Statistical Analysis Plan

NCT Number: NCT05059977

Title: A Phase 1, Single-Dose, Single-Center, Open-Label, Three-Arm Study to Assess the Tolerability and Safety of Immune Globulin Subcutaneous (Human), 20% Solution with Recombinant Human Hyaluronidase (TAK-881) at Various Infusion Rates in Healthy Adult Subjects

Study Number: TAK-881-1001

Document Version and Date: Statistical Analysis Plan Version 2.0, 27-JAN-2022

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-881-1001

A Phase 1, Single-Dose, Single-Center, Open-Label, Three-Arm Study to Assess the Tolerability and Safety of Immune Globulin Subcutaneous (Human), 20% Solution with Recombinant Human Hyaluronidase (TAK-881) at Various Infusion Rates in Healthy Adult Subjects

Phase: I

Version: 2.0

Date: 27-JAN-2022

Prepared by: [redacted]

Based on:

Protocol Version: Amendment 1

Protocol Date: 09-JUL-2021

REVISION HISTORY

Version	Date	Primary Rationale for Revision
Original version	30-AUG-2021	Not Applicable
Amendment 1 (Version 2.0)	27-JAN-2022	Separate listings for clinical laboratory parameters and vital signs considered as TEAEs and the shift tables from baseline of normal versus abnormal clinically significant/not-clinically significant laboratory values cannot be generated as the required data is not collected in the eCRF, see Appendix 9.1. Summaries by BMI group for tolerability events, extent of exposure, and infusion status were added. Section 8.0 was added to describe and justify the deviation of the SAP from the planned analyses specified in the protocol.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	Adverse event
BMI	Body mass index
COVID-19	Coronavirus disease 2019
CTCAE	Common terminology criteria for adverse events
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
IgG	Immunoglobulin G
IGSC 20%	Immune Globulin Subcutaneous (Human) 20%
MedDRA	Medical dictionary for regulatory activities
PK	Pharmacokinetic
PT	Preferred term (MedDRA)
rHuPH20	Recombinant human hyaluronidase
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO	World health organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To assess the tolerability of TAK-881 at various SC infusion rates in healthy adult subjects.

1.1.2 Secondary Objectives

To assess the safety of TAK-881 at various SC infusion rates and immunogenicity of TAK-881 in healthy adult subjects.

1.1.3 Exploratory Objective

To assess serum total IgG levels.

1.2 Endpoints

1.2.1 Primary Endpoint

The primary endpoint corresponding to the primary objective of the study is the occurrence of tolerability events related to the infusion of TAK-881 per infusion site.

Definition: A tolerability event is considered to have occurred if an infusion was tolerable. An infusion is considered tolerable if the infusion rate was not reduced or the infusion was not interrupted or stopped, due to any treatment-emergent adverse event (TEAE) related to TAK-881.

1.2.2 Secondary Endpoints

1.2.2.1 Safety and Immunogenicity Endpoints

- *Occurrence of TEAEs, including but not limited to: TAK-881-related and non-related TEAEs*
- *Clinical laboratory parameters*
- *Vital signs*
- *Immunogenicity: occurrence of binding and neutralizing antibodies to rHuPH20*

1.2.2.2 SC Administration Endpoints

- *Maximum tolerable infusion rate achieved per infusion site*
- *Total volume infused per infusion site*
- *Time to deliver the total infused volume per infusion site*

1.2.3 Exploratory Endpoint

Serum total IgG levels at predose and postdose of TAK-881 SC administration.

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This study is a Phase 1, single-dose, single-center, open-label, three-arm study to evaluate the tolerability, safety, and immunogenicity of TAK-881 at various infusion rates in healthy adult subjects. Section 9.5 provides a schematic of the study design. The overall study design is presented in Figure 1 and the sentinel dosing design in Figure 2. This study is not randomized and *comprises 3 treatment arms:*

- *Treatment Arm 1 - Subjects will receive a single dose of TAK-881 comprising of 0.4 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.*
- *Treatment Arm 2 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.*
- *Treatment Arm 3 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (un-warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.*

The infusion rates as presented in Section 9.4 will be followed for the study. Dosing will be first initiated at the lower dose level (Treatment Arm 1, 0.4 g/kg, in-line warmed) followed by the higher dose level (Treatment Arm 2, 1.0 g/kg, in-line warmed) and then the un-warmed arm (Treatment Arm 3, 1.0 g/kg, un-warmed). Subjects in all 3 treatment arms will be dosed according to a sentinel dosing design with ongoing safety monitoring by the investigator to ensure optimal tolerability and safety.

The study consists of 3 periods with an *approximate overall duration of 14 to 16 weeks from screening to* end of study (*EOS*)*:*

- *Screening period: up to 21 days prior to dosing.*
- *Study treatment period: 4 days.*
- *Follow-up period: up to 12 (±1) weeks after TAK-881 infusion.*

Tolerability and safety including immunogenicity of TAK-881 will be assessed during the treatment and follow-up periods for all 3 treatment arms.

