Statistical Analysis Plan

NCT Number: NCT05755035

Title: Multicenter, Prospective, Open-label, Randomized, Crossover Study to Evaluate Pharmacokinetics (PK), Safety, and Tolerability of TAK-881 in Primary Immunodeficiency Diseases (PIDD)

Study Number: TAK-881-3001

Document Version and Date: Version 5.0, 19 Nov 2025

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-881-3001

Multicenter, Prospective, Open-label, Randomized, Crossover
Study to Evaluate Pharmacokinetics (PK), Safety, and Tolerability
of TAK-881 in Primary Immunodeficiency Diseases (PIDD)

Phase: 2/3

Version: 5.0

Date: 19 Nov 2025

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REVISION HISTORY

Version	Date	Primary Rationale for Revision
Version 1.0	31-JAN-2023	Not Applicable
Version 2.0	26-SEP-2023	Due to the short time interval between protocol amendment 2 (25 April 2023) and protocol amendment 3 (28 June 2023), this SAP amendment covers updates according to both protocol amendments.
Version 3.0	16-OCT-2024	Due to the short time interval between protocol amendment 4 (05 March 2024) and protocol amendment 5 (29 July 2024), this SAP amendment covers updates according to both protocol amendments.
Version 4.0	26-JUN-2025	*) Changes to the analyses regarding antibiotics (see section 6.8.2). *) Addition of change from baseline for visual analogue scale; addition of 95% CI of mean for TSQM-9 scores and visual analogue scale (see section 6.8.1). *) Changes to improve readability and clarity.
Version 5.0	19-NOV-2025	*) Updates to ensure alignment with the modifications in the clinical pharmacology analysis plan, version 2.0, dated 28 Aug 2025. *) Clarification that subjects who receive their infusion within three days before or after the scheduled date at specified visits – where such deviations do not impact the reliability of total IgG level time profiles at steady state - are to be included in the PK Per-Protocol Analysis Set provided that no other protocol deviations that may impact the reliability of the total IgG level time profiles at steady state, as outlined in section 5.3, are present (see section 5.3).

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ASBI	Acute Serious Bacterial Infection
$AUC_{0-\tau,ss}$	Area under the Curve during the Dosing Interval at Steady-State
BMI	Body Mass Index
BW	Body weight
CI	Confidence Interval
cIGSC	Conventional subcutaneous IgG
CL/F	Apparent Clearance
C_{max}	Maximum Concentration
COVID-19	Coronavirus Disease 2019
CPAP	Clinical Pharmacology Analysis Plan
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DMC	Data Monitoring Committee
DVU	Dual-Vial Unit
EOS	End of Study
EQ-5D-5L	EuroQol 5 Dimensions Questionnaire
ET	Early Termination
FDA	Food and Drug Administration
HCP	Healthcare Professional
HRU	Healthcare Resource Utilization
HYQVIA	Immune Globulin Infusion 10% (Human) Solution with rHuPH20
ICF	Informed Consent Form
IP	Investigational Product
ICE	Intercurrent Event
IgG	Immunoglobulin G
IGIV	Intravenous IgG
log	Natural Logarithm
MAR	Missing at Random
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of Subjects with non-missing Values
NCA	Non-Compartmental Analysis
PIDD	Primary Immunodeficiency Diseases
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per-Protocol Analysis Set
PRO	Patient-Reported Outcomes

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PT	Preferred Term (MedDRA)
rHuPH20	Recombinant Human Hyaluronidase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
$t_{1/2}$	Terminal Half-life
TAK-881	Immune Globulin Subcutaneous 20% (Human) Solution with rHuPH20
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time of Maximum Concentration
TSQM-9	Treatment Satisfaction Questionnaire for Medication - 9 Items
V_z/F	Apparent Volume of Distribution
WHO	World Health Organization

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1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

- *To demonstrate PK comparability of TAK-881 and HYQVIA at steady-state after subcutaneous (SC) administration in subjects aged ≥16 years with PIDD.*

1.1.2 Secondary Objectives

- *To assess infections in all subjects.*
- *To assess healthcare resource utilization (HRU) for subjects using TAK 881/HYQVIA.*
- *To evaluate PK, safety, tolerability and immunogenicity of TAK-881 in subjects aged ≥16 years with PIDD.*
- *To characterize the PK of TAK-881 between subjects aged ≥16 years and subjects aged 2 to <16 years with PIDD.*
- *To assess IgG trough levels and to evaluate safety, tolerability, and immunogenicity of TAK-881 in pediatric subjects aged 2 to <16 years with PIDD.*
- *To evaluate infusion parameters at full dose for both TAK-881 and HYQVIA in all subjects.*

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1.1.3 Exploratory Objectives

- *To assess subject satisfaction with TAK-881/HYQVIA treatment in subjects aged ≥16 years.*
- *To assess subject HRQoL while on TAK-881/HYQVIA treatment in subjects aged ≥12 years.*
- *To assess infusion preparation time for TAK-881 and HYQVIA by nurse/pharmacist recordings in subjects aged ≥16 years.*

1.2 Endpoints

1.2.1 Primary Endpoint

- *Area under the curve during the dosing interval at steady-state ($AUC_{0-\tau,ss}$) based on total immunoglobulin G (IgG) levels.*

1.2.2 Secondary Endpoints

1.2.2.1 Efficacy Endpoints

- *Annualized rate of all infections.*
- *Annualized rate of acute serious bacterial infections (ASBIs).*
- *Annualized rate of episodes of fever.*

- *Time to first ASBI.*
- *Duration of infections.*

1.2.2.2 Healthcare Resource Utilization Endpoints

- *Days not able to go to school, work, daycare or to perform normal daily activities due to infections and/or their treatment, or other illnesses.*
- *Days on antibiotics.*
- *Number of hospitalizations, indication for the hospitalization (infection or other illnesses) and days hospitalized.*
- *Number of acute physician visits due to infection or other illnesses.*

1.2.2.3 Pharmacokinetic Endpoints

- *Pharmacokinetics at steady-state including maximum concentration (C_{max}), time of C_{max} (T_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), apparent volume of distribution (V_z/F), and $AUC_{0-\tau,ss}$/week based on total IgG levels.*
- *Trough level of total IgG.*
- *Trough level of IgG subclasses.*
- *Trough level of antigen-specific IgG antibodies (only for subjects ≥16 years).*

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1.2.2.4 Safety Endpoints

- *Occurrence of treatment-emergent adverse events (TEAEs).*
- *Occurrence of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881-related TEAEs.*
- *Occurrence of positive binding (defined as titer ≥1:160) and neutralizing antibodies to rHuPH20.*

1.2.2.5 Infusion Endpoints at Full Dose

- *Number of infusions per month.*
- *Number of infusion sites (needle sticks) per month.*
- *Number of infusion sites (needle sticks) per infusion.*
- *Duration of infusions (minutes).*
- *Monthly infusion time (minutes/month).*
- *Maximum infusion rate per site (mL/hour/site).*
- *Infusion volume per site (mL/site).*

1.2.3 Exploratory Endpoints

- *Subject satisfaction evaluated by subject-reported scores on the Treatment Satisfaction Questionnaire for Medication – 9 items (TSQM-9).*
- *Subject HRQoL evaluated via the EuroQol 5 Dimensions 5 level Questionnaire (EQ-5D-5L).*
- *HCP measured time of infusion preparation.*

1.3 Estimand

Attributes of the primary estimand corresponding to the primary objective:

- *Target population: Subjects aged ≥16 years with PIDD.*
- *Treatment: TAK-881 and HYQVIA administered every 3 or 4 weeks at the subject's prestudy weekly equivalent of IgG dose at screening.*
- *Analysis variable: $AUC_{0\text{-}\tau,ss}$ based on total IgG levels (primary endpoint).*
- *Intercurrent events (ICE):*
  - *ICE 1: Nonadherence to study medication.*
  - *ICE 2: Treatment discontinuation due to loss to follow-up.*
  - *ICE 3: Treatment discontinuation due to a TEAE.*

  The hypothetical strategy envisions that an ICE would not occur and will be used to address ICEs 1-3 based on the missing completely at random (MCAR) premise utilizing a complete case analysis (as reflected in the definition of the PK Per-Protocol Analysis Set [PKPPAS]) which is unbiased under the MCAR premise.
- *Population level summary: Ratio of geometric means in $AUC_{0\text{-}\tau,ss}$ between TAK-881 and HYQVIA.*
- *Estimator: Antilog of the restricted maximum likelihood (REML) estimator for the difference in means and corresponding two-sided 90% confidence interval (CI) in log-transformed variables assuming normally distributed errors.*
- *Estimate: Numerical result of the estimator based on data of the PKPPAS.*

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2.0 STUDY DESIGN

This study is a phase 2/3, multicenter, prospective, open-label, randomized, crossover PK comparability study in PIDD subjects aged ≥16 years. Pediatric subjects (aged 2 to <16 years) will participate in the prospective, open-label, single arm study part. The age cohort assignment will be based on the age at the time of signing the ICF (either by the subject or, in the case of minors, their legally designated representative[s]). Subjects must have received regular IgG treatment (HYQVIA, IGIV, or cIGSC) over a period of at least 12 weeks prior to screening. For a schematic of the study design, see Section 9.5.

