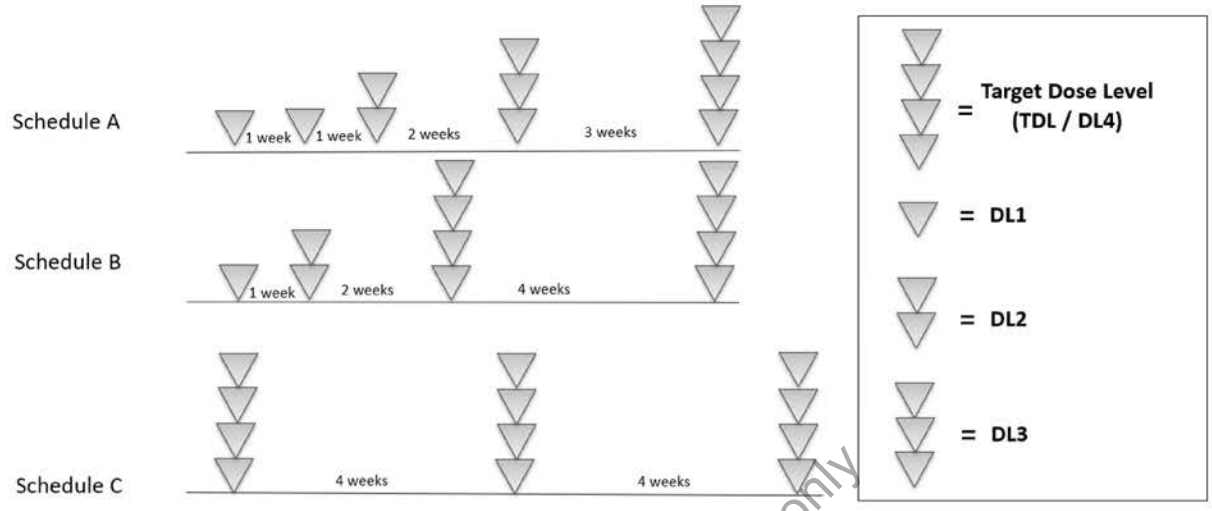
Dosing schedules will be as follows (refer to Figure 2.a):

- *Schedule A:*
  - *DL1 (¼TDL) → 1 week interval → DL1 (¼TDL) → 1 week interval → DL2 (½TDL) → 2 weeks interval → DL3 (¾TDL) → 3 weeks interval → DL4 (full TDL)*
- *Schedule B:*
  - *DL1 (¼TDL) → 1 week interval → DL2 (½TDL) → 2 weeks interval → DL4 (full TDL) → 4 weeks interval → DL4 (full TDL)*
- *Schedule C:*
  - *DL4 (full TDL) → 4 weeks interval → DL4 (full TDL) → 4 weeks interval → DL4 (full TDL)*

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Figure 2.a Trial Schema (Ramp-Up and no Ramp-Up Schedules)



TDL=Target dose level; DL4=full TDL; DL1=¼ TDL; DL2=½TDL; DL3=¾TDL.

The dose levels that will be administered via SC infusion are shown in Table 2.a.