Final analysis will be performed after database lock. *There is no planned interim analysis, adaptive design, or Data Monitoring Committee in this study. However, before the dosing in Treatment Arm*

2, the tolerability and safety data through Day 4 of the last subject in Treatment Arm 1 will be reviewed by a safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician. Similarly, the tolerability and safety data through Day 4 of the last subject in Treatment Arm 2 will be reviewed by the safety review team before the dosing in Treatment Arm 3.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Statistical analysis for this study will be descriptive in nature; no statistical hypothesis testing will be performed. Tolerability/safety/immunogenicity of TAK-881 will be based on clinical judgment on the totality of evidence, with no predefined statistical margin or criteria.

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 study plans to enroll 8 subjects in each of the 3 treatment arms, and a minimum of 3 subjects in each of the 2 BMI groups (18 to <25 kg/m^2, ≥25 to 30 kg/m^2) in each treatment arm. In this study, enrolled subjects are the same as treated subjects. This study is not designed for statistical hypothesis testing; therefore, the sample size was not based on statistical considerations.

Of the 24 subjects to be enrolled, a minimum of 18 subjects are expected to complete the study, assuming a conservative overall dropout rate of 25% in this healthy subject study (overall dropout rates assumed for HYQVIA patient studies are generally 10%-15%). The number of subjects expected to complete the study (≥18) is considered adequate for claiming tolerability and safety of TAK-881 based on clinical judgment.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who received a partial or a full dose of TAK-881.

5.2 PK Analysis Set

The PK Analysis Set will consist of all subjects in the Safety Analysis Set who have at least one evaluable postdose serum concentration for total IgG.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline is defined as the last non-missing value before TAK-881 administration. The initiation of treatment with TAK-881 refers to the start of rHuPH20 administration. Post-baseline assessments at scheduled visits that are collected outside the defined visit windows (see Section 9.2.3) or at unscheduled visits will not be included in summaries by visit, except for immunogenicity endpoints (occurrence of binding and neutralizing anti-rHuPH20 antibodies). All assessments including those at unscheduled visits will be presented in the subject data listings. Assessments that are not included for summaries by visit will be flagged in the subject data listings.

Continuous endpoints will be summarized using the following descriptive statistics: number of subjects with non-missing values (n), mean, median, standard deviation (SD), minimum value, and maximum value. In addition, total IgG levels will be summarized using geometric means with corresponding two-sided 95% confidence intervals. Means, medians, and geometric means with confidence intervals will be presented to 1 more decimal place as the recorded data. Standard deviations (SDs) will be presented to 2 more decimal places as the recorded data. Minimum and maximum will be presented to the same number of decimal places as the recorded data. For BMI, individual subject data will be presented to 1 decimal place in listings, means and medians will be presented to 2 decimal places, SD to 3 decimal places, and minimum and maximum to 1 decimal place.

Categorical endpoints will be summarized in terms of number and percentage of subjects with non-missing values and number of occurrences in each category. Percentages will be presented to 1 decimal place, except when the percentage equals exactly 100 where it will be presented as an integer (100). For zero, only count and no percentage will be presented.

Outcome specific handling of missing data is described in the relevant sections. Missing data due to the COVID-19 pandemic will not be handled any differently than missing data for other reasons.

If data are considered spurious, it will be documented along with the reason for exclusion and the analyses from which the data were excluded. No statistical techniques will be used to identify spurious data.

Subjects who prematurely discontinue from the study will be included in the analyses up to the time point of discontinuation.

6.1.1 Handling of Treatment Misallocations

Not applicable.

6.1.2 Analysis Approach for Continuous Variables

All continuous endpoints in this study will be summarized descriptively.

6.1.3 Analysis Approach for Binary Variables

All binary and categorical endpoints in this study will be summarized descriptively.

6.1.4 Analysis Approach for Time-to-Event Variables

Not applicable.

6.2 Disposition of Subjects

Subject disposition will be summarized and listed based on the Safety Analysis Set.

The number and percentage of subjects who completed the study and prematurely discontinued will be presented by treatment arm and total, along with primary reasons for discontinuation.

All subjects who completed and prematurely discontinued the study will be presented in a subject data listing along with reasons for discontinuation.

In addition, the number of subjects included in each analysis set (Safety Analysis Set and PK Analysis Set) will be presented by treatment arm and total.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographics will be summarized based on the Safety Analysis Set and the PK Analysis Set.

The following demographic characteristics will be summarized and presented by treatment arm and total: age (years), sex, ethnicity, race. Age at informed consent will be used as reported in the eCRF and will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum. Sex, ethnicity, and race will be summarized by the number and percentage of subjects in each category.

All demographic data will be presented in a subject data listing based on the Safety Analysis Set.

6.3.2 Medical History

Medical history will be summarized and listed based on the Safety Analysis Set. Missing dates will not be imputed.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or newer and includes any significant or relevant diseases, surgeries/procedures, or other medical events.

Medical history will be summarized by system organ class (SOC) and preferred term (PT) and will be presented by treatment arm and total. The summary will show the number and percentage of subjects who experienced the event, and the number of events experienced. SOC will be sorted alphabetically, and PT within SOC will be sorted in descending frequency based on total occurrence. If more than one event occurs with the same PT for the same subject, then the subject will be counted only once for that PT.

All medical history data will be presented in a subject data listing.

6.3.3 Baseline Characteristics

Baseline characteristics will be summarized based on the Safety Analysis Set and the PK Analysis Set.