The IgG dose (in g IgG per kg BW/week) should remain stable throughout the study. In order to maintain the same dose in g/kg BW when there has been a change in kg BW, it will be necessary to adjust the absolute IgG dose (g) administered, after the first full dose of the study treatment. If a subject's BW has increased or decreased by more than 5% relative to the subject's BW used for the most recent dose calculation, the absolute dose should be calculated using the current BW. To allow for sufficient infusion preparation time, the new absolute IgG dose will be administered at the subsequent visit.

Serum trough levels of total IgG >5 g/L must be maintained throughout the study. In all subjects the dose in g/kg BW/week after the first full dose of study treatment may be changed only if clinically indicated (eg, increased incidence of infections, low IgG trough level [≤5 g/L]) at the investigator's discretion. However, if the dose (in g/kg BW/week) is changed by >10% relative to the prestudy IgG screening dose (in g/kg BW/week), the sponsor must be informed, the subject must not undergo serial PK (if ≥16 years) or sparse PK (if 2 to <16 years) of total IgG measurements for the rest of study participation and will be followed for other assessments in the study. The rationale for such dose adjustment must be documented in the subject's file, and it must be entered in the case report forms (CRFs).

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The study consists of a screening epoch, a ramp-up epoch, if applicable, and treatment epoch(s). The number of study epochs that a subject enters depends on their prestudy IgG treatment and age at the time of signing the ICF.

Screening and Ramp-up Epochs: The duration of the screening epoch will be up to 4 weeks. Approximately 75 subjects in total (51 subjects aged ≥16 years and 24 subjects aged 2 to <16 years) will be screened, assuming a screen failure rate of 25%.

For subjects who have been receiving IGIV or cIGSC, screening will be followed by a ramp-up epoch that will start 1, 2, 3, or 4 weeks after the last IGIV/cIGSC prestudy dose, depending on the subjects' prestudy IGIV/cIGSC treatment interval. The first ramp-up visit is 3 weeks before the first treatment epoch starts, and the second ramp-up visit will be 2 weeks before the first treatment epoch starts. Subjects who have already been receiving HYQVIA treatment will not enter the ramp-up epoch.

AB/BA Crossover Treatment Epochs (subjects aged ≥16 years): At least 38 eligible subjects aged ≥16 years will be randomized (1:1) within 4 days prior to the first planned infusion and treated according to the following treatment sequences: either TAK-881 followed by HYQVIA (Sequence 1) or HYQVIA followed by TAK-881 (Sequence 2). Randomization will be stratified by IgG

treatment interval (every 3 or 4 weeks) during the study. The minimum number of subjects per prestudy IgG treatment (HYQVIA, IGIV, or cIGSC) and per treatment interval (every 3 or 4 weeks regardless of their prestudy IgG treatment) is 3. Each subject aged ≥16 years will complete both crossover epochs (crossover epochs 1 and 2). The subjects will have 6 or 8 infusions at full dose depending on the study treatment interval (every 3 or 4 weeks) in both crossover epochs 1 and 2. An accelerated switch between crossover epochs 1 and 2 is not allowed. The treatment intervals of TAK-881 and HYQVIA after the ramp-up, if applicable, in crossover epochs 1 and 2 must remain unchanged and no ramp-up will be used between crossover epochs. The 3- or 4- weekly treatment interval must be maintained in both crossover epochs, ie, no change to the treatment interval is allowed when changing from TAK-881 to HYQVIA or vice versa. The first full dose of TAK-881 or HYQVIA, depending on the sequence, will be administered either 2 weeks after the second ramp-up dose (applicable for subjects pretreated with IGIV or cIGSC) or 3 or 4 weeks after the last infusion of their prestudy IgG treatment, depending on their prestudy IgG treatment interval (applicable for subjects pretreated with HYQVIA).

Serial PK of total IgG measurements will be performed at the following time points in each crossover epoch at the eighth infusion at full dose in 3-week treatment interval or at the sixth infusion at full dose in 4-week treatment interval:

- *Preinfusion: Day 1 predose (within 1 hour of the start of infusion).*
- *Postinfusion: Day 1 postdose, immediately after infusion, and at the following times from completion of the infusion:*
    - *Day 2 (ie, 24 hours) (±4 hours),*
    - *Day 3 (ie, 48 hours) (±4 hours),*
    - *Day 4 (ie, 72 hours) (±8 hours),*
    - *Day 8 (±1 day),*
    - *Day 15 (±1 day),*
    - *Day 22 (±1 day) (as the end of PK assessment for the 3-week treatment interval), and if applicable*
    - *Day 29 (±1 day) (as the end of PK assessment for the 4-week treatment interval).*

<u>Single-arm Treatment Epoch (subjects aged 2 to <16 years)</u>: At least 18 eligible pediatric subjects aged 2 to <16 years will participate in the single-arm treatment epoch. They will receive 6 or 8 infusions of TAK-881 at full dose, depending on the study IgG treatment interval, after the ramp-up, if applicable. At least 6 pediatric subjects in each of the age groups of 2 years to <6 years, 6 years to <12 years and 12 years to <16 years will be treated. No minimum number of pediatric subjects per prestudy IgG treatment or per treatment interval is required in this study. The enrollment of subjects aged 2 to <16 years in the single-arm treatment epoch will begin based on recommendation of a Data Monitoring Committee (DMC) after acceptable safety and tolerability have been demonstrated in subjects aged ≥16 years. The first full dose of TAK-881 will be administered either 2 weeks after the second ramp-up dose (applicable for subjects pretreated with IGIV or cIGSC) or 3 or 4 weeks after the last infusion of their prestudy IgG treatment, depending

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on their prestudy IgG treatment interval (applicable for subjects pretreated with HYQVIA). Serum trough levels of total IgG with TAK-881 will be assessed prior to each infusion, and additionally 1 nontrough PK sample at the eighth infusion at full dose in 3-week study treatment interval or at the sixth infusion at full dose in 4-week study treatment interval will be assessed. Subjects will be randomized (1:1:1:1:1:1) within 4 days prior to the first planned TAK-881 infusion to 1 of the following sparse PK sampling times (from the completion of the infusion):

- Day 1 postdose, immediately after infusion
- Day 2 (ie, 24 hours) (±4 hours),
- Day 3 (ie, 48 hours) (±4 hours),
- Day 4 (ie, 72 hours) (±8 hours),
- Day 8 (±1 day),
- Day 15 (±1 day) (for the 3-week treatment interval), or Day 22 (±1 day) (for the 4-week treatment interval).

Randomization will be stratified by pediatric age cohort (2 to <6, 6 to <12, 12 to <16).

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3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

PK comparability of TAK-881 and HYQVIA at steady-state after SC administration in subjects aged ≥16 years with PIDD will be assessed by the CI inclusion approach to test the following hypothesis:

$$H_0: \frac{\mu_T}{\mu_R} \notin \{\theta_1, \theta_2\} \text{ vs. } H_1: \theta_1 < \frac{\mu_T}{\mu_R} < \theta_2$$

where μ_T and μ_R are the geometric means of TAK-881 and HYQVIA and θ_1 and θ_2 refer to 0.8000 and 1.2500, respectively. The conclusion of PK comparability is reached if the null hypothesis H_0 is rejected at the significance level α=0.05 (type I error) for $AUC_{0\text{-}\tau,ss}$. This means that PK comparability is claimed if the two-sided 90% CI for the ratio of geometric means in $AUC_{0\text{-}\tau,ss}$ is completely contained within the acceptance interval of 80.00 to 125.00%.

