



Statistical Analysis Plan

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Title: A Phase 1, Randomized, Open-Label, Pharmacokinetic Trial of TAK-881 and HyQvia in Healthy Adult Participants

Study Number: TAK-881-1002

Document Version and Date: Final version, 08 April 2025

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STATISTICAL ANALYSIS PLAN

Trial Number: TAK-881-1002

Trial Title: A Phase 1, Randomized, Open-Label, Pharmacokinetic Trial of TAK-881 and HyQvia in Healthy Adult Participants

Phase: 1

Version: Final

Date: 08 April 2025

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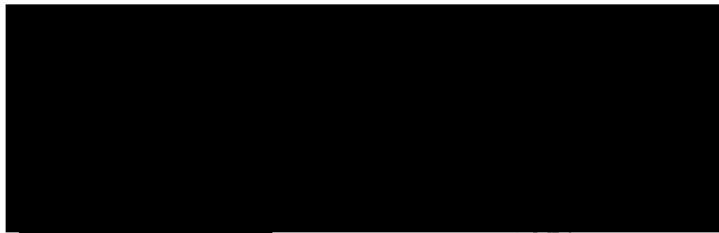
APPROVAL SIGNATURE

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Approval:

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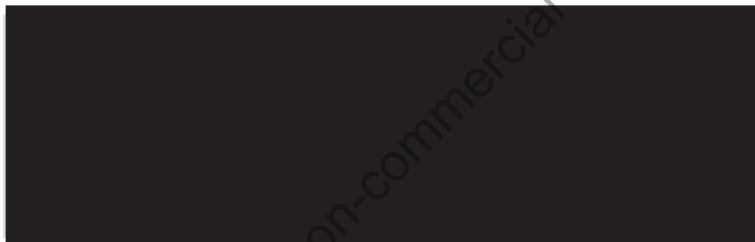
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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
AUC _{Day1-29}	baseline-corrected area under the concentration-time curve from Day 1 to Day 29
AUC _{inf}	area under the concentration-time curve from Day 1 to infinity
AUC _{last}	area under the concentration-time curve from Day 1 to time of the last measurable concentration
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance
C _{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CV%	percent coefficient of variation
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMP	data management plan
ECG	electrocardiogram
EOT	end of treatment
ET	early termination
geom mean	geometric mean
GMR	geometric least-squares mean ratio
ICF	informed consent form
IE	intercurrent event
IgG	immunoglobulin G
IP	investigational product
LLN	lower limit of normal
LSM	geometric least-squares means
MAV	markedly abnormal value
MCAR	missing completely at random
mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
NCI	National Cancer Institute
PK	pharmacokinetic
PKFAS	pharmacokinetic full analysis set
PKPPAS	pharmacokinetic per-protocol analysis set
PT	Preferred Term (MedDRA)
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event

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SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
t_{last}	time of last measurable concentration
t_{max}	time to C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution
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 and Associated Endpoint

<i>Primary Objective</i>	<i>Primary Endpoint</i>
<i>To characterize the PK of TAK-881 and HyQvia following single SC administration in healthy adult participants.</i>	<i>Baseline-corrected $AUC_{Day1-29}$ based on serum total IgG levels.</i>

1.1.2 Secondary Objectives + Associated Endpoints

Table 1.b Secondary Objectives and Associated Endpoints

<i>Secondary Objective</i>	<i>Secondary Endpoint</i>
<i>To assess baseline-uncorrected and baseline-corrected PK exposure parameters of TAK-881 and HyQvia following single SC administration in healthy adult participants.</i>	<i>Baseline-uncorrected PK parameters based on serum total IgG levels:</i> <ul style="list-style-type: none"> • C_{max} • t_{max} • $AUC_{Day1-29}$ <i>Baseline-corrected PK parameters based on serum total IgG levels:</i> <ul style="list-style-type: none"> • AUC_{inf} • AUC_{last} • C_{max} • t_{max} • t_{last} • $t_{1/2z}$ • CL/F • V_z/F
<i>To assess the safety, tolerability, and immunogenicity of TAK-881 and HyQvia following single SC administration in healthy adult participants.</i>	<i>Safety:</i> <ul style="list-style-type: none"> • <i>Occurrence of TEAEs.</i> <i>Tolerability:</i>

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Table 1.b Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
	<ul style="list-style-type: none">Occurrence of tolerability events during the infusion of IPs. <p>Immunogenicity:</p> <ul style="list-style-type: none">Occurrence of positive binding (defined as titer $\geq 1:160$) antibodies to rHuPH20.Occurrence of neutralizing antibodies to rHuPH20.