The following baseline characteristics at screening will be summarized and presented by treatment arm and total: weight (kg), height (cm), BMI (kg/m^2), and BMI by group (18 to <25 kg/m^2 and ≥ 25 to 30 kg/m^2). BMI will be calculated as (weight in kg) / (height in m)^2. Weight, height, BMI, and BMI by group will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum.

All baseline characteristics data will be presented in a subject data listing based on the Safety Analysis Set.

6.4 Medication History and Concomitant Medications

Prior medications and concomitant medications and procedures will be summarized and listed based on the Safety Analysis Set. Missing dates will not be imputed.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version Global B3 March 2020 or newer.

6.4.1 Prior Medications

Prior medication is defined as any medication with the start date within 60 days prior initiation of treatment with TAK-881 and stop date prior to initiation of treatment with TAK-881.

The number and percentage of subjects using prior medication will be summarized by therapeutic class and PT and will be presented by treatment arm and total. Therapeutic class will be sorted alphabetically, and PT within therapeutic class will be sorted in descending frequency based on total occurrence. Multiple medication usage by a subject in the same PT category will be counted only once.

All prior medication data will be presented in a subject data listing.

6.4.2 Concomitant Medications

Concomitant medication is defined as any medication with start and/or stop date after the initiation of treatment with TAK-881. Any medication with a start date after the end of the follow-up period will be considered post-treatment medication and not concomitant medication.

The number and percentage of subjects using concomitant medication will be summarized by therapeutic class and PT and will be presented by treatment arm and total. Therapeutic class will be sorted alphabetically, and PT within therapeutic class will be sorted in descending frequency based on total occurrence. Multiple medication usage by a subject in the same PT category will be counted only once.

All concomitant medication data will be presented in a subject data listing.

6.4.3 Concomitant Procedures

Concomitant procedure is defined as any procedure with start and/or stop date after the initiation of treatment with TAK-881. Any procedure with a start date after the end of the follow-up period will be considered post-treatment procedure and not concomitant procedure.

The number and percentage of subjects with concomitant procedures will be presented by treatment arm and total.

All concomitant procedure data will be presented in a subject data listing.

6.5 Protocol Deviations

Protocol deviations will be summarized and listed based on the Safety Analysis Set.

Protocol deviations will be recorded separately from the clinical database using a protocol deviation tracker. Protocol deviations will be classified as significant or not significant per the agreed deviation rules document and will be documented in the protocol deviation tracker. The sponsor study team will review the protocol deviations and their classification throughout the study and before database lock. The number and percentage of subjects with protocol deviations, and the number of protocol deviations, will be summarized by significance and category and will be presented by treatment arm and total. If more than one protocol deviation occurs within the same category for the same subject, then the subject will be counted only once for that category.

All protocol deviations will be presented in a protocol deviation listing. In addition, protocol deviations related to the COVID-19 pandemic will be presented in a separate listing.

6.6 Efficacy Analysis

Not applicable.

6.7 Tolerability Analysis

The tolerability analysis will be based on the Safety Analysis Set.

The primary endpoint is the occurrence of tolerability events related to the infusion of TAK-881 per infusion site. The number and percentage of subjects with tolerability events will be summarized per infusion site and by treatment arm and total. The summary will also be provided by BMI group (18 to <25 kg/m^2, ≥25 to 30 kg/m^2).

All tolerability data will be presented in a subject data listing. In addition, separate listings will be presented for subjects requiring two infusion sites with:

- tolerability event at infusion site 1 and no tolerability event at infusion site 2
- tolerability events at both infusion sites

Definition: A tolerability event is considered to have occurred if an infusion was tolerable. An infusion is considered tolerable if the infusion rate was not reduced or the infusion was not interrupted or stopped, due to any TEAE related to TAK-881.

6.8 Safety Analysis

The safety analysis will be based on the Safety Analysis Set.

Secondary safety endpoints cover occurrence of TEAEs, clinical laboratory parameters, vital signs, and the occurrence of binding and neutralizing antibodies to rHuPH20 (immunogenicity).

6.8.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA version 23.0 or newer.

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. If either the start time or the stop time of the AE is missing, or the duration is > 24 hours, then the duration will be presented in days 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.

A treatment-emergent adverse event (TEAE) is defined as any AE that started at or after the initiation of treatment with TAK-881. If the start date/time is incomplete, an indication is provided in the eCRF on whether the AE started prior to or after initiation of treatment with TAK-881. No imputation of dates/times will be required to determine if an AE is treatment-emergent or not.

The time since TAK-881 administration will be calculated for TEAEs only. The time since TAK-881 administration will be calculated as (start date/time of TEAE) – (start date/time of TAK-881 administration) and will be presented in hours if the time since TAK-881 administration is ≤ 24 hours. If either the start time of the TEAE or the start time of the TAK-881 administration is missing, or the time since TAK-881 administration is > 24 hours, then the time since TAK-881 administration will be presented in days calculated as (start date of TEAE) – (start date of TAK-881 administration) + 1. If either the start date of the TEAE or the start date of TAK-881 administration is missing, no time since TAK-881 administration will be calculated.

A temporally associated TEAE is defined as any TEAE that started between the initiation of treatment with TAK-881 and 72 hours (or 3 days if start time of the TEAE is missing) after completion of TAK-881 administration, irrespective of being related or not related to TAK-881.