No other hypotheses will be tested in this study.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

No adjustments for multiplicity will be performed.

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4.0 SAMPLE-SIZE DETERMINATION

Subjects aged ≥16 years: The anticipated sample size of 30 completed and evaluable subjects is based on FDA recommendations and not on statistical considerations. To account for an assumed drop-out rate of 20% (including early withdrawals, subjects who miss at least one of the doses during the crossover epochs, subjects who have unevaluable PK profiles, or subjects who have protocol violations that may affect the reliability of the total IgG level time profiles), 38 subjects will be randomized and treated (19 per sequence).

However, considering an AB/BA crossover design and assuming a within-subject variability of 14% for $AUC_{0-\tau,ss}$ and a true ratio for $AUC_{0-\tau,ss}$ (TAK-881/HYQVIA) of 0.90, comparability between TAK-881 and HYQVIA based on the acceptance interval of 80.00% to 125.00% can be demonstrated with a power of 94% and a type I error of 5% based on 30 subjects (15 subjects per sequence).

Three historical studies investigating different IgG products have been used to estimate the within-subject coefficient of variation (CV) for $AUC_{0-\tau,ss}$: 160603 (NCT00814320), 170903 (EudraCT Number: 2010-019459-23), and 170904 (NCT01218438). For each CV, the upper limit of a two-sided 50% CI was calculated. The within-subject variability of 14% for $AUC_{0-\tau,ss}$ used for sample size calculation was the highest upper limit across the 3 studies.

Subjects aged 2 to <16 years: Statistical analysis will be descriptive in nature and no statistical hypothesis testing will be performed. Therefore, the sample size is not based on statistical considerations. At least 6 pediatric subjects in each of the age groups of 2 years to <6 years, 6 years to <12 years, and 12 years to <16 years will be treated, as recommended in FDA guidance "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency".

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5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set (SAS) will consist of all subjects 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

Subjects aged ≥16 years: The Pharmacokinetic Full-Analysis Set (PKFAS) will consist of all subjects who received all TAK-881 and HYQVIA infusions with evaluable PK profiles in each crossover epoch. Analysis will be performed according to the actual treatment received.

Subjects aged 2 to <16 years: The PKFAS will consist of all subjects who received all TAK-881 infusions with a total IgG trough level measurement at the end of the last dosing interval.

5.3 Pharmacokinetic Per-Protocol Analysis Set

Subjects aged ≥16 years: The PKPPAS is a subset of the PKFAS and will contain all subjects who have no protocol violations that may affect the reliability of the total IgG level time profiles. Deviations will include the following: incorrect treatment applied (ie, randomization error), infusion window deviation of >3 days when the visit window is ±3 days, infusion window deviation of >1 day when the visit window is ±1 day, or dose deviation of >10% in g/BW kg/week for one of the infusions in the crossover part. Exception: Infusion window deviations within ±3 days of the scheduled visits where a visit window of ±1 day is allowed per study protocol, specifically Ramp-up 1 Visit, Ramp-up 2 Visit, and Week 25 Visit (1st IP administration of epoch 2), do not affect the reliability of the total IgG level time profiles at steady state and do not lead to exclusion of those subjects from the PKPPAS. Additional deviations will be the violation of study inclusion criteria 1, 3, or 4 and the receipt of other IGIV or IGSC products or hyperimmune serum or other polyclonal and monoclonal IgG products (prohibited concomitant medication). *Analysis will be performed according to the actual treatment received.*

Subjects aged 2 to <16 years: The PKPPAS is a subset of the PKFAS and will contain all subjects who have no protocol violations that may affect the reliability of the total IgG trough levels. Deviations will include the following: infusion window deviation of >3 days when the visit window is ±3 days, infusion window deviation of >1 day when the visit window is ±1 day, or dose deviation of >10% in g/BW kg/week for one of the TAK-881 infusions. Additional deviations will be the violation of study inclusion criteria 1, 3, or 4 and the receipt of other IGIV or IGSC products or hyperimmune serum or other polyclonal and monoclonal IgG products (prohibited concomitant medication).

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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 investigational product (IP). The first administration of IP refers to the first ramp-up dose if ramp-up is applicable, or to the first full dose at Week 1 if ramp-up is not applicable. The start date/time of IP administration refers to the start date/time of rHuPH20 administration. If two infusion sites are used, 50% of the total volume of rHuPH20 and IgG will be delivered into each infusion site simultaneously.

Post-baseline assessments at unscheduled visits will not be included in summaries by study visit, except for immunogenicity endpoints (occurrence of positive binding and neutralizing anti-rHuPH20 antibodies) and hemolysis panel. Post-baseline assessments at scheduled visits that are collected outside the defined visit windows (see Section 9.2.3) will be included in summaries by study visit. Post-baseline assessments that are erroneously collected after instead of before IP administration (for example collection of IgG trough levels) will not be included in summaries by study visit. All assessments including those at unscheduled visits will be presented in subject data listings. Assessments that are outside the defined visit windows or are erroneously collected after instead of before IP administration will be flagged.

Continuous endpoints and variables 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, PK endpoints and total IgG levels will be summarized using geometric means with corresponding two-sided 95% CIs. Untransformed endpoints and variables are those that are presented in the same units as recorded and will use the following rule for presentation: Means, medians, and geometric means with CIs will be presented to 1 more decimal place as the recorded data. Standard deviations 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. Derived or transformed endpoints and variables are those that are presented in different units than recorded and will use the following rule for presentation: All descriptive statistics will be presented to 3 significant digits.

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. 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. 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 based on the SAS up to the time point of discontinuation, see Section 5.0.

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6.1.1 Handling of Treatment Misallocations

See Section 5.0.

6.1.2 Analysis Approach for Continuous Variables

All continuous variables will use the analysis method as described in the respective section.

6.1.3 Analysis Approach for Binary Variables

All binary variables will use the analysis method as described in the respective section.

6.1.4 Analysis Approach for Time-to-Event Variables

Not applicable.

6.2 Disposition of Subjects

A subject is defined as screened if the subject signed the informed consent form (ICF).

A subject is defined as enrolled when all of the following have occurred:

- *The subject or, in the case of minors, legally designated representative(s) has/have provided informed consent (that is, in writing, documented via a signed and dated ICF or eConsent [if available]).*
- *The subject has provided assent to participate in the study (for minors capable of assent).*
- *The subject has satisfied all entry criteria.*
- *The subject has been randomized.*

Subjects are considered screen failures if they were not enrolled.

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A subject is defined as prematurely discontinued if the subject has been enrolled but discontinued the study before the end of study (EOS) visit.

6.2.1 Disposition by Age Group

Disposition by age will be summarized based on all randomized subjects.

The number and percentage of subjects who completed the study, who prematurely discontinued the study along with the primary reason for discontinuation, and who were randomized but not treated will be presented by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined). Percentages will be based on the number of randomized subjects.

All disposition data will be presented in a subject data listing. Subjects who were randomized but not treated will be flagged. The randomization assignments will be also presented in a separate subject data listing.

6.2.2 Disposition by Site

Disposition by site will be summarized based on all subjects.

The date of the first signed ICF, the date of the last subject exit, the duration in days calculated as (date of the last subject exit) – (date of first ICF) + 1, and the number of randomized and completed subjects will be presented by region, country, and site.

6.2.3 Screen Failures

Screen failures will be summarized based on all subjects.

The number of screen failures and the number and percentage of primary reasons for screen failures will be presented. In addition, the following characteristics will be summarized for screen failures: age in years, age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 16 to <18 years, 18 to <65 years, ≥65 years), sex, sex assigned at birth, ethnicity, and race. Age at the time of signing the ICF will be used as reported in the CRF and will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum. Age group, sex, sex assigned at birth, ethnicity, and race will be summarized by the number and percentage of subjects in each category. Percentages will be based on the number of screen failures.

All screen failure data will be presented in a subject data listing.

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6.2.4 Analysis Sets

The number of subjects included in each analysis set (SAS, PKFAS, PKPPAS) will be presented by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined).

6.2.5 Protocol Deviations

Protocol deviations will be summarized based on all randomized subjects.

Protocol deviations will be recorded separately from the clinical database using a protocol deviation tracker. Protocol deviations will be classified as key or non-key per the protocol deviation criteria form 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 site, classification, and category and will be presented by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined). 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. Protocol deviations that may affect the reliability of the total IgG level time profiles or total IgG trough levels will be flagged.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

The following demographic characteristics will be summarized by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined) for the SAS, PKFAS, PKPPAS: age in years, sex, sex assigned at birth, ethnicity, race. Age at the time of signing the ICF will be used as reported in the CRF and will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum. Sex, sex assigned at birth, ethnicity, and race will be summarized by the number and percentage of subjects in each category.