1.2 Estimands

Table 1.c Primary Estimand

Trial objective	The primary objective of the trial is to characterize the PK of TAK-881 and HyQvia following single SC administration in healthy adult participants.
Target population	Healthy adult participants.
Analysis variable	Baseline-corrected $AUC_{Day1-29}$ based on serum total IgG levels.
Treatment	TAK-881 or HyQvia
IEs and strategy	<p>IEs: Any protocol deviation that may affect the reliability of the primary endpoint following the definition of the PKPPAS.</p> <p>Hypothetical strategy will be utilized to address IEs. The hypothetical strategy envisions that the IE would not occur under the MCAR premise.</p>
Population level summary	Ratio of geometric means in baseline-corrected $AUC_{Day1-29}$ between TAK-881 and HyQvia.
Estimator	Antilog of the estimator from a two-sample t-test allowing for unequal variances by using the Welch-Satterthwaite correction of degrees of freedom and corresponding two-sided 95% CI in log-transformed variables.
Estimate	Numerical result of the estimator based on data of the PKPPAS.

2.0 TRIAL DESIGN

This is a phase 1, randomized, parallel, open-label, single dose, 2-arm, PK trial in healthy adult participants.

The trial schematic is shown in [Figure 2.a](#).

Enrollment		Treatment Arms 1, 2				
Screening Period		Treatment Period			Follow-up Period	
Study Enrollment	Eligibility Screening	Admission	Randomization & IP Administration	Discharge		
		<div>Healthy participants (males or females)</div> <div> <div>Arm 1 TAK-881 1.0 g/kg SC</div> <div>Arm 2 HyQvia 1.0 g/kg SC</div> </div>				
Up to 28 days prior to dosing	Day -1	Day 1	Day 8	Day 15,18,22,25,29,43,57		Day 85 (±3) (EOT/ET)
Ambulatory Visit	Confinement			Ambulatory Visit		

PK Sampling : Screening, Day -1, 1 (pre-infusion and post-infusion), 2, 3, 4, 5, 6, 7, 8, 15, 18, 22, 25, 29, 43, 57, 85 (EOT/ET)

All participants who received at least one dose of IP (including participants who terminate the trial early) will return to the CRU on Day 85 (± 3 days) for the final follow-up procedures, and to determine if any AE has occurred since the last trial visit.

The planned total sample size for this trial is at least 24 participants in the PKPPAS and is considered sufficient to achieve the trial objectives. To account for an assumed drop-out rate of 20% (including participants who have unevaluable PK profiles and participants who have

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protocol violations that may affect the reliability of the total IgG level time profiles), 30 participants will be randomized and treated (15 per treatment arm).

5.0 ANALYSIS SETS

The analysis performed for PK parameters will be presented for the PKFAS and the PKPPAS. Safety, tolerability, and immunogenicity endpoints will be presented for the safety analysis set.

5.1 Safety Analysis Set

The safety analysis set will consist of all participants who received any amount of TAK-881 or HyQvia. Analysis will be performed according to the actual treatment received.

5.2 Pharmacokinetic Full Analysis Set

The PKFAS is a subset of the safety analysis set and will consist of all participants with an evaluable PK profile. Analysis will be performed according to the actual treatment received.

In order to be considered an evaluable PK profile, the following minimum data requirements must be met:

- *Measurable IgG at baseline;*
- *At least 6 PK samples collected during confinement (Day 1 – Day 8);*
- *Day 15 or Day 18 PK sample;*
- *Day 22 or Day 25 PK sample;*
- *Day 29 PK sample.*

5.3 Pharmacokinetic Per-Protocol Analysis Set

The PKPPAS is a subset of the PKFAS and will consist of all participants who have no protocol violations that may affect the reliability of the total IgG PK profiles. Analysis will be performed according to the actual treatment received.

Deviations will include the following:

- Missed PK sampling resulting in a participant not having an evaluable PK profile as described in [Section 5.2](#).
- Incorrect treatment applied (randomization error).
- Deviations from the PK sampling visit windows as outlined in the protocol deviation management plan.
- >10% deviation in the g/BW kg dose received by a participant, including incorrect calculation of weight-based dose, device not delivering the entire dose, or significant catheter leakage.