The relationship to TAK-881 will be assigned only for TEAEs and will be used as reported in the eCRF (non-related/related). If the relationship to TAK-881 is missing, TEAEs will be considered related to TAK-881. The imputed values will be used for summaries but not for listings.

The severity of AEs will be assigned for all AEs (TEAEs and non-TEAEs) and will be used as reported in the eCRF using the common terminology criteria for adverse events (CTCAE), version 5.0, consisting of 5 grades:

- grade 1: mild
- grade 2: moderate
- grade 3: severe or medically significant but not immediately life-threatening
- grade 4: life-threatening consequences
- grade 5: death related to AE

If the severity assessment is missing, TEAEs will be considered as grade 1. The imputed values will be used for summaries but not for listings. Severity for non-TEAEs will not be imputed.

An overall summary of the number and percentage of subjects with TEAEs, as well as the number of TEAEs, will be presented by treatment arm and total, using the following categories:

- any TEAE
- serious TEAEs
- TEAEs considered related to TAK-881
- local TEAEs
- systemic TEAEs
- temporally associated TEAEs within 72 hours
- TEAEs by maximum severity (CTCAE grades 1-5)
- TEAEs leading to study discontinuation
- TEAEs of special interest (allergy, catheter leakage, and thromboembolic events)

The overall summary will also be provided by BMI group (18 to <25 kg/m^2, ≥25 to 30 kg/m^2). In addition, summaries by SOC and PT of the number and percentage of subjects with TEAEs, as well as the number of TEAEs, will be presented by treatment arm and total, using the following categories:

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

SOC will be sorted alphabetically, and PT within SOC will be 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, summaries by SOC and PT will be further grouped by severity (grade 1/grade 2/grade 3/grade 4 and 5 combined) and relationship to TAK-881 (non-related/related). The number and percentage of subjects with TEAEs will be presented by treatment arm and total, using the following categories:

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

SOC will be sorted alphabetically, and PT within SOC will be sorted in descending frequency based on total occurrence. The summaries will include subject identifiers within each PT. 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.

All AEs (TEAEs and non-TEAEs) will be presented in a listing including the relationship and severity assessment as well as the duration and the time since TAK-881 administration.

6.8.2 Adverse Events of Special Interest

Adverse events of special interest (allergy, catheter leakage, and thromboembolic events) will be included in the overall TEAE summary as defined in Section 6.8.1.

6.8.3 Clinical Laboratory Parameters

Clinical laboratory parameters cover hematology, serum chemistry, urinalysis, hemolytic panel, and coagulation tests. The following clinical laboratory parameters will be presented:

Hematology Hematocrit (Hct), Hemoglobin (Hgb), red blood cell (RBC) count, red cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cells (WBC) with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Chemistry Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), potassium (K+), sodium (Na+), chloride (Cl-), calcium (Ca2+), magnesium (Mg2+), bilirubin (total and direct), lactate dehydrogenase (LDH), Blood urea nitrogen (BUN), creatinine, uric acid, glucose, albumin, and lipid profile.

Urinalysis Color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocyte esterase.

Hemolytic Panel Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, and urine hemosiderin.

Coagulation Activated partial thromboplastin time (aPTT) and international normalized ratio (INR).

Quantitative clinical laboratory parameters and their change from baseline at each visit will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum and will be presented by treatment arm. Change from baseline will be calculated as (value at post-baseline visit) – (value at baseline) and will be presented for post-baseline visits only.

Qualitative clinical laboratory parameters will be summarized by the number and percentage of subjects in each category and will be presented by treatment arm.

Any quantitative laboratory measurement recorded as "<X", i.e., below the lower limit of quantification, or ">X", i.e., above the upper limit of quantification, will be treated as X for the calculation of summary statistics but will be presented as recorded in the subject data listing, i.e. as "<X" or ">X".

In addition, summaries of shift-from-baseline to each post-baseline visit will be presented for each clinical laboratory parameter that has a reference range to assess normality/abnormality, using the following categories:

- low (below the lower limit of the reference range)
- normal (within the reference range)
- high (above the upper limit of the reference range)
- missing

The summaries of shift-from-baseline regarding the normality/abnormality assessment will show the number and percentage of subjects presented by treatment arm.

All clinical laboratory data will be presented in a subject data listing.

6.8.4 Vital Signs

Vital signs cover respiratory rate (RR), heart rate (HR), systolic and diastolic blood pressure (BP), and body temperature.

Vital signs and their percentage change from baseline at each visit and, if applicable, at each time point per visit will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum and will be presented by treatment arm. Percentage change from baseline will be calculated as (value at post-baseline visit – value at baseline) / (value at baseline) × 100 and will be presented for post-baseline visits only.

All vital signs data will be presented in a subject data listing.

6.8.5 Immunogenicity

Immunogenicity analyses cover the occurrence of binding anti-rHuPH20 antibodies (ADA) and neutralizing anti-rHuPH20 antibodies (nADA) representing secondary endpoints as well as other immunogenicity variables from the immunogenicity panel which are not defined as endpoints in the study protocol.