For the SAS, additional separate tables for the demographic characteristics will be created by the following age groups:

- 2 to <18 years, ≥18 years; 18 to <65 years, ≥65 years
- 2 to <6 years, 6 to <12 years; 12 to <16 years

Additional tables of demographic characteristics will be performed for the subset of subjects who completed the semi-structured qualitative interviews.

All demographic data will be presented in a subject data listing for the SAS.

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6.3.2 Medical History and Concurrent Medical Conditions

Medical history is defined as *any significant conditions or diseases relevant to the disease under study that resolved before, or at the time when the subject provided informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided.*

Medical history and concurrent medical conditions will be summarized and listed for the SAS and for the subset of subjects who completed the semi-structured qualitative interviews. Missing dates will not be imputed.

Medical history and concurrent medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or newer.

Medical history including concurrent medical conditions will be summarized by system organ class (SOC) and preferred term (PT) and will be presented by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined). 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

The following baseline characteristics will be summarized by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined) for the SAS, PKFAS, and PKPPAS: weight (kg), height

(cm), BMI (kg/m^2), pre-study infusion interval, infusion interval during the study (3-week, 4-week), pre-study IgG treatment (HYQVIA, IGIV, cIGSC), pre-study IgG dose at screening (grams), and pre-study body weight adjusted weekly IgG dose at screening (g/kg BW/week) (defined as the pre-study dose for IgG (grams) at screening divided by body weight (kg) at the screening visit divided by the pre-study infusion interval (1, 2, 3 or 4 weeks)). BMI will not be used as reported in the CRF but will be calculated as (weight in kg) / (height in m)^2.

Weight, height, BMI, pre-study IgG dose at screening and pre-study body weight adjusted weekly IgG dose at screening will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum.

Infusion interval and pre-study IgG treatment will be summarized by the number and percentage of subjects in each category.

For the SAS, additional separate tables for the baseline characteristics will be created by the following age groups:

- 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years
- 2 to <6 years, 6 to <12 years; 12 to <16 years

All baseline characteristics data including PIDD disease characteristics will be presented in a subject data listing for the SAS.

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6.4 Medication History and Concomitant Medications/Procedures

Prior medications and concomitant medications and procedures will be summarized and listed for the SAS and for the subset of subjects who completed the semi-structured qualitative interviews. Missing dates will not be imputed.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version Global B3 September 2022 or newer. Concomitant procedures will be coded using MedDRA version 25.1 or newer.

6.4.1 Prior Medications

Prior medications/treatments (including prestudy IgG treatment) are defined as those that were stopped at or within 60 days prior to receiving the first dose of IP.

If the end date/time is incomplete, an indication is provided in the CRF on whether the medication stopped prior to the start of the first IP administration. No imputation of dates/times will be required to determine if medication is prior.

The number and percentage of subjects using prior medication will be summarized by therapeutic class and PT and will be presented by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined). 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 medications/treatments are defined as those given in addition to the study intervention and were stopped after the start of the first dose of IP or were ongoing at the end of the study. Any medication with a start date after the EOS visit for subjects not rolling over to the long-term follow-up Study TAK-881-3002, or after treatment initiation in the long-term follow-up Study TAK-881-3002 for subjects rolling over, or after the early termination (ET) visit for subjects who prematurely discontinue the study will be considered post-treatment medication and not concomitant medication.

If the end date/time is incomplete, an indication is provided in the CRF on whether the medication stopped after the start of the first IP administration. No imputation of dates/times will be required to determine if medication is concomitant.

The number and percentage of subjects using concomitant medication will be summarized by therapeutic class and PT and will be presented by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined). 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. A flag will be added in the listing whether the concomitant medication was a pre-medication or not.

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6.4.3 Concomitant Procedures

Concomitant procedures are defined as those performed during the use of study intervention and were stopped after the start of the first dose of IP or were ongoing at the end of the study. Any procedure with a start date after the EOS visit for subjects not rolling over to the long-term follow-up Study TAK-881-3002, or after treatment initiation in the long-term follow-up Study TAK-881-3002 for subjects rolling over, or after the ET visit for subjects who prematurely discontinue the study will be considered post-treatment procedure and not concomitant procedure.

If the end date/time is incomplete, an indication is provided in the CRF on whether the procedure stopped after the start of the first IP administration. No imputation of dates/times will be required to determine if the procedure is concomitant.

The number and percentage of subjects with concomitant procedures will be summarized by SOC and PT and will be presented by age group (subjects aged 2 to <16 years, subjects aged ≥16 years, combined). SOC will be sorted alphabetically, and PT within SOC will be sorted in descending frequency based on total occurrence. Multiple procedures by a subject in the same PT category will be counted only once.

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

6.5 Efficacy Analysis

Pharmacokinetic endpoints are considered surrogate endpoints for efficacy in this study. The analysis performed for PK endpoints will be presented for the PKFAS as well as for the PKPPAS with the analysis on PKPPAS considered the primary analysis. Descriptive summaries for PK endpoints and subject data listings *will be presented for the SAS. Infections are considered efficacy endpoints and will be analyzed based on the SAS.*

The PK analysis and population PK modeling details will be described in a clinical pharmacology analysis plan (CPAP) and a population PK Data Analysis Plan (DAP). All PK analyses will use the actual sampling times (not nominal times) and nonbaseline-corrected total IgG levels.

The following PK metrics at steady-state for subjects aged ≥16 years with evaluable PK profiles *will be calculated by the non-compartmental analysis (NCA) for TAK-881 and HYQVIA: $AUC_{0-\tau,ss}$, C_{max}, T_{max}, $t_{1/2}$, CL/F, V_z/F, and $AUC_{0-\tau,ss}$/week. The criteria for considering a PK profile as evaluable* as well as for considering a PK metric as reliable, *and details regarding the calculation of PK metrics using NCA will be described in a separate CPAP.* Subjects with unreliable PK parameter results in a given epoch will have those specific results treated as missing values and those values will be excluded from all analysis sets. Only their reliable PK results from the other epoch will be included. Additional information regarding the criteria for unreliable results is available in the CPAP version 2.0, dated 28 Aug 2025, section 4.2. In the subject listings, unreliable PK parameters will be presented and flagged. *PK characterization between subjects aged ≥16 years and subjects aged 2 to <16 years will be assessed according to a population pharmacokinetic model incorporating covariates including allometric scaling of parameters according to body weight.* Details will be described in a separate analysis plan.

Analysis of total IgG trough levels and trough levels for IgG subclasses and antigen-specific IgG antibodies will be based on results from the Q2 BioA laboratory. Total IgG trough level results from the central laboratory will be listed only.

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6.5.1 Primary Endpoint Analysis

6.5.1.1 Derivation

<u>Subjects aged ≥16 years</u>: The primary endpoint $AUC_{0-\tau,ss}$ will be calculated during the dosing interval after the last dose in each crossover epoch by the NCA based on total IgG levels for TAK-881 and HYQVIA.

6.5.1.2 Main Analytical Approach

$AUC_{0-\tau,ss}$ will be transformed prior to analysis using a logarithmic transformation. The difference in means and the corresponding two-sided 90% CI on the log-transformed scale will be obtained from a linear mixed effects model. The terms used in the linear mixed effects model will be sequence, epoch, treatment, and dosing interval (stratification variable) as fixed effects and subject nested in sequence as random effect. In case a subject has a missing $AUC_{0-\tau,ss}$ estimate in at least one epoch, including those classified as unreliable and therefore set to missing, the respective subject will not be included in the linear mixed effects model.