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- Deviations in dose administration that affect absorption of the IP, including switching order of rHuPH20 and IgG administration.
- Deviations in PK sample collection, storage, or handling that affect the reliability of the bioanalytical result, including temperature excursions outside of stability.
- Any prohibited concomitant medication use.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Noncompartmental analyses of PK parameters will be conducted in this trial using Phoenix WinNonlin Version 8.4, or higher. The details on PK parameter calculations will be outlined in the CPAP and the details on PK TFLs will be outlined in the TFL Shells document. All statistical analyses will be conducted using SAS Version 9.4 or higher. All TFL 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). Formats of concentration and PK parameter data and their descriptive statistics will be detailed in the CPAP.

Geometric least-squares mean (LSMs) will be reported with 1 more level of precision than the individual data. GMRs and 95% CIs for the GMRs will be reported to 2 decimal places, and intra-subject CV% will be reported to 1 decimal place. The details on the linear mixed-effect model are presented in [Section 6.8](#). Details regarding in-text and end-of-text tables are specified in the TFL Shells document.

For demographic and safety data where appropriate, variables will be summarized descriptively by treatment. For categorical variables, the count and percentages of each reported value will be tabulated, where applicable. The denominator for the percent calculation will be the number of participants in the safety analysis set for overall summaries, and the number of participants dosed with each treatment in by-treatment summaries. For continuous variables, the number of participants 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. Unless otherwise stated, baseline is defined as the last observation, including recheck and unscheduled assessments, taken prior to the first dose of any IP.

Participants who prematurely discontinue from the trial will be included in the descriptive analyses as applicable. Missing data will not be imputed unless otherwise specified.

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6.2 Trial Information

A trial information table will be generated including the following items: Date of first participant's signed informed consent form, date/time of first dose of IP, date/time 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, completed treatment, discontinued from the trial and/or treatment, and reason(s) for discontinuation(s)) will be summarized by treatment and overall.

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

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, PKFAS and PKPPAS. 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 from the screening visit will be used in the summaries, while weight and the corresponding BMI from the Baseline (Day – 1) visit will be used in the summaries.

All demographic and baseline characteristics will be presented in a subject data listing for the Safety Analysis Set.

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 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.

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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 dose of the IP and the 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 Safety Analysis

Safety 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 AEs

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

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.*
- *Grade 3: severe or medically significant but not immediately life-threatening.*
- *Grade 4: life-threatening consequences.*
- *Grade 5: death related to AE.*

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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.

All AEs captured in the database will be listed in by-participant data listings including verbatim term, preferred term, SOC, severity (based on NCI 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, 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. Only TEAEs will be summarized.

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

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.

6.6.2 TEAEs

A TEAE is defined as any AE that is starting or worsening at the time of or after dosing of IP. Each TEAE will be attributed to the treatment based on the AE onset date and time.

The time since IP administration will be calculated of TEAEs only. It will be calculated as (start date/time of TEAE) – (start date/time of 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 IP administration is missing, then the time will be calculated as (start date of TEAE) – (start date of IP administration) +1. If either the start date of the TEAE or the start date of the IP administration is missing, no time since IP administration will be calculated.

A temporally associated TEAE 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.

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

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The number and percentage of participants with TEAEs and the number of TEAEs will be summarized by treatment (TAK-881 or HyQvia) and overall using the following categories:

- *Any TEAE,*
- *Serious TEAEs,*
- *TEAEs considered related to TAK-881 or HyQvia*
- *Local TEAEs,*
- *Systemic TEAEs,*
- *Temporally associated TEAEs within 72 hours,*
- *TEAEs by maximum severity grade (NCI CTAE grades 1-5),*
- *TEAEs leading to study discontinuation,*
- *TEAEs of special interest (allergy, catheter leakage, and thromboembolic events).*

In addition, the number and percentage of participants with TEAEs and the number of TEAEs will be summarized for each treatment (TAK-881 or HyQvia) and overall by SOC and PT using the following categories:

- Any TEAE,
- Serious TEAEs,
- TEAEs considered related to TAK-881 or HyQvia
- Temporally associated TEAEs within 72 hours.

SOC will be sorted in descending frequency using total occurrence, 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 participant, the participant will only be counted once for that PT.

In addition, the number and percentage of participants with TEAEs will be summarized for each treatment (TAK-881 or HyQvia) and overall by SOC, PT, severity grade (grade 1 – 5 and combined), and relationship to IP (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 and PT within SOC will be sorted in descending frequency using total occurrence. If more than one TEAE occurs with the

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same PT and relationship assessment for the same participant, then the participant 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 CSR.