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Table 2.a Dose Levels

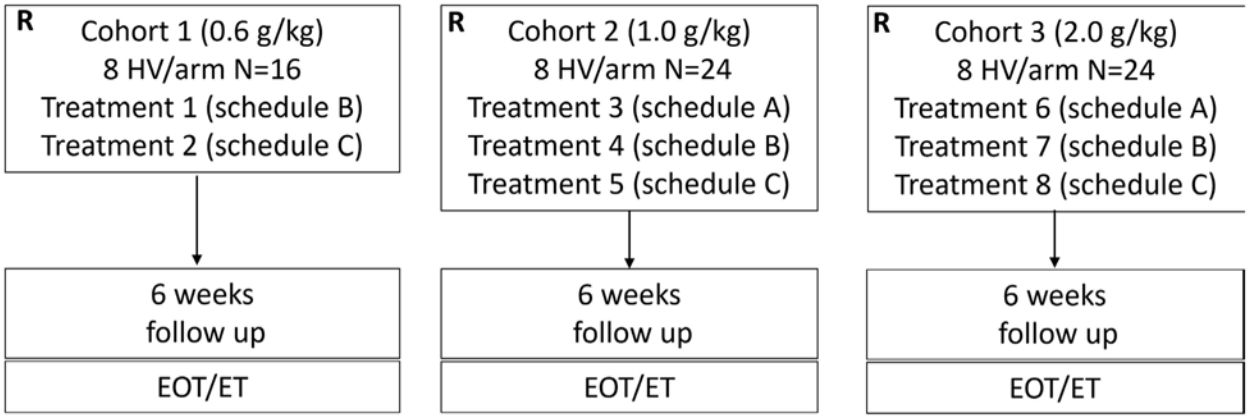
			Dosing day						
Cohort	**Dosing schedule**	**Treatment**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 50**	**Day 57**
1	B	1	0.15 g/kg	0.3 g/kg	N/A	0.6 g/kg	N/A	0.6 g/kg	N/A
	C	2	0.6 g/kg	N/A	N/A	N/A	0.6 g/kg	N/A	0.6 g/kg
2	A	3	0.25 g/kg	0.25 g/kg	0.5 g/kg	N/A	0.75 g/kg	1.0 g/kg	N/A
	B	4	0.25 g/kg	0.5 g/kg	N/A	1.0 g/kg	N/A	1.0 g/kg	N/A
	C	5	1.0 g/kg	N/A	N/A	N/A	1.0 g/kg	N/A	1.0 g/kg
3	A	6	0.5 g/kg	0.5 g/kg	1.0 g/kg	N/A	1.5 g/kg	2.0 g/kg	N/A
	B	7	0.5 g/kg	1.0 g/kg	N/A	2.0 g/kg	N/A	2.0 g/kg	N/A
	C	8	2.0 g/kg	N/A	N/A	N/A	2.0 g/kg	N/A	2.0 g/kg

NOTE: The maximum daily absolute dose of TAK-881 is 120 g/600 mL; some TAK-881 doses may require administration (and equal division) over multiple days. If the dose is over 120 g/600 mL and less than 240 g/1200 mL, half of the dose will be infused on the scheduled day and the other half of the dose will be infused on the following day. By-weight TAK-881 dose calculation will use body weight measured on check-in day prior to dosing.

The initial 16 participants will be allocated to Cohort 1 (0.6 g/kg) and be randomly assigned (1:1) to Treatment 1 or 2. The following 24 participants will be allocated to Cohort 2 (1.0 g/kg) and be randomly assigned (1:1:1) to Treatment 3, 4, or 5. Another 24 participants will be allocated to Cohort 3 (2.0 g/kg) and be randomly assigned (1:1:1) to Treatment 6, 7, or 8 (refer to Figure 2.b).

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Figure 2.b Trial Schema (Trial Design)



EOT/ET=end of trial/early termination; R=open-label randomization (within dose-level cohort) to 1 ramp-up schedule and 1 no-ramp-up schedule with a randomization ratio of 1:1 for Cohort 1 and open-label randomization to 2 ramp-up schedules and 1 no-ramp-up schedule with a randomization ratio of 1:1:1 for Cohorts 2 and 3.

Within-cohort randomization will be conducted on Day 1. PK sampling for measurement of total IgG serum concentrations will be collected on Day -1 and prior to dosing on Day 1 and up to the follow-up/EOT visit.

Throughout the trial, safety will be monitored by repeated clinical and laboratory evaluations. Sampling for ADA will be performed on Day -1 and up to the follow-up/EOT visit.

All participants who received at least one dose of TAK-881 (including participants who terminate the trial early) will return to the CRU 6 weeks (±1 week) after the last dose for the follow-up/EOT procedures, and to determine if any AE has occurred since the last trial visit.

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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

This trial is not designed for statistical hypothesis testing; therefore, the sample size is not based on statistical considerations. The planned total sample size for this trial is 64 randomized and treated participants (8 participants per treatment; 8 treatments). Of the 64 participants to be

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randomized and treated, 48 participants are expected to complete the trial, assuming a conservative overall dropout rate of 25%.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will consist of all participants who received any amount of TAK-881. Safety, tolerability, and immunogenicity endpoints will be presented for the safety analysis set.

5.2 PK Analysis Set

The PK analysis set is a subset of the safety analysis set and will consist of all participants who received at least one dose of TAK-881 and have at least one evaluable postdose serum concentration for total IgG. Analysis will be performed according to the actual treatment received. The analysis performed for PK parameters will be presented for the PK analysis set.

A participant's PK parameter data will be included in the listings but may be excluded from the descriptive statistics.

More details regarding the exclusion criteria will be specified in the CPAP.

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6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline is defined as the last non-missing value before the first administration of the IP. All PK analyses will be conducted using Phoenix WinNonlin Version 8.4, or higher. All statistical analyses will be conducted using SAS Version 9.4 or higher.