Results will be back transformed from the logarithmic scale. *Comparability between TAK-881 and HYQVIA will be assessed based on the 90% CI for the ratio of geometric means for $AUC_{0-\tau,ss}$ in reference to the acceptance interval of 80.00% to 125.00%. In addition, geometric means and corresponding two-sided 95% CIs of $AUC_{0-\tau,ss}$ will be presented separately for TAK-881 and HYQVIA.*

The following SAS® code will be used where SEQ represents sequence, EPO represents epoch, TRT represents treatment, INT represents dosing interval, SUBJ represents unique subject identifier, and LOGAUC represents log-transformed $AUC_{0-\tau,ss}$:

```
PROC MIXED DATA = <DATA-SET-NAME>;
  CLASS <SUBJ> <SEQ> <EPO> <TRT> <INT>;
  MODEL <LOGAUC> = <SEQ> <EPO> <TRT> <INT> / S DDFM=SATTERTH;
  RANDOM <SUBJ>(<SEQ>) / S;
  LSMEANS <TRT> / DIFF CL ALPHA=0.1;
  LSMEANS <TRT> / CL ALPHA=0.05;
RUN;
```

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Descriptive summaries for each treatment (TAK-881, HYQVIA) will be presented by sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881, combined), by infusion interval (3-week, 4-week, combined), and by prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined). Descriptive summaries will include n, mean, SD, median, minimum, maximum, geometric mean, and two-sided 95% CI.

The primary endpoint $AUC_{0-\tau,ss}$ will be also presented in a subject data listing.

6.5.1.3 Sensitivity Analysis

A sensitivity analysis to assess the robustness of inferences to departures from the MCAR premise in the hypothetical strategy (used for ICEs 1-3) will be performed based on the missing at random (MAR) premise by including all subjects who received all TAK-881 or HYQVIA infusions with evaluable PK profiles in at least one crossover epoch and have no protocol violations that may affect the reliability of the total IgG level time profiles in the respective crossover epoch. Additionally, subjects who have a non-missing $AUC_{0-\tau,ss}$ estimate in at least one crossover epoch (i.e., those with non-missing $AUC_{0-\tau,ss}$ - including those classified as reliable and therefore set to non-missing - in at least one epoch) will be also included in the linear mixed effects model. *This sensitivity analysis utilizing the same linear mixed effects model as described above is unbiased under the MAR premise.*

6.5.2 Secondary Endpoints Analysis

6.5.2.1 Pharmacokinetics

6.5.2.1.1 Derivation

Subjects aged ≥16 years: The secondary PK endpoints C_{max}, T_{max}, $t_{1/2}$, CL/F, V_z/F, and $AUC_{0-\tau,ss}$/week will be calculated during the dosing interval after the last dose in each crossover epoch by the NCA based on total IgG levels for TAK-881 and HYQVIA. Total IgG trough levels and trough levels of IgG subclasses and antigen-specific IgG antibodies will be analyzed using the last trough level per subject in each crossover epoch (at the end of the last dosing interval). In addition, total IgG trough levels will be analyzed using the geometric mean of the last 2 trough levels per subject in each crossover epoch (predose level prior to the last dose and at the end of the last dosing interval).

Subjects aged 2 to <16 years: Total IgG trough levels at the end of the last TAK-881 dosing interval and trough levels of IgG subclasses at Week 22 (3-week treatment interval) or Week 21 (4-week treatment interval) will be summarized using geometric means and corresponding two-sided 95% CIs. In addition, total IgG trough levels will be summarized using the geometric mean of the last 2 trough levels per subject (predose level prior to the last dose and at the end of the last dosing interval).

Secondary PK endpoints referring to the objective to characterize the PK of TAK-881 between subjects aged ≥16 years and subjects aged 2 to <16 years will be addressed in a separate population PK analysis plan.

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6.5.2.1.2 Main Analytical Approach

Subjects aged ≥16 years: The same linear mixed effects model as for the primary endpoint $AUC_{0-\tau,ss}$ will be used for the analysis of secondary PK endpoints, except T_{max}. The models will be used to estimate the geometric mean for TAK-881 and HYQVIA and corresponding two-sided 95% CIs. Consistent with the primary endpoint analysis, in case a subject has a missing pharmacokinetic parameter estimate in at least one epoch, including those classified as unreliable and therefore set to missing, the respective subject will not be included in the linear mixed effects model for the respective PK estimate.

The following SAS® code will be used where SEQ represents sequence, EPO represents epoch, TRT represents treatment, INT represents dosing interval, SUBJ represents unique subject identifier, and LOGPK represents log-transformed PK metric:

```
PROC MIXED DATA = <DATA-SET-NAME>;
  CLASS <SUBJ> <SEQ> <EPO> <TRT> <INT>;
  MODEL <LOGPK> = <SEQ> <EPO> <TRT> <INT> / S DDFM=SATTERTH;
  RANDOM <SUBJ>(<SEQ>) / S;
  LSMEANS <TRT> / CL ALPHA=0.05;
RUN;
```

Descriptive summaries for each treatment (TAK-881, HYQVIA) will be presented by sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881, combined), by infusion interval (3-week, 4-week, combined), and by prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined). Descriptive summaries will include n, mean, SD, median, minimum, maximum, geometric mean, two-sided 95% CI.

In addition, trough levels will be also summarized by study visit. Summaries for total IgG trough levels and trough levels for IgG subclasses and antigen-specific IgG antibodies will be presented by infusion interval (3-week, 4-week), study visit, and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881) using the following descriptive statistics: n, mean, SD, median, minimum, maximum, geometric mean, two-sided 95% CI.

Total IgG trough levels in g/L will be also presented graphically by individual subject plots with a line connecting total IgG trough levels at different study visits. In addition, geometric means (connected with a line) and two-sided 95% CIs of total IgG trough levels at different study visits will be presented graphically by infusion interval (3-week, 4-week) and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881). The plots will be color marked by treatment (TAK-881, HYQVIA) and will display a horizontal line at 5 g/L.

All secondary PK endpoints will be also presented in a subject data listing.

<u>Subjects aged 2 to <16 years</u>*: Descriptive summaries for each pediatric age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years) will be presented by infusion interval (3-week, 4-week, combined) and by prestudy treatment (HYQVIA, IGIV, cIGSC, combined).* Descriptive summaries will include n, mean, SD, median, minimum, maximum, geometric mean, two-sided 95% CI.

In addition, trough levels will be also summarized by study visit. Summaries for total IgG trough levels and trough levels for IgG subclasses will be presented by infusion interval (3-week, 4-week), study visit, and age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years) using the following descriptive statistics: n, mean, SD, median, minimum, maximum, geometric mean, two-sided 95% CI.

Total IgG trough levels in g/L will be also presented graphically by individual subject plots with a line connecting total IgG trough levels at different study visits. In addition, geometric means (connected with a line) and two-sided 95% CIs of total IgG trough levels at different study visits will be presented graphically by infusion interval (3-week, 4-week). The plots will display a horizontal line at 5 g/L.

All secondary PK endpoints will be also presented in a subject data listing.

6.5.2.2 Infections

6.5.2.2.1 Derivation

The number of all infections, the number of ASBIs, and the number of episodes of fever will be analyzed separately for TAK-881 for each age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, combined)

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and for HYQVIA for subjects aged ≥16 years, ≥18 years, 18 to <65 years, ≥65 years, combined. In addition, episodes of fever will be analyzed for episodes related to infections as well as for all episodes. An episode of fever is related to an infection if at least one day of fever is related to an infection. The observational period for each subject will start with the first administration of IP referring to the first ramp-up dose, if ramp-up is applicable, or to the first full dose at Week 1, if ramp-up is not applicable, and will include the transition period between the EOS visit and the first dose in the long-term follow-up Study TAK-881-3002 for subjects rolling over, if applicable.

The subject or, in case of minors, legally designated representative(s) will collect information on fever (defined as a body temperature of ≥38°C/100.4°F per NCI CTCAE, Version 5.0, dated November 27, 2017) in the subject diary. After a fever episode subsides, if the fever recurs after ≥3 days it will be counted as a new fever episode. The number of days of fever for a given episode is defined as the number of days from the first to the last day with a body temperature of ≥38°C/100.4°F. For example, if a fever is reported for days 16, 17, 19, 22, and 26 this will count as two fever episodes with durations of 7 days and 1 day, respectively. If date of fever is partially missing (day missing and only month and year available), this will be considered as a fever episode of 1 day.

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6.5.2.2.2 Main Analytical Approach

The number of all infections, the number of ASBIs, and the number of episodes of fever will be analyzed using a generalized linear model. The response distribution will be assumed to be Poisson with a logarithmic link function. The model will include the natural logarithm of the length of the observational period in years as an offset to account for potential differences in lengths of the observational periods per subject. The observational period for each subject will be calculated for each treatment including ramp-up, if applicable. The model will also account for potential overdispersion by allowing the variance to have a multiplicative dispersion factor given by the deviance divided by the degrees of freedom.