Tolerability:

For each treatment (TAK-881 or HyQvia) and overall, the number and percentage of participants with infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881 or HyQvia-related TEAEs as well as the number of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881 or HyQvia-related TEAEs will be presented.

All tolerability events will be displayed in a data listing.

6.6.3 AESI

AESI will be flagged in the data listings and discussed in the CSR, 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 6.6.1.

6.6.4 Clinical Laboratory Assessments

Clinical laboratory tests will be measured as described in [Appendix A](#):

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 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 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.

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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 B](#). 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.

Coagulation tests will be performed at screening and on Day -1. Results will be listed by participant.

6.6.5 Vital Signs

Vital signs will be measured as described in [Appendix A](#).

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 listed 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 considered a MAV if it meets one of the criteria described in [Appendix C](#). 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

Single 12-lead safety ECGs will be measured as described in [Appendix A](#).

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 D](#). 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, and at the end of trial. 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, local AEs will be reported separately for each site.

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.

6.6.10 Extent of Exposure and Compliance

The start date and time, end date and time, time in hours to administer treatment, and treatment administered will be listed by participant.

6.6.11 Immunogenicity Analysis

Blood for immunogenicity analysis will be collected on Day -1, Day 29, and Day 85/EOT.

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

The number and percentage of participants with at least one positive binding antibody to rHuPH20 (defined as titer $\geq 1:160$) and the number and percentage of participants with at least one positive neutralizing antibody to rHuPH20 will be presented for each treatment arm (TAK-881 or HyQvia) and overall. 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.

6.7 Pharmacokinetic Analyses

PK Analyses will be presented on the PKFAS and PKPPAS. The main analysis for the primary endpoint will be presented on the PKPPAS and a secondary analysis for the primary endpoint will be presented on the PKFAS.

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6.7.1 Pharmacokinetic Analysis

Blood samples for the determination of total serum IgG concentrations will be collected as outlined in [Table 6.a](#) below.

Table 6.a Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Scheduled Time Relative to First Dose (Hours)*
Total IgG	Serum	Day -1; pre-infusion and Days 1, 2, 3, 4, 5, 6, 7, 8, 15, 18, 22, 25, 29, 43, 57, and 85 post-infusion

*Actual dates and times of sample collection will be recorded in the CRF.

Total serum IgG concentrations will be listed and summarized descriptively by PK sampling timepoint according to treatment arm, as described in the CPAP. Additional details on the presentation of total serum IgG concentration-time plots, total serum IgG concentrations and PK parameters will be described in the CPAP.

Individual total serum IgG concentrations will be presented in a data listing by participant and will include all analyzed samples (Safety Analysis Set).

The full list of total serum IgG PK parameters is included in the CPAP.

Statistical Analysis

Statistical analysis of PK data will be based on the PKFAS and PKPPAS. Deviations that may exclude participants from the PKPPAS are listed in [Section 5.3](#). Additional details will be provided in CPAP.

All PK analyses will use the actual sampling times. If actual sampling times are not available, nominal times may be used for analyses. PK parameters for total IgG concentrations will be calculated using NCA based on participants with evaluable PK profiles.

Primary Endpoint:

Baseline-corrected $AUC_{Day1-29}$ will be log-transformed prior to analysis. The difference in means between TAK-881 and HyQvia and the corresponding two-sided 95% CI on the log-transformed scale will be obtained by a two-sample t-test allowing for unequal variances by using the Welch-Satterthwaite correction of degrees of freedom. Results will be back-transformed from the logarithmic scale to obtain the ratio of geometric means. The ratio of geometric means (TAK-881/HyQvia) will be presented together with a corresponding two-sided 95% CI. In addition, the geometric means and corresponding two-sided 95% CIs of baseline-corrected $AUC_{Day1-29}$ will be presented separately for TAK-881 and HyQvia.

The following SAS code will be used to perform the analysis. Original values may be used in the input data, as the SAS procedure will perform the ln-transformation automatically:

```
PROC TTEST DIST=LOGNORMAL COCHRAN ALPHA=0.05;
CLASS TREAT;
VAR AVAL;
RUN;
```

Treatment geometric means and 95% CI will be obtained using the following code. Original values may be used in the input data, as the SAS procedure will perform the ln-transformation automatically:

```
PROC TTEST DIST=LOGNORMAL ALPHA=0.05;
BY TREAT;
VAR AVAL;
RUN;
```

Handling of IEs of the Primary Estimand:

IEs represent events that affect the interpretation of the analysis variable collected after the IE has occurred. The estimand framework requires strategies to define how these events are addressed in the assessment of the trial objective.