The level of precision will be presented as follows: number of subjects with non-missing values (n) will be presented as an integer (no decimal places), mean, median, and geometric mean (Geom Mean) 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. Coefficient of variation (CV%) and geometric CV% (Geom CV%) will be presented to 1 decimal place.

Continuous endpoints and variables will be summarized using the following descriptive statistics: n, mean, SD, minimum, median, and maximum values. In addition, PK endpoints will be summarized using n, mean, SD, CV%, SEM, minimum, median, maximum, Geom Mean, and Geom CV%. Categorical endpoints and variables will be summarized in terms of number and percentage of subjects with non-missing values and number of occurrences in each category. A corresponding two-sided 95% CI for the percentage will be presented if specified in the relevant sections. Percentages will be presented to 1 decimal place, except when the percentage equals exactly 100 where it will be presented as an integer (100).

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Participants who prematurely discontinue from the trial will be included in the descriptive analyses up to the time point of discontinuation. Missing data will not be imputed unless otherwise specified.

6.1.1 Handling of Treatment Misallocations

Analysis will be performed according to the actual treatment received.

6.2 Trial Information

A trial information table will be generated including the following items: date of first participant's signed ICF, date of first dose of IP, date of last dose of IP, date of last participant's completion or discontinuation, date of last participant's last procedure for collection of data for primary endpoint, the version of MedDRA, the version of WHO Drug Dictionary, and SAS version used for creating the datasets.

6.3 Disposition of Participants

Disposition of participants (for example, number of participants dosed, completed the trial, discontinued from the trial and/or treatment, and reason(s) for discontinuation) will be summarized by treatment and overall based on the Safety Analysis Set.

Trial completion status, date of completion, and whether IP was discontinued will be listed by participant. Reasons for discontinuation of IP and/or trial and dates of discontinuation will be listed, if applicable.

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6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized by treatment and overall based on the safety analysis set. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age, weight, height, and BMI) and the number and percentage of participants within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and the corresponding BMI from the screening visit will be used in the summaries. If weight at the screening visit is missing, then baseline (Day-1) weight will be presented.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history will include any significant conditions or diseases that were resolved at or before signing the ICF. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Medical history and concurrent medical conditions will be listed based on the safety analysis set.

Any medical condition starting or worsening after first dosing will be classified as a TEAE. All medical history will be coded using the MedDRA version specified in the DMP. If available, the

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medical history and concurrent medical condition listings will include the coded term (preferred term and SOC), start date (if known) and end date (if known) or whether the condition was ongoing, and a description of the condition or event. No summaries or statistical analysis will be performed for these data.

6.5 Medication History and Concomitant Medications

Medication history includes any medication relevant to eligibility criteria and safety evaluation stopped prior to dosing. Concomitant medication includes any medication given in addition to the IP between the first dose of IP and then end of the follow-up period. All medication history and concomitant medications recorded will be coded with the WHO Drug Dictionary version specified in the DMP and listed based on the safety analysis set. If available, the listings will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time (if known), or whether it continued after trial completion, and indication for use. No summaries or statistical analysis will be performed for these data.

6.6 Tolerability and Safety Analysis

Safety, tolerability, and immunogenicity analyses will be presented for the Safety Analysis Set.

Safety will be evaluated by the incidence of TEAEs, severity and relationship(s) of TEAEs, and changes from baseline in the participants' clinical laboratory results, vital signs, and 12-lead ECGs using the safety analysis set. Note that clinically significant treatment-emergent changes in clinical laboratory measurements and vital signs will be recorded in the trial database as TEAEs. All safety data will be listed by participant, and assessment time points, including rechecks, unscheduled, and ET assessments, chronologically.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

Tables summarizing clinical laboratory, vital sign, and ECG results by treatment and assessment time point will only include summaries for baseline and post-baseline time points. Post-baseline recheck, unscheduled, and ET assessments will not be included in summaries by time point but will be considered in overall abnormality summaries (that is, MAV summaries).

6.6.1 Infusion Tolerability Analysis

Infusion Tolerability Analysis will be based on the Safety Analysis Set.

The following summary tables will be presented for each treatment arm within cohort:

1. Number and percentage of participants who tolerated all initiated infusions and the 95% Clopper-Pearson CI (Clopper and Pearson, 1934) for the percentage.
2. Number and percentage of tolerable infusions and the 95% Clopper-Pearson CI for the percentage.