Results will be back transformed from the logarithmic scale. *Mean annualized rates and corresponding two-sided 95% CIs will be estimated for TAK-881 for each age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years,* 18 to <65 years, ≥65 years*, combined) and for HYQVIA for subjects aged ≥16 years, ≥18 years,* 18 to <65 years, ≥65 years, combined. In addition, mean annualized rates and corresponding two-sided 95% CIs for episodes of fever will be estimated for episodes related to infections as well as for all episodes.

The following SAS® code will be used to run separate models for each subgroup where COUNT represents number of infections and LOGTIME represents log-transformed length of observational period in years:

```
PROC GENMOD DATA = <DATA-SET-NAME>;
  MODEL <COUNT> = / SCALE=DEVIANCE DIST=POISSON LINK=LOG
                    OFFSET=<LOGTIME> ALPHA=0.05 LRCI;
RUN;
```

If no event is observed, CIs will not be computed by the maximum likelihood-based method for analyzing the Poisson model using PROC GENMOD. In these instances, the 97.5% upper confidence limit (UCL) will be obtained directly by inverting the Poisson probabilities:

$$UCL = -\frac{log(\alpha/2)}{(total_duration/365.2425)}$$

where α=0.05 and total_duration is the total number of observation days in each subgroup.

The number and percentage of subjects with at least one infection, with at least one ASBI, and with at least one episode of fever as well as the number of infections, the number of ASBIs, and the number of episodes of fever will be presented by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, *combined) and treatment (TAK-881, HYQVIA).* The number of episodes of fever will be presented for episodes related to infections as well as for all episodes.

The duration of all infections, the duration of ASBIs, and the duration of episodes of fever will be summarized descriptively by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, *combined) and treatment (TAK-881, HYQVIA).* The duration of episodes of fever will be presented for episodes related to infections as well as for all episodes. Descriptive statistics will include n, mean, SD, median, minimum, and maximum.

The time to first ASBI will be summarized descriptively by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, *combined) and treatment (TAK-881, HYQVIA) for subjects with at least one ASBI in the corresponding treatment epoch.* Descriptive statistics will include n, mean, SD, median, minimum, and maximum.

All infection data will be presented in a subject data listing including the number of events, the length of the observational period, and the rate of events per year calculated as (365.2425 / length of observational period in days × number of events).

6.5.3 Other Analyses

Subjects aged ≥16 years: Serial PK of total IgG levels in g/L for subjects aged ≥16 years will be summarized by infusion interval (3-week, 4-week), serial PK time point (see Section 2.0), and treatment (TAK-881, HYQVIA) using the following descriptive statistics: n, mean, SD, median, minimum, maximum, geometric mean and two-sided 95% CI.

Serial PK of total IgG levels in g/L will be also presented graphically by individual subject plots with a line connecting total IgG levels at different time points. In addition, geometric means and two-sided 95% CIs of serial PK of total IgG measurements at different time points will be

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presented graphically by infusion interval (3-week, 4-week). The plots will be color marked and superimposed by treatment (TAK-881, HYQVIA) and will be presented on linear-linear and log-linear scale.

All total IgG measurements of serial PK will be presented in a subject data listing.

Subjects aged 2 to <16 years: Sparse PK of total IgG levels in g/L for subjects aged 2 to <16 years will be summarized by infusion interval (3-week, 4-week) and sparse PK time point (see Section 2.0) using the following descriptive statistics: n, mean, SD, median, minimum, maximum, geometric mean, two-sided 95% CI.

Geometric means and two-sided 95% CIs of sparse PK of total IgG measurements at different time points will be presented graphically by infusion interval (3-week, 4-week). The plots will be presented on linear-linear and log-linear scale.

All total IgG measurements of sparse PK will be presented in a subject data listing.

6.6 Safety Analysis

Safety analyses will be presented for the SAS.

6.6.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA version 25.1 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; 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.

A treatment-emergent adverse event (TEAE) is defined as any AE that started at or after the start of the first IP administration. The first administration of IP refers to the first ramp-up dose if ramp-up is applicable, or to the first full dose at Week 1 if ramp-up is not applicable. The observational period for each subject will include the transition period between the EOS visit and the first dose in the long-term follow-up Study TAK-881-3002, if applicable. If the 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.

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A temporally associated TEAE is defined as any TEAE that started between the start of the most recent IP administration and 72 hours after completion of the most recent IP administration, irrespective of being related or not related to TAK-881/HYQVIA.

The relationship to IP will be used as reported in the CRF (non-related/related). If the 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 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.*

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

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

The number and percentage of subjects with TEAEs, the number of TEAEs, and the number of TEAEs per infusion will be summarized by treatment (TAK-881, HYQVIA, combined) using the following categories:

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- *Any TEAE.*
- *TEAEs considered related* and not-related *to TAK-881/HYQVIA.*
- *Serious TEAEs*, related serious TEAEs, and not-related serious TEAEs.
- Non-serious TEAEs, related non-serious TEAEs, and not-related non-serious TEAEs
- *Local TEAEs,* related local TEAEs, and not-related local TEAEs.
- *Systemic TEAEs,* related systemic TEAEs, and not-related 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).*

The summary will be presented including and excluding infections, and by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18

to <65 years, ≥65 years, *combined), by infusion interval (3-week, 4-week, combined), and by prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined).*

The number of TEAEs per infusion will be calculated as the number of TEAEs divided by the number of infusions. The assignment of TEAEs to treatment (TAK-881, HYQVIA) will be based on the most recent treatment administered. TEAEs will be classified into infections and non-infections using SOC.

In addition, the number and percentage of subjects with TEAEs, the number of TEAEs, and the number of TEAEs per infusion will be summarized for each treatment (TAK-881, HYQVIA, combined) by age group(2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, *combined), SOC and PT* using the following categories:

- any TEAE.
- serious TEAEs.
- TEAEs considered related to TAK-881/HYQVIA.
- 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 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 (TAK-881, HYQVIA, combined) and age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, combined) by SOC, PT, severity grade (grade 1/grade 2/grade 3/grade 4 and 5 combined), and relationship to TAK-881/HYQVIA (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.

In addition, the number and percentage of subjects with frequently occurring (>5% for any treatment) non-serious TEAEs, the number of frequently occurring non-serious TEAEs, and the number of frequently occurring non-serious TEAEs per infusion will be summarized for each treatment (TAK-881, HYQVIA, combined) by PT (sorted in descending frequency using total occurrence).

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All AEs (TEAEs and non-TEAEs) will be presented in a subject data listing including the relationship and severity assessment as well as the duration and the time since the most recent IP administration.

Note that clinically significant treatment-emergent changes in clinical laboratory measurements and vital signs will be recorded in the study database as TEAEs.

6.6.2 Adverse Events of Special Interest

Adverse events of special interest (allergy, catheter leakage, and thromboembolic events) will be included in the TEAE summary as defined in Section 6.6.1.

6.6.3 Other Safety Analysis

6.6.3.1 Tolerability

The number and percentage of subjects with infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881/HYQVIA-related TEAEs as well as the number of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881/HYQVIA-related TEAEs and the number of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881/HYQVIA-related TEAEs per infusion *for each treatment (TAK-881, HYQVIA) will be presented by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years,* 18 to <65 years, ≥65 years, *combined), by infusion interval (3-week, 4-week, combined), and by prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined). If more than 1 intervention is made to a particular infusion, the final intervention will be considered for the endpoint.*

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For the analysis, interventions related to the infusion of rHuPH20 / IgG will be considered.

The number of events per infusion will be calculated as the number of events divided by the number of applied infusions.

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

6.6.3.2 Immunogenicity

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 age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, *combined), by infusion interval (3-week, 4-week, combined), and by prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined).*

In addition, binding antibody to rHuPH20 (defined as titer ≥1:160) and neutralizing antibody to rHuPH20 will be also summarized by study visit. Summaries for subjects aged ⩾16 years will be presented by infusion interval (3-week, 4-week, combined), study visit, and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881). Summaries for subjects aged 2 to <16

years will be presented by infusion interval (3-week, 4-week, combined), study visit, and age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years).

Subject with any positive binding antibody to rHuPH20 (defined as titer ⩾1:160) at any time point will be graphically displayed [x-axis: Study Day starting with screening visit, y-axis: reciprocal antibody titer, z-axis: IgG dose (g) – with different annotations for TAK-881 and HYQVIA)]. A similar graph will be created for any positive neutralizing antibody to rHuPH20 at any time point.