The occurrence of ADA and nADA will be summarized by visit and will use the number and percentage of subjects presented by treatment arm and total, using the following categories:

- positive ADA (titer ≥ 1:160)
- positive nADA

Other immunogenicity variables from the immunogenicity panel cover 50% hemolytic complement activity of serum (CH50), serum complement component 3 (C3), serum complement component 4 (C4), C1q binding assay, and circulating immune complex (CIC) Raji cell assay and will be summarized by visit using descriptive statistics n, mean, SD, median, minimum, and maximum and will be presented by treatment arm and total.

All immunogenicity data will be presented in subject data listings.

6.8.6 Other Safety Analyses

Other safety variables are not defined as endpoints in the study protocol and cover electrocardiogram, physical examination, and pregnancy data.

6.8.6.1 Electrocardiogram

Electrocardiogram (ECG) data will be provided in subject data listings only. No statistical summary is planned.

6.8.6.2 Physical examination

No listing or statistical summary is planned.

6.8.6.3 Pregnancy

Pregnancy data will be provided in the subject data listing only. No statistical summary is planned.

6.8.7 Extent of Exposure

The exposure summary and listing include but are not limited to the secondary subcutaneous (SC) administration endpoints and will be based on the Safety Analysis Set.

Secondary SC administration endpoints cover maximum tolerable infusion rate achieved per infusion site (mL/hours), total volume infused per infusion site (mL), and time to deliver the total infused volume per infusion site (min). The maximum tolerable infusion rate achieved refers to the administration of IGSC 20% at progressively increasing infusion rates (see Section 9.4) and is defined as the highest infusion rate achieved at which the infusion was tolerable (i.e., no stopping, interruption, or infusion rate reduction due to a TAK-881-related TEAE). Total volume infused will be presented for rHuPH20 and IGSC 20% and time to deliver the total infused volume will be calculated as (stop date/time of IGSC 20% administration) – (start date/time of rHuPH20 administration).

In addition, for subjects requiring two infusion sites, total volume infused (rHuPH20 and IGSC 20%) and time to deliver the total infused volume (excluding the time between end of IGSC 20% administration at infusion site 1 and start of rHuPH20 administration at infusion site 2) will also be presented for both infusion sites combined.

Other exposure variables cover actual total rHuPH20 dose (U) and actual total IGSC 20% dose (g).

The maximum tolerable infusion rate achieved will be summarized by the number and percentage of subjects in each category (30, 60, 120, 180, and 300 mL/hour) and will be presented per infusion site and by treatment arm. Total volume infused per infusion site and combined, time to deliver the total infused volume per infusion site and combined, and other exposure variables will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum and will be presented by treatment arm. The summary will also be provided by BMI group (18 to <25 kg/m2, ⩾25 to 30 kg/m2).

All exposure data will be presented in a subject data listing.

6.8.8 Infusion status

The infusion status summary and listing will be based on the Safety Analysis Set.

The number and percentage of subjects with IGSC 20% infusions that have been completed as planned, stopped, and interrupted, as well as with IGSC 20% infusions for which the infusion rate was reduced will be summarized per infusion site and by treatment arm. If not completed as planned, the number and percentage of subjects will be further presented by reason, i.e., due to TAK-881-related TEAEs or due to any other reason. The summary will also be provided by BMI group (18 to <25 kg/m2, ⩾25 to 30 kg/m2).

All infusion status data will be presented in a subject data listing.

6.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.9.1 Pharmacokinetic Analysis

The pharmacokinetic (PK) analysis will be based on the PK Analysis Set. Missing total IgG levels will not be imputed.

Total IgG level is an exploratory endpoint and will be summarized for each visit using descriptive statistics n, mean, SD, median, minimum, maximum, and geometric mean with corresponding two-sided 95% confidence interval and will be presented by treatment arm.

Any total IgG level recorded as "<X", i.e. below the lower limit of quantification, will be treated as zero for the calculation of summary statistics but will be presented as recorded in the subject data listing, i.e. as "<X".

In addition, baseline-corrected total IgG levels calculated as (total IgG level at post-baseline visit) – (total IgG level at baseline visit) will be summarized for each post-baseline visit. Negative baseline-corrected total IgG levels will be treated as zero for the calculation of summary statistics.

Total IgG levels will be presented in a subject data listing.

6.9.2 Pharmacodynamic Analysis

Not applicable.

6.9.3 Biomarker Analysis

Not applicable.

6.10 Patient Reported Outcomes and Health Care Utilization Endpoints Analysis

Not applicable.

6.11 Other Analyses

Not applicable.

6.12 Interim Analyses

Not applicable.

6.13 Safety Review

The safety reviews will be based on uncleaned data, no statistical summaries are planned.