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3. Average number of intolerable infusions per IG received (g/kg).
   - For each treatment arm, the calculation is: (total number of intolerable infusions) / (total actual IG received (g/kg) by all participants within that arm).
4. Number and percentage of participants who tolerated all initiated infusions and the 95% Clopper-Pearson confidence interval (CI) for the percentage, including only infusions before the initiation of the first full TDL and infusions of the first full TDL.
   - For Schedule A, this includes doses scheduled on Day 1, 8, 15, 29, and 50; For Schedule B, this includes doses scheduled on Day 1, 8, and 22; For Schedule C, this includes only dose scheduled on Day 1.
5. Average number of intolerable infusions per IG received (g/kg), including only infusions before the initiation of the first full TDL and infusions of the first full TDL.
   - For Schedule A, this includes doses scheduled on Day 1, 8, 15, 29, and 50; For Schedule B, this includes doses scheduled on Day 1, 8, and 22; For Schedule C, this includes only dose scheduled on Day 1.
6. Number and percentage of participants who tolerated all initiated infusions and the 95% Clopper-Pearson confidence interval (CI) for the percentage, including only full TDL infusions.
   - For Schedule A, this includes only doses scheduled on Day 50; For Schedule B, this includes doses scheduled on Day 22 and 50; For Schedule C, this includes dose scheduled on Day 1, 29, and 57.
7. Number and percentage of tolerable infusions and the 95% Clopper-Pearson CI for the percentage, including only full TDL infusions.
   - For Schedule A, this includes only doses scheduled on Day 50; For Schedule B, this includes doses scheduled on Day 22 and 50; For Schedule C, this includes dose scheduled on Day 1, 29, and 57.

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95% Clopper-Pearson CI will be derived using the following SAS code:

```
PROC FREQ;
BY TREAT;
TABLES AVALC / BINOMIAL(CL=EXACT LEVEL=<'tolerable'>) ALPHA=0.05;
RUN;
```

Where AVALC contains the result of whether an infusion was 'tolerable' or 'intolerable' or the participant level result of whether a participant tolerated all infusions.
A tolerable infusion is considered to have occurred if an infusion is completed without interruption (discontinuing the infusion or infusion rate reduction) due to any TEAE related to TAK-881. An infusion is considered as intolerable if it is interrupted (discontinuation of the infusion or infusion rate reduction) due to TEAE related to TAK-881.

In addition, the number and percentage of subjects with infusion discontinuations, infusion rate reductions due to TAK-881-related TEAEs, as well as the number of infusion discontinuations, infusion rate reductions due to TAK-881-related TEAEs per infusion will be presented for each

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treatment. If more than 1 intervention is made to a particular infusion, only the final intervention will be considered.

6.6.2 Adverse Events

All AEs occurring during this trial will be coded using the MedDRA version specified in the DMP.

All AEs captured in the database will be listed in by-participant data listings including verbatim term, preferred term, SOC, severity (based on CTCAE version 5.0 consisting of 5 grades (except systemic allergic reactions [SARs])), seriousness, local/systemic TEAEs), relationship to IP (related or not related), frequency, and action relative to the IP as recorded in the CRF. TEAEs leading to trial discontinuation will be flagged in the listings. Trial procedures given due to AEs will also be listed, including the procedure name, start date and time, and associated AE. Only TEAEs will be summarized.

A TEAE is defined as any AE that started at or after the start of the first IP administration. A temporally associated TEAEs within 72 hours is defined as any TEAE that started between the start of the IP administration and 72 hours after completion of the most recent IP administration, irrespective of being related or not related to IP.

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The duration of the AE will be calculated as (stop date/time of AE) – (start date/time of AE). The duration will be presented in hours if the duration is ≤ 24 hours; otherwise the duration will be presented in days. If either the start time or the stop time of the AE is missing, then the duration will be calculated as (stop date of AE) – (start date of AE) + 1. If either the start date or stop date of the AE is missing, no duration of AE will be calculated.

If the AE start date/time is incomplete, an indication is provided in the CRF on whether the AE started prior to or after the first IP administration. No imputation of dates/times will be required to determine if an AE is treatment-emergent or not.

The time since the most recent IP administration will be calculated for TEAEs only. It will be calculated as (start date/time of TEAE) – (start date/time of most recent IP administration). The time will be presented in hours if the time is ≤ 24 hours; otherwise the time will be presented in days. If either the start time of the TEAE or the start time of the most recent IP administration is missing, then the time will be calculated as (start date of TEAE) – (start date of the most recent IP administration) + 1. If either the start date of the TEAE or the start date of the most recent IP administration is missing, no time since the most recent IP administration will be calculated.