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

6.6.3.3 Clinical Laboratory Parameters

Standardized international (SI) units will be presented together with each clinical laboratory parameter.

Quantitative clinical laboratory parameters and their change from baseline for subjects aged ≥16 years will be summarized by infusion interval (3-week, 4-week, combined), study visit, and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881) using descriptive statistics n, mean, SD, median, minimum, and maximum. For subjects aged 2 to <16, descriptive statistics will be presented by infusion interval (3-week, 4-week, combined) and study visit. 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 analogously using the number and percentage of subjects in each category.

In addition, shift-from-baseline for subjects aged ≥16 years will be summarized by the number and percentage of subjects and will be presented by infusion interval (3-week, 4-week, combined), study visit, and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881) for each clinical laboratory parameter that has a reference range to assess normality/abnormality, using the following categories:

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Continuous data:

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

Categorical data – will use the categorized values, e.g.:

- normal
- abnormal
- missing

- total

For subjects aged 2 to <16, the number and percentage of subjects will be presented by infusion interval (3-week, 4-week, combined) and study visit.

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".

All clinical laboratory data will be presented in a subject data listing. Abnormal clinical laboratory parameters outside the reference range will be flagged.

6.6.3.4 Vital Signs

Vital signs, their percentage change from baseline, and their percentage change from pre-infusion vital signs at the same visit for subjects aged ≥16 years will be summarized by infusion interval (3-week, 4-week, combined), study visit, assessment time point, and treatment (TAK-881, HYQVIA) using descriptive statistics n, mean, SD, median, minimum, and maximum. For subjects aged 2 to <16, descriptive statistics will be presented by infusion interval (3-week, 4-week), study visit, and assessment time point. 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. Percentage change from pre-infusion vital signs at the same visit will be calculated as (value at post-infusion time point – value at pre-infusion time point) / (value at pre-infusion time point) × 100 and will be presented for post-infusion time points only.

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

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6.6.3.5 Physical examination

No listing or statistical summary is planned.

6.6.3.6 Pregnancy

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

6.6.4 Extent of IgG Exposure and Compliance

Descriptive summaries for the following IgG exposure parameters (including ramp-up epoch) will be presented by infusion interval (3-week, 4-week, combined), age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, combined), and treatment (TAK-881, HYQVIA):

- The total number of IgG infusions including ramp-up infusions in spring and summer (spring: March to May, summer: June to August), fall and winter (fall: September to November, winter: December to February), and combined.

- The total time on IgG treatment (months and years) including ramp-up period in spring and summer (spring: March to May, summer: June to August), fall and winter (fall: September to November, winter: December to February), and combined.
- The time on IgG treatment per subject (months) including ramp-up period will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum.
- The ramp-up 1 and 2 doses for IgG (grams) will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum.
- The average full dose for IgG (grams) will be calculated per subject and will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum.
- The average body weight adjusted full dose for IgG (grams/kg BW) will be calculated per subject and will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum. Body weight adjusted full dose for IgG is defined as full dose for IgG (grams) divided by body weight (kg) at the same study visit.
- The average body weight adjusted weekly full dose for IgG (grams/kg BW/week) will be calculated per subject and will be summarized using descriptive statistics n, mean, SD, median, minimum, and maximum. Body weight adjusted weekly full dose for IgG is defined as body weight adjusted full dose for IgG (grams/kg BW) divided by the infusion interval (3 or 4 weeks).
- The number and percentage of subjects changing the number of infusion sites for full dose infusions (i.e. excluding ramp-up infusions).
- The number and percentage of subjects with a dose adjustment due to change in body weight, due to the discretion of the investigator, and due to other reason. Percentages will be based on the number of subjects who received any amount of IP.

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

Descriptive summaries for the following compliance parameters (including ramp-up epoch) will be presented by infusion interval (3-week, 4-week, combined), age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, combined) and treatment (TAK-881, HYQVIA):

- The number and percentage of infusions administered according to the randomization scheme (subjects ≥16 years only).
- The number and percentage of infusions with administered IgG (grams) doses within 10% of planned doses.
- The number and percentage of infusions administered within the protocol specified infusion windows.

All compliance data will be provided in a subject data listing.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

See Section 6.5.

6.7.2 Pharmacodynamic Analysis

Not Applicable.

6.7.3 Biomarker Analysis

Not Applicable.

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

6.8.1 PRO Analysis

PRO analyses will be presented for the SAS and the subset of subjects who completed the semi-structured qualitative interviews.

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6.8.1.1 Treatment Satisfaction Questionnaire for Medication - 9 Items (TSQM-9)

Subject satisfaction with TAK-881/HYQVIA treatment will be assessed by the TSQM-9 in subjects aged ≥16 years. The TSQM-9 is a reliable and validated 9-item questionnaire designed to measure satisfaction with medication across 3 domains: effectiveness, convenience, and global satisfaction.

TSQM-9 items are shown in Section 9.4. The number and percentage of subjects in each response category (1 to 5 or 7 where 1 is the worst response category) will be presented for each item by infusion interval (3-week, 4-week), study visit, and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881). In addition, the number and percentage of subjects in each response category will be also summarized by treatment (TAK-881, HYQVIA) in a separate table.

The TSQM-9 will be analyzed based on the developer instructions to obtain the scores for each domain:

Effectiveness:

- If there is no missing response for items 1 to 3, then the effectiveness score is computed as: [(TSQM01 + TSQM02 + TSQM03) – 3] / 18 × 100.
- If there is one missing response for items 1 to 3, then the effectiveness score is computed as: [(TSQM01 + TSQM02 + TSQM03) – 2] / 12 × 100.
- If there is more than one response missing for items 1 to 3, then the effectiveness score is missing.

Convenience:

- If there is no missing response for items 4 to 6, then the convenience score is computed as: [(TSQM04 + TSQM05 + TSQM06) – 3] / 18 × 100.

- If there is one missing response for items 4 to 6, then the convenience score is computed as: [(TSQM04 + TSQM05 + TSQM06) – 2] / 12 × 100.
- If there is more than one response missing for items 4 to 6, then the convenience score is missing.

Global satisfaction:

- If there is no missing response for items 7 to 9, then the global satisfaction score is computed as: [(TSQM07 + TSQM08 + TSQM09) – 3] / 14 × 100.
- If there is one missing response for item 7 or 8 but item 9 is not missing, then the global satisfaction score is computed as: [(TSQM07 + TSQM08 + TSQM09) – 2] / 10 × 100.
- If there is one missing response for item 9 but items 7 and 8 are not missing, then the global satisfaction score is computed as: [(TSQM07 + TSQM08 + TSQM09) – 2] / 8 × 100.
- If there is more than one response missing for items 7 to 9, then the global satisfaction score is missing.

Domain scores range between 0 to 100, whereby higher scores represent better treatment satisfaction. Missing responses will be treated as zero for the calculation of domain scores. Domain scores will be summarized by infusion interval (3-week, 4-week, combined), study visit, and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881) for subjects ≥16 years and subjects ≥18 years using descriptive statistics n, mean and corresponding 95% CI, SD, median, minimum, and maximum. In addition, descriptive statistics for domain scores will be summarized by treatment (TAK-881, HYQVIA) as well as by prestudy IgG treatment (HYQVIA, IGIV, cIGSC) for subjects ≥16 years and subjects ≥18 years in a separate table.

All TSQM-9 data will be presented in a subject data listing.

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6.8.1.2 EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

The EQ-5D-5L will be used to assess subject HRQoL in subjects aged ≥12 years*. The EQ-5D-5L is a validated, self-administered assessment of overall health designed by the EuroQol Group. It is a descriptive system of HRQoL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).*

For subjects aged ≥16 years, the number and percentage of subjects in each response category (1 to 5 where 1 is the best response category) will be presented for each question by infusion interval (3-week, 4-week, combined), study visit, and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by TAK-881). For subjects aged 12 to <16 years, the number and percentage of subjects in each response category will be presented for each question by infusion interval (3-week, 4-week) and study visit.

The visual analogue scale (VAS) ranges between 0 to 100, whereby higher scores represent better health state. For subjects aged ≥16 years, the VAS as well as the change from baseline will be summarized by infusion interval (3-week, 4-week, combined), study visit, prestudy IgG treatment (HYQVIA, IGIV, cIGSC) and sequence (TAK-881 followed by HYQVIA, HYQVIA followed by

TAK-881) using descriptive statistics n, mean and corresponding 95% CI, SD, median, minimum, and maximum. For subjects aged 12 to <16 years, descriptive statistics will be presented by infusion interval (3-week, 4-week, combined), prestudy IgG treatment (HYQVIA, IGIV, cIGSC) and study visit.