7.0 REFERENCES

U.S. Department of Health and Human Services 2017. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017. Web Link: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Secondary SC administration endpoints, clinical laboratory parameters, and vital signs will be summarized by treatment arm only. A total summary for all treatment arms combined is not performed due to the dose escalation from treatment arm 1 to treatment arm 2 and the switch from warmed to un-warmed administration from treatment arm 2 to treatment arm 3.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

SAP Section	Impacted Text	Change	Rationale for Change
6.2	All subjects who completed and prematurely discontinued the study will be presented in a subject data listing along with reasons for discontinuation.	Adapted	Added clarification that all subjects (completed and prematurely discontinued) will be listed.
6.3.2	SOC will be sorted alphabetically, and PT within SOC will be sorted in descending frequency based on total occurrence. If more than one event occurs with the same PT for the same subject, then the subject will be counted only once for that PT.	Added	Added clarification about sorting of table and handling of multiple occurrences with the same PT for the same subject.
6.4	Concomitant procedures will be coded using MedDRA version 23.0 or newer.	Deleted	Concomitant procedures are not coded using MedDRA.
6.4.1	Prior medication is defined as any medication with the start date within 60 days prior initiation of treatment with TAK-881 and stop date prior to initiation of treatment with TAK-881.	Adapted	Added clarification that only prior medications with start data within 60 days prior initiation of treatment with TAK-881 are considered as prior medications according to protocol.
6.4.1	Therapeutic class will be sorted alphabetically, and PT within therapeutic class will be sorted in descending frequency based on total occurrence.	Added	Added clarification about sorting of table.
6.4.2	Therapeutic class will be sorted alphabetically, and PT within therapeutic class will be sorted in descending frequency based on total occurrence.	Added	Added clarification about sorting of table.
6.4.3	The number and percentage of subjects with concomitant procedures will be presented by treatment arm and total.	Adapted	Concomitant procedures are not coded using MedDRA. Therefore, no summary by SOC and PT can be generated.
6.5	If more than one protocol deviation occurs within the same category for the	Added	Added clarification about handling of multiple occurrences within the same category for the same subject.

	same subject, then the subject will be counted only once for that category.		
6.7	The summary will also be provided by BMI group (18 to <25 kg/m2, ≥25 to 30 kg/m2).	Added	The tolerability summary will also be provided by BMI group.
6.7	In addition, separate listings will be presented for subjects requiring two infusion sites with: • tolerability event at infusion site 2 and no tolerability event at infusion site 1 • no tolerability events at both infusion sites	Deleted	If no tolerability event occurs at infusion site 1, then infusion site 2 will not be used.
6.8.1	In addition, separate listings will be presented for: • Clinical laboratory parameters considered as TEAEs • Vital signs considered as TEAEs	Deleted	Required data is not collected in the eCRF. Clinically significant changes in clinical laboratory measurements and vital signs will be recorded in the study database as TEAEs at the discretion of the investigator but cannot be linked to specific clinical laboratory parameters or vital sign measurements.
6.8.3	In addition, summaries of shift-from-baseline to each post-baseline visit will be presented for each clinical laboratory parameter that has a reference range to assess normality/abnormality and a clinical significance assessment, using the following categories: • normal (within the reference range) • abnormal (outside the reference range) and not clinically significant • abnormal (outside the reference range) and clinically significant • abnormal missing (clinical significance assessment missing) • missing The summaries of shift-from-baseline regarding the clinical significance assessment will show the number and percentage of subjects presented by treatment arm.	Deleted	Required data is not collected in the eCRF. Clinical significance of abnormal clinical laboratory measurements will not be recorded in the study database. Clinical significance assessed by the investigator will be documented in the source data only.
6.8.5	positive ADA (titer ≥ 1:160)	Adapted	Added the definition of positive ADA in parentheses for clarification.

6.8.7	Secondary SC administration endpoints cover maximum tolerable infusion rate achieved per infusion site (mL/hours), total volume infused per infusion site (mL), and time to deliver the total infused volume per infusion site (min). The maximum tolerable infusion rate achieved refers to the administration of IGSC 20% at progressively increasing infusion rates (see Section 9.4) and is defined as the highest infusion rate achieved at which the infusion was tolerable (i.e. no stopping, interruption, or infusion rate reduction due to a TAK-881-related TEAE). Total volume infused will be presented for rHuPH20 and IGSC 20% and time to deliver the total infused volume will be calculated as (stop date/time of IGSC 20% administration) – (start date/time of rHuPH20 administration).	Adapted	Added additional clarification including units of endpoints.
6.8.7	In addition, for subjects requiring two infusion sites, total volume infused (rHuPH20 and IGSC 20%) and time to deliver the total infused volume (excluding the time between end of IGSC 20% administration at infusion site 1 and start of rHuPH20 administration at infusion site 2) will also be presented for both infusion sites combined.	Adapted	Added additional clarification.
6.8.7	Other exposure variables cover actual total rHuPH20 dose (U) and actual total IGSC 20% dose (g).	Adapted	IgG adjusted rHuPH20 dose (U/g) was deleted from the list as it is planned to be 80 U/g per infusion site for all subjects. Body weight adjusted IGSC 20% dose (g/kg) was deleted from the list as it is planned to be 0.4 g/kg or 1.0 g/kg for all subjects.
6.8.7	The summary will also be provided by BMI group (18 to <25 kg/m2, ≥25 to 30 kg/m2).	Added	The exposure summary will also be provided by BMI group.
6.8.8	The summary will also be provided by BMI group (18 to <25 kg/m2, ≥25 to 30 kg/m2).	Added	The infusion status summary will also be provided by BMI group.
8.0	Secondary SC administration endpoints, clinical laboratory	Added	Text was added to describe and justify the deviation of the SAP from

	parameters, and vital signs will be summarized by treatment arm only. A total summary for all treatment arms combined is not performed due to the dose escalation from treatment arm 1 to treatment arm 2 and the switch from warmed to un-warmed administration from treatment arm 2 to treatment arm 3.		the planned analyses specified in the protocol.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

In case that there are no observations contributing to a table/listing, a statement within the respective table/listing will be displayed ("No subjects met the table/listing criteria.").