The severity of AEs will be assigned for all AEs (TEAEs and non-TEAEs) and will be used as reported in the CRF using the common terminology criteria for adverse events (CTCAE), version 5.0, consisting of 5 grades (except systemic allergic reactions [SARs]):

- *Grade 1: mild.*
- *Grade 2: moderate.*

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• *Grade 3: severe or medically significant but not immediately life-threatening.*

• *Grade 4: life-threatening consequences.*

• *Grade 5: death related to AE.*

The severity of SARs will be assessed by The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System, consisting also of 5 grades.

If severity is missing, the AE will be considered ungraded and will not be used for any summaries by severity grade.

The relationship to IP will be used as reported in the CRF (non-related/related). If relationship to IP is missing, TEAEs will be considered related to IP. The imputed values will be used for summaries but not for listings.

The number and percentage of subjects with TEAEs (i.e. number of TEAEs / total number of TAK-881 treated subjects in the respective arms), and the number of TEAEs will be summarized by each treatment (Treatments 1 to 8) and combined for each cohort, using the following categories:

- Any TEAE
- TEAEs considered related and not-related to TAK-881
- Serious and non-serious TEAEs
- Local TEAEs
- Systemic TEAEs
- Temporally associated TEAEs within 72 hours
- TEAEs by maximum severity (grades 1-5).
- TEAEs leading to study discontinuation.
- TEAEs of special interest (allergy, catheter leakage, and thromboembolic events).

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In addition, the number and percentage of subjects with TEAEs, and the number of TEAEs will be summarized for each treatment (Treatments 1 to 8) and combined for each cohort, by SOC and PT using the following categories:

- any TEAE.
- serious TEAEs.
- TEAEs considered related to TAK-881.
- temporally associated TEAEs within 72 hours.

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SOC will be sorted in descending frequency using total occurrence. PT within SOC will be also sorted in descending frequency using total occurrence. If more than one TEAE occurs with the same PT for the same subject, then the subject will be counted only once for that PT.

In addition, the number and percentage of subjects with TEAEs will be summarized for each treatment (Treatments 1 to 8) and combined for each cohort, by SOC, PT, severity grade (grade 1-5 and combined), and relationship to TAK881 (non-related/related) using the following categories:

- any TEAE.
- serious TEAEs.
- temporally associated TEAEs within 72 hours.

SOC will be sorted in descending frequency using total occurrence. PT within SOC will be also sorted in descending frequency using total occurrence. If more than one TEAE occurs with the same PT and relationship assessment for the same subject, then the subject will be counted only once for that PT and relationship assessment using the most severe occurrence.

If any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAEs. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the CTR.

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6.6.3 AESI

AESIs will be flagged in the data listings and discussed in the CTR, as appropriate. The following are AESIs for TAK-881:

- Allergy
- Catheter leakage
- Thromboembolic events

Adverse events of special interest will be included in the TEAE summary as defined in Section 6.6.2.

6.6.4 Clinical Laboratory Assessments

Clinical laboratory tests will be measured as described in Table 6.a:

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Table 6.a Collection of Laboratory Samples

Clinical Laboratory Parameters	Time Point			
	Schedule	Period	CRF/Listing Day and Hour	Table Presentation
Chemistry, Hematology, Urinalysis, Coagulation*	Ramp-Up Schedule A	Screening		NA
		1	Day -1 Check-in Day 3# Day 7 Day 14 (±2 days) Day 28 (±2 days) Day 49 (±3 days) Week 14 (±1 week)	Baseline Day 3 Day 7 Day 14 (±2 days) Day 28 (±2 days) Day 49 (±3 days) Week 14 (±1 week)
	Ramp-Up Schedule B	Screening		NA
		1	Day -1 Check-in Day 3# Day 7 Day 21 (±2 days) Day 49 (±3 days) Week 14 (±1 week)	Baseline Day 3 Day 7 Day 21 (±2 days) Day 49 (±3 days) Week 14 (±1 week)
	No Ramp-Up Schedule C	Screening		NA
		1	Day -1 Check-in Day 3# Day 28 (±2 days) Day 56 (±3 days) Week 15 (±1 week)	Baseline Day 3 Day 28 (±2 days) Day 56 (±3 days) Week 15 (±1 week)

Baseline is defined as the last non-missing value before the first administration of the IP
Time points in the CRF/Listing column are based on the protocol, and it should be noted that the data listings will reflect the data found in the final participant CRFs.
Period is not defined in the protocol, but will be recorded in the CRF and displayed in the listings.
Period 1 = Treatment period.
*Coagulation tests will be performed at screening, check-in, and EOT. # = Hemoglobin only
If applicable, an ET assessment will be performed.
NA = Not Applicable (Individual results may be required for baseline)

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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 and time point of collection. Change from baseline will be summarized in a similar manner.