All EQ-5D-5L data will be presented in a subject data listing.

6.8.2 Health Care Utilization Analysis

The observational period for each subject will start with the first administration of IP referring to the first ramp-up dose, if ramp-up is applicable, or to the first full dose at Week 1, if ramp-up is not applicable, and will include the transition period between the EOS visit and the first dose in the long-term follow-up Study TAK-881-3002 for subjects rolling over, if applicable.

The number and percentage of subjects with at least one day not able to go to school, work, daycare or to perform normal daily activities and the number of days not able to go to school, work, daycare or to perform normal daily activities will be presented by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined), treatment (TAK-881, HYQVIA), and reason (infections and/or their treatment, other illnesses, combined). In addition, days not able to go to school, work, daycare or to perform normal daily activities per patient year will be summarized descriptively by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined), treatment (TAK-881, HYQVIA), and reason (infections and/or their treatment, other illnesses, combined). If both, "infections and/or their treatment" and "other illnesses" are selected as reason, the reason is considered as "infections and/or their treatment".

The number and percentage of subjects with at least one day on antibiotics and the number of days on antibiotics will be presented by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined) and treatment (TAK-881, HYQVIA). In addition, days on antibiotics per patient year, days on antibiotics per patient, courses on antibiotics per patient, and the duration of courses on antibiotics will be summarized descriptively by age group (2 to <6 years, 6 to <12◦years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined) and treatment (TAK-881, HYQVIA). Summaries regarding number and percentage of subjects with at least one day on antibiotics *will be presented for antibiotics* used for *prophylaxis and treatment of infection separately as well as for all antibiotics combined.* Summaries regarding days, courses and duration of courses on antibiotics will be only presented for antibiotics that were given for treatment of an infection.

For all analyses regarding antibiotics, 1) oral, parenteral, or oral plus parenteral antibiotics and 2) all antibiotics will be taken into account.

The number and percentage of subjects with at least one hospitalization and the number of hospitalizations will be presented by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined), treatment (TAK-881, HYQVIA), and reason (infection, other illnesses, combined). In addition, days hospitalized per patient year and duration of hospitalization will be summarized descriptively by age group (2 to <6 years, 6 to

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<12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined), treatment (TAK-881, HYQVIA), and reason (infection, other illnesses, combined).

The number and percentage of subjects with at least one acute physician visit and the number of acute physician visits will be presented by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined), treatment (TAK-881, HYQVIA), and reason (infection, other illnesses, combined). In addition, the number of acute physician visits per patient year will be summarized descriptively by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, combined), treatment (TAK-881, HYQVIA), and reason (infection, other illnesses, combined). If both, "infection" and "other illnesses" are selected as reason, the reason is considered as "infection".

Other illnesses refer to non-infections. The rate of days/events per year will be calculated as (365.2425 / length of observational period in days × number of days or events). Descriptive statistics will include n, mean, SD, median, minimum, and maximum.

All HRU data will be presented in a subject data listing including the number of days/events, the length of the observational period, and the rate of days/events per year.

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6.9 Other Analyses

Other Analyses will be presented for the SAS and the subset of subjects who completed the semi-structured qualitative interviews.

6.9.1 Infusion Parameters at Full Dose

Descriptive summaries for the following infusion parameters at full dose will be presented by age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 2 to <16 years, ≥16 years, 2 to <18 years, ≥18 years, 18 to <65 years, ≥65 years, *combined)*, prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined), *and treatment (TAK-881, HYQVIA):*

- *Average number of infusions per month will be calculated as the total number of infusions divided by the total time in months on treatment.*
- *Average number of infusion sites (needle sticks) per month will be calculated as the total number of infusion sites divided by the total time in months on treatment.*
- *Average number of infusion sites (needle sticks) per infusion will be calculated as the total number of infusion sites divided by the total number of infusions.*
- 1st *Duration of infusions (minutes) is defined as time from the start of rHuPH20 infusion until the stop time of IgG infusion (including the time to complete flushing). The average 1st duration of infusions per subject will be summarized using descriptive statistics* (n, mean, SD, median, minimum, and maximum) and by infusion interval (3-week, 4-week, combined).
- 2nd Duration of infusions (minutes) – excluding of breaks between the different steps of IgG infusion - first, the following will be calculated:

- ❖ rHuPH20: Stop time of rHuPH20 – start time of rHuPH20: <dur_ph20>
- ❖ IgG: Sum of all individual duration steps (i.e. actual IgG infusion duration without any interruptions: <dur_igg>
- ❖ Start time of IgG – Stop time of rHuPH20 (i.e. break between rHuPH20 and IgG due to clinical practice): <dur_break>
- ❖ Duration of all interruptions (i.e. all duration interruptions independent of reason of interruption): <dur_interrupt>

→2nd Duration of infusions = <dur_ph20> + <dur_igg> + <dur_break> + <dur_interrupt>

The average 2nd duration of infusions per subject will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) and by infusion interval (3-week, 4-week, combined).

- *Average monthly infusion time (minutes/month) will be calculated per subject as total duration of infusions* (using "1st duration of infusions" and "2nd duration of infusions") *divided by the total time in months on treatment and will be summarized using descriptive statistics* (n, mean, SD, median, minimum, and maximum).
- *Maximum* tolerated *infusion rate per site (mL/hour/site) will be summarized using the following descriptive statistics: n, minimum, median, and maximum across infusions and subjects.* Maximum tolerated infusion rate will be presented for rHuPH20 and IgG.
- *Infusion volume per site (mL/site) as well as total infusion volume (mL) will be summarized using descriptive statistics* (n, mean, SD, median, minimum, and maximum) *for the average infusion volume per subject.* Infusion volume will be presented for rHuPH20 and IgG.
- The number and percentage of infusions per needle length (6, 9, 12 and 14 mm) will be presented.
- The number and percentage of infusions per IgG infusion step time interval [1) all steps using 5 minutes, 2) all steps using 10 minutes, 3) all steps using 15 minutes and 4) mixture of durations across all steps] will be presented. Definition of all steps: All steps except the last step before the flushing step and the flushing step. Infusions with any intervention during IgG infusion (infusion withdrawals, interruptions, or infusion rate reductions) irrespective of the reason will be excluded.
- The number and percentage of infusions per number of IgG infusion rate escalation steps (1, 2, 3, 4, and 5) will be presented. Infusions with infusion rate reductions or infusion withdrawals during IgG infusion irrespective of the reason will be excluded. The flushing step is not considered as a rate escalation step.

In addition, the average duration of infusions (using "1st duration of infusions" and "2nd duration of infusions") *and the average monthly infusion time* (using "1st duration of infusions" and "2nd duration of infusions") *will be presented by* prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined) and *treatment (TAK-881, HYQVIA) for the following subgroups:*

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- *All subjects.*
- *Subjects aged 2 to <16 years with 1 infusion site with all TAK-881 infusions.*
- *Subjects aged 2 to <16 years with 2 infusion sites with all TAK-881 infusions.*
- *Subjects aged ≥16 years with 1 infusion site with all TAK-881 and HYQVIA infusions.*
- *Subjects aged ≥16 years with 2 infusion sites with all TAK-881 and HYQVIA infusions.*
- *Subjects aged ≥16 years with 2 infusion sites with all HYQVIA and 1 infusion site with all TAK-881 infusions.*
- *Subjects aged ≥16 years with 1 infusion site with all HYQVIA and 2 infusion sites with all TAK-881 infusions.*

The following descriptive statistics will be used: n, mean, SD, median, minimum, and maximum.

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

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6.9.2 Infusion Preparation Time

The duration of the time it takes to prepare TAK-881 and HYQVIA for infusion will be recorded by a nurse/pharmacist for subjects ≥16 years. Seven time points will be recorded:

1. *The time at which the DVUs of TAK-881/HYQVIA are removed from refrigeration.*
2. *The time at which the preparation of the rHuPH20 component into a syringe begins.*
3. *The time at which the preparation of the rHuPH20 component is completed.*
4. *The time at which the preparation of the IGI, 10% or IGSC, 20% component begins.*