In case that the PK Analysis Set is identical to the Safety Analysis Set, tables based on the PK Analysis Set that have already been generated based on the Safety Analysis set will not be repeated, but a statement within the respective tables will be displayed ("PK Analysis Set is identical to the Safety Analysis Set, therefore this table was not repeated.").

9.2.2 Definition of Baseline

Baseline is defined as the last non-missing value before TAK-881 administration. The initiation of treatment with TAK-881 refers to the start of rHuPH20 administration.

9.2.3 Definition of Visit Windows

Assessments will be assigned to visits based on the date the assessment took place using visit windows as defined in Table 1. If the assessment is performed prior to the initiation of treatment with TAK-881, then the visit day will be calculated as (date of assessment) – (date of TAK-881 administration). If the assessment is performed at or after the initiation of treatment with TAK-881, then the visit day will be calculated as (date of assessment) – (date of TAK-881 administration) + 1.

Table 1. Visit Windows

Visit	Visit window		
	Planned visit day	Start visit day	End visit day
Screening/Baseline	-	-21	0
Day 1	1	1	1
Day 2	2	2	2

Day 3	3	3	3
Day 4	4	4	4
Day 30	30	27	33
Week 12	78	71	85

9.3 Analysis Software

Statistical analyses will be performed using SAS®, Version 9.4 or higher, on a suitably qualified environment.

9.4 Step-wise Infusion Rate Escalation Regimen

Table 2. Infusion Rates for Treatment Arm 1 (0.4 g/kg, in-line warmed)

Administration		Rate Per Infusion Site (mL/hour) Single Needle Set	Volume Delivered	Accumulative Volume for IG per Site
rHuPH20	To be infused first	120	TBD	N/A
IGSC 20% (in-line warmed)	First 10 min	30	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL
	Next 10 min	120	20 mL	35 mL
	Next 10 min	180	30 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*

Abbreviations: IG=immune globulin; N/A=not applicable; TBD=to be determined
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

Table 3. Infusion Rates for Treatment Arm 2 (1.0 g/kg, in-line warmed)

Administration		Rate Per Infusion Site (mL/hour) for Each Pump	Volume Delivered for Each Pump	Accumulative Volume Site 1# (Pump A)	Accumulative Volume Site 2# (Pump B)
rHuPH20	To be infused first	120	TBD	TBD	TBD
IGSC 20% (in-line warmed)	First 10 min	30	5 mL	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL	15 mL
	Next 10 min	120	20 mL	35 mL	35 mL
	Next 10 min	180	30 mL	65 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*	TBD (remainder)

Abbreviations: TBD=to be determined
Each site will be evaluated separately
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

Table 4. Infusion Rates for Treatment Arm 3 (1.0 g/kg, un-warmed)

Administration		Rate Per Infusion Site (mL/hour) for Each Pump	Volume Delivered for Each Pump	Accumulative Volume Site 1# (Pump A)	Accumulative Volume Site 2# (Pump B)
rHuPH20	To be infused first	120	TBD	TBD	TBD
IGSC 20% (un-warmed)	First 10 min	30	5 mL	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL	15 mL
	Next 10 min	120	20 mL	35 mL	35 mL
	Next 10 min	180	30 mL	65 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*	TBD (remainder)