All clinical laboratory listings and tables will be presented in international system (SI) units. If the SI unit is equivalent to the reported unit for a given test, the individual clinical laboratory results will be presented with the same precision as the reported values. If the SI unit is not equivalent to the reported unit for a given test, the individual clinical laboratory results will be presented to a maximum precision of 3 decimal places.

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), if applicable) with

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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.

Individual postdose chemistry or hematology results that meet Takeda's MAV criteria, including recheck, unscheduled, and ET results, will be listed and tabulated. A participant's value will be considered a MAV if it meets one of the criteria described in Appendix A. The number and percentage of participants in each treatment with at least one postdose result considered a MAV will be tabulated. A participant mapping listing will also be provided to show which participants with postdose values met each category. All clinical laboratory MAV values will be listed in by-participant data listings. Postdose unscheduled, recheck, or ET assessments will be included in MAV summaries, if applicable.

A hemolytic panel will be conducted at check-in and Day 4 for each schedule, and at other times as needed at the discretion of the PI. Scheduled time points will be summarized by treatment and time point. Unscheduled results from the hemolytic panel will be listed.

6.6.5 Vital Signs

Vital signs will be measured as described in Table 6.b:

Table 6.b Collection of Vital Signs

Parameter	Time Point			
	Schedule	Period	CRF/Listing Day and Hour	Table Presentation
Blood Pressure, Pulse Rate, Respiration, Temperature	Ramp-Up Schedule A	Screening		NA
		1	Day -1 Check-in	NA
			Day 1 Predose	Baseline
			Day 1 <Hour*>	Day 1 <Hour*>
			Day 2	Day 2
			Day 3	Day 3
			Day 4	Day 4
			Day 7	Day 7
			Day 8 <Hour*>	Day 8 <Hour*>
			Day 9	Day 9
			Day 14 (±2 days)	Day 14 (±2 days)
			Day 15 <Hour*>	Day 15 <Hour*>
			Day 16	Day 16
			Day 28 (±2 days)	Day 28 (±2 days)
			Day 29 <Hour*>	Day 29 <Hour*>
			Day 30	Day 30
			Day 49 (±3 days)	Day 49 (±3 days)
			Day 50 <Hour*>	Day 50 <Hour*>
			Day 51	Day 51
			Week 14 (±1 week)	Week 14 (±1 week)

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Parameter	Time Point			
	Schedule	Period	CRF/Listing Day and Hour	Table Presentation
	Ramp-Up Schedule B	Screening		NA
		1	Day -1 Check-in Day 1 Predose Day 1 <Hour*> Day 2 Day 3 Day 4 Day 7 Day 8 <Hour*> Day 9 Day 21 (±2 days) Day 22 <Hour*> Day 23 Day 49 (±3 days) Day 50 <Hour*> Day 51 Week 14 (±1 week)	NA Baseline Day 1 <Hour*> Day 2 Day 3 Day 4 Day 7 Day 8 <Hour*> Day 9 Day 21 (±2 days) Day 22 <Hour*> Day 23 Day 49 (±3 days) Day 50 <Hour*> Day 51 Week 14 (±1 week)
	No Ramp-Up Schedule C	Screening		NA
		1	Day 1 Predose Day 1 <Hour*> Day 2 Day 3 Day 4 Day 8 Day 28 (±2 days) Day 29 <Hour*> Day 30 Day 56 (±3 days) Day 57 <Hour*> Day 58 Week 15 (±1 week)	Baseline Day 1 <Hour*> Day 2 Day 3 Day 4 Day 8 Day 28 (±2 days) Day 29 <Hour*> Day 30 Day 56 (±3 days) Day 57 <Hour*> Day 58 Week 15 (±1 week)

Baseline is defined as the last non-missing value before the first administration of the IP
*BP, pulse rate, respiration rate and temperature will be measured predose, every 30 minutes post infusion start until the end of the infusion, then every 1 hour post-infusion end for 4 hours. Time points may vary between TDL and schedule.
Time points in the CRF/Listing column are approximated/based on the protocol and it should be noted that the data listing will reflect the data found in the final participant CRFs.
Period is not defined in the protocol, but will be recorded in the CRF and displayed in the listings.
Period 1 = Treatment period.
If applicable, an ET assessment will be performed.
NA = Not applicable (Individual results may be required for baseline)

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital signs by treatment and time point of collection. Change from baseline will be summarized in a similar manner. Vital sign data will be displayed in a data listing by participant.