IEs are defined as protocol deviations that may affect the reliability of the primary endpoint following the definition of the PKPPAS. A primary endpoint (baseline-corrected $AUC_{Day1-29}$) collected after an IE occurred will be excluded from the analysis based on the PKPPAS.

The hypothetical strategy envisions that IEs would not occur under the MCAR premise (the probability of missing baseline-corrected $AUC_{Day1-29}$ is the same for all participants). The hypothetical strategy utilizes a complete case analysis (that is, baseline-corrected $AUC_{Day1-29}$ collected after an IE occurred will be excluded from the analysis based on the PKPPAS) which is unbiased under the MCAR premise.

Secondary Endpoints:

Secondary PK parameters (baseline-corrected [C_{max} , AUC_{inf} and AUC_{last}] and baseline-uncorrected [C_{max} and $AUC_{Day1-29}$]) will be log-transformed prior to analysis. Means and corresponding two-sided 95% CIs on the log-transformed scale for TAK-881 and HyQvia will be obtained by one-sample t-tests. Results will be back-transformed from the logarithmic scale. The geometric means and corresponding two-sided 95% CIs will be presented separately for TAK-881 and HyQvia. Baseline-corrected t_{max} , t_{last} , $t_{1/2z}$, CL/F , and V_z/F will be summarized descriptively.

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The following SAS code will be used to perform the analysis. Original values may be used in the input data, as the SAS procedure will perform the ln-transformation automatically:

```
PROC TTEST DIST=LOGNORMAL ALPHA=0.05;  
BY TREAT;  
VAR AVAL;  
RUN;
```

6.8 Preliminary Analysis

Not applicable.

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

Not applicable.

9.0 CHANGES FROM THE PREVIOUS VERSION OF THE SAP

Not applicable.

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10.0 APPENDICES

Appendix A Safety Collection Time Point Information

Collection of Laboratory Samples

Clinical Laboratory Panels	Time Point	
	Protocol Visit/Hour	Table Presentation
Chemistry, Hematology, Urinalysis	Screening	NA
	Day -1	Baseline
	Day 8	Day 8
	Day 29	Day 29
	Day 85 (±3 days)	Day 85 (±3 days)

Time points in the Protocol Day and Hour 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.

If applicable, an ET assessment will be performed.

NA = Not Applicable (Individual results may be required for baseline)

Collection of Vital Signs

Parameter	Time Point		
	Period	Protocol Visit/Hour	Table Presentation
Blood Pressure, Heart Rate, Respiration Rate, Temperature	Screening		NA
	1	Day -1	NA
		Day 1 Predose	Baseline
		Day 1 Hour 0.5	Day 1 Hour 0.5
		Day 1 Hour 1	Day 1 Hour 1
		Day 1 Hour 1.5*	Day 1 Hour 1.5*
		Day 1 Hour 2	Day 1 Hour 2
		Day 1 Hour 3	Day 1 Hour 3
		Day 1 Hour 4	Day 1 Hour 4
		Day 2	Day 2
		Day 3	Day 3
		Day 4	Day 4
		Day 5	Day 5
		Day 6	Day 6
		Day 7	Day 7
		Day 8	Day 8
		Day 15	Day 15
		Day 18	Day 18
		Day 22	Day 22
		Day 25	Day 25
		Day 29	Day 29
		Day 43	Day 43
		Day 57	Day 57
		Day 85 (±3 days)	Day 85 (±3 days)

Time points in the Protocol Day and Hour column are based on the protocol and it should be noted that the data listing will reflect the data found in the final participant CRFs.

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*Vital signs will be measured every 30 minutes post infusion start until the end of the infusion. Time points may be added as applicable.

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)

Collection of ECG Measurements

Parameter	Time Point		
	Period	Protocol Day and Hour	Table Presentation
HR, PR, QRS, QT, QTcF, RR	Screening		Baseline
	1	Day 85 (±3 days)	Day 85 (±3 days)

Time points in the Protocol Day and Hour column are 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)

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:

Appendix B 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

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Bicarbonate	SI	<8.0 mmol/L
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ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

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.

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Appendix C 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 D 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

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