Abbreviations: TBD=to be determined

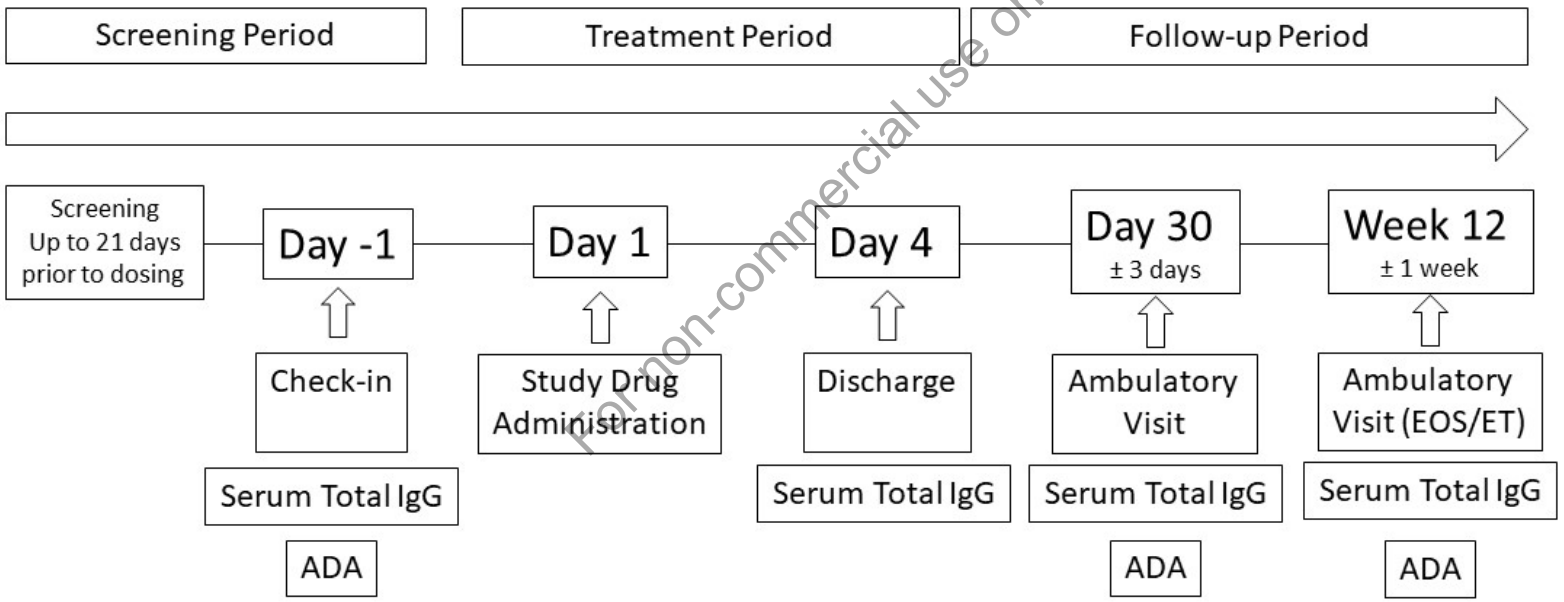
Each site will be evaluated separately

* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

9.5 Study schematic

9.5.1 Overall Study Design

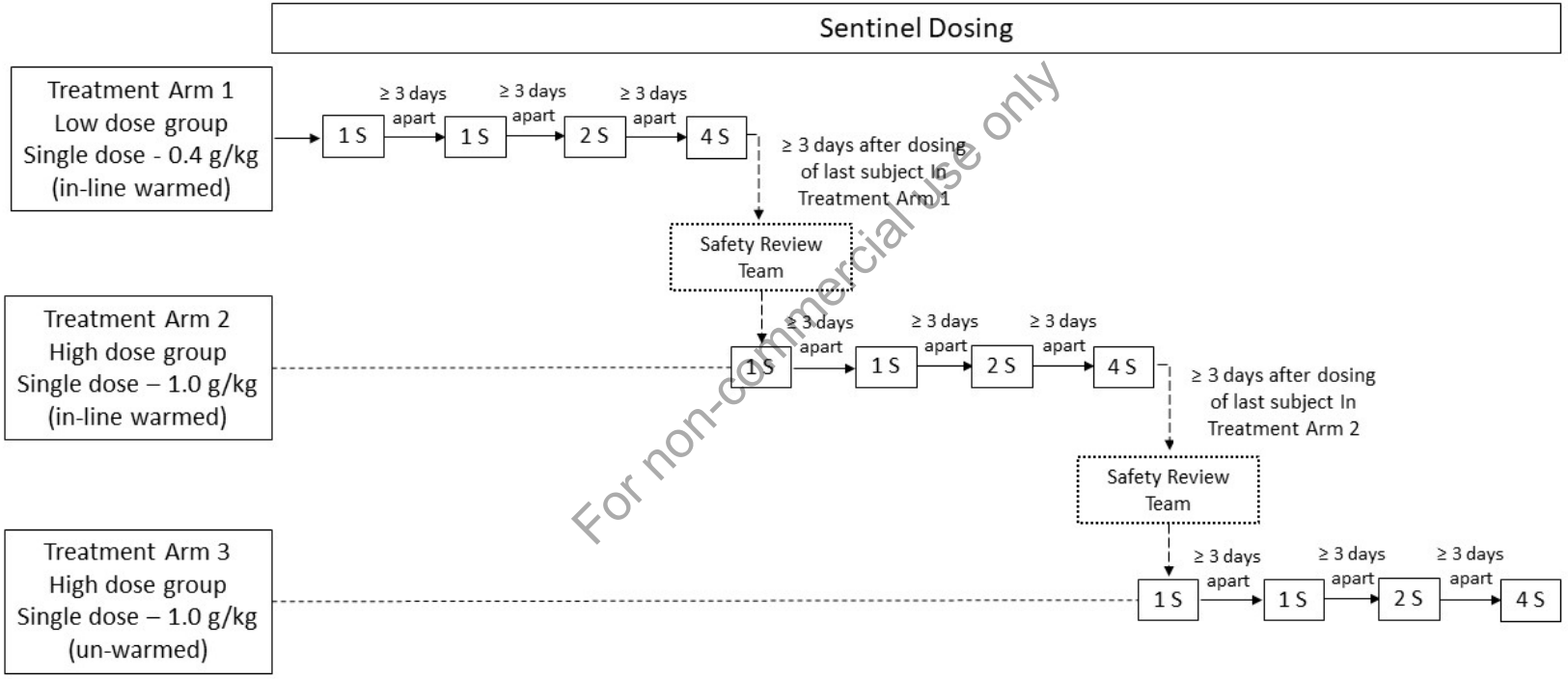
Figure 1. Overall Study Design



Note: All subjects will be admitted to Clinical Research Center on Day -1 prior to dosing and discharged on Day 4.
Abbreviations: ADA=anti-drug antibody; EOS=end of study; ET=early termination; IgG=immunoglobulin G

9.5.2 Sentinel Dosing Design

Figure 2. Sentinel Dosing Design



Abbreviation: S=subject(s)