Individual postdose vital signs results that meet Takeda's MAV criteria, including recheck, unscheduled, and ET results, will be listed and tabulated. A participant's value will be

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considered a MAV if it meets one of the criteria described in Appendix B. The number and percentage of participants treatment with at least one postdose result considered a MAV will be provided. A participant mapping listing will also be provided to show which participants with postdose values met each category. All vital signs MAVs will also be listed in by-participant data listings. Postdose unscheduled, recheck, or ET assessments will be included in MAV summaries, if applicable.

6.6.6 12-Lead ECG

12-lead ECGs will be collected at Screening and EOT for each schedule. If applicable, an ET assessment will be performed.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for each ECG parameter by treatment and time point of collection. Change from baseline will be summarized in a similar manner. All ECG data will be displayed in a data listing by participant.

Individual postdose ECG results that meet Takeda's MAV criteria, including recheck, unscheduled, and ET results, will be listed and tabulated. A participant's value will be considered MAV if it meets one of the criteria described in Appendix C. The number and percentage of participants in each treatment with at least one postdose result considered MAV will be provided. A participant mapping listing will also be provided to show which participants with postdose values met each category. All ECG MAV values will also be listed in by-participant data listings.

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6.6.7 Physical Examination

A full physical examination will be performed at screening, check-in, prior to each dosing day [Day 7, Day 14(±2), Day 28(±2), and Day 49(±3) for Schedule A, Day 7, Day 21(±2), and Day 49(±3) for Schedule B, and Day 8, Day 28(±2), and Day 56(±3) for Schedule C], and at the EOT. If applicable, an ET assessment will be performed. Abnormal physical examination findings will be recorded as AEs at the discretion of the investigator. Physical examination findings will be presented in the data listings by participant.

6.6.8 Infusion Site Reaction Assessment

Infusion sites will be evaluated at 12 hours post-infusion on Day 1, on each of Days 2 through 8, and as clinically indicated. Any abnormal findings will be reported as AEs. For dose administrations that require 2 infusion sites used simultaneously, local AEs will be reported separately for each site. Results reported on the CRF will be listed, if applicable.

6.6.9 Overdose

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

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6.6.10 Extent of Exposure and Compliance

A summary of exposure will be presented, including a frequency count of the number of doses administered and descriptive statistics of the amount of IP administered by treatment. Administration times and amounts will be listed by participant.

6.6.11 Immunogenicity Analysis

Blood samples for rHuPH20 immunogenicity assessments will be collected at the time points listed in Table 6.c.

Table 6.c Collection of Blood Samples for rHuPH20 Immunogenicity Assessments

Schedule	Cohorts	Scheduled Time (Hours)*
A	2 and 3	Day -1, Day 28 (±2 days), Day 49 (±3 days), and EOT/ET (±1 week)
B	1, 2, and 3	Day -1, Day 21 (±2 days), Day 49 (±3 days), and EOT/ET (±1 week)
C	1, 2, and 3	Day -1, Day 28 (±2 days), Day 56 (±3 days), and EOT/ET (±1 week)

*The actual dates and times of sample collections will be recorded on the source document in the CRF. At any time during the trial, participants who have a moderate or severe AE which may be a result of immune-mediated response will be asked to return to the trial site to undergo a repeat test for anti-rHuPH20 binding antibody titers, test (or repeat test, as applicable) for the presence of neutralizing anti-rHuPH20 antibodies.

All participants will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection assay (also known as the Screening and Confirmatory Binding Assay). Postdose samples with antibody titers ≥1:160 will be analyzed for the presence of neutralizing-ADA using a validated assay based on neutralization of rHuPH20 activity.

Immunogenicity (occurrence of binding (ADA) and neutralizing antibodies to rHuPH20) data will be listed for all participants in the safety analysis set and will be summarized using descriptive statistics. Positive binding (defined as titer ≥1:160) and neutralizing antibodies to rHuPH20 will be flagged in the individual listings and summarized separately.

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The number and percentage of subjects with at least one positive binding antibody to rHuPH20 (defined as titer ≥1:160) and the number and percentage of subjects with at least one positive neutralizing antibody to rHuPH20 will be presented by each treatment (Treatments 1 to 8) and combined for each cohort.

In addition, positive binding antibody to rHuPH20 (defined as titer ≥1:160) and positive neutralizing antibody to rHuPH20 will be also summarized by study visit.

All immunogenicity data will be presented in a data listing by participant.

6.6.12 Additional Immunogenicity Panel Tests

At baseline (Day -1), samples will be collected for CH50, C3, C4, C1q binding assay, circulating immune complex, and Raji binding assay. Any results will be listed by participant, as applicable.

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6.7 Pharmacokinetic Analysis

Serum Total IgG Concentrations

Blood samples for assessment of serum total IgG concentrations will be collected at the time points listed in Table 6.d below.

Table 6.d Collection of Blood Samples for PK Analysis of Serum Total IgG

Schedule	Cohorts	Scheduled Time (Hours)*
A	2 and 3	Day -1; predose on Days 1, 8, 15, and 29; predose and 24 (±12), 72 (±24), 120 (±24), and 168 (±24) hours postdose on Day 50; and EOT/ET (±1 week)
B	1, 2, and 3	Day -1; predose on Days 1, 8, and 22; predose and 24 (±12), 72 (±24), 120 (±24), and 168 (±24) hours postdose on Day 50; and EOT/ET (±1 week)
C	1, 2, and 3	Day -1; predose on Days 1 and 29; predose and 24 (±12), 72 (±24), 120 (±24), and 168 (±24) hours postdose on Day 57; and EOT/ET (±1 week)

*The actual dates and times of sample collections will be recorded on the source document in the CRF.

Serum total IgG concentrations will be listed and summarized by treatment 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 participant concentration-time curves will be plotted by treatment on linear and semi-log scales. The 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 mean concentration-time plots, nominal PK sampling time will be used. For individual participant concentration-time plots, actual PK sampling times will be used.

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PK Parameters

All PK analyses will be based on the PK analysis set. As per the CPAP, PK parameters (both baseline corrected and uncorrected) using serum total IgG after the last dose of TAK-881 (including after Week 8 [Day 50] dosing for Schedules A and B and after Week 9 [Day 57] dosing for Schedule C), including C_{max}, t_{max}, and C_{trough} will be summarized descriptively by n, Mean, SD, CV%, SEM, minimum, median, maximum, Geom Mean, and Geom CV% for each treatment. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

Noncompartmental analyses will be used in this study. 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 the lower limit of quantitation (LLOQ) for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters.

6.8 Preliminary Analyses

Not applicable.

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6.9 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

There were no changes to protocol planned analyses.

9.0 CHANGES FROM THE PREVIOUS VERSION OF THE SAP

Not applicable

10.0 APPENDICES

MAVs are only applied to values that are more extreme than those seen at baseline (eg, if the baseline value is below the critical value, then the postdose value must be lower). Safety laboratory, vital sign, and ECG MAVs will be identified using the following criteria:

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Appendix A Criteria for Identification of Markedly Abnormal Safety Laboratory Values

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	SI	--	>3x ULN
AST	SI	--	>3x ULN
GGT	SI	--	>3x ULN
Alkaline phosphatase	SI	--	>3x ULN
Total Bilirubin	SI	--	>1.5x ULN
Albumin	SI	<25 g/L	--
Total protein	SI	<0.8x LLN	>1.2x ULN
Creatinine	SI		>1.5x ULN
Blood urea nitrogen	SI		>10.7 mmol/L
Sodium	SI	<130 mmol/L	>150 mmol/L
Potassium	SI	<3.0 mmol/L	>5.3 mmol/L
Glucose	SI	<2.8 mmol/L	>19.4 mmol/L
Chloride	SI	<75 mmol/L	>126 mmol/L
Calcium	SI	<1.92 mmol/L	>2.77 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.

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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.

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<40	>115
Systolic blood pressure	mm Hg	<90	≥140
Diastolic blood pressure	mm Hg	<50	≥90
Heart rate change from baseline	bpm		≥15
Systolic blood pressure change from baseline	mm Hg		≥20
Diastolic blood pressure change from baseline	mm Hg		≥15

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Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart rate	bpm	<40	>115
PR	msec	≤80	≥200
QRS	msec	≤80	≥180
QTcF	msec	<300	>500 Or >450 and ≥30 msec change from baseline
QTcF change from baseline	msec		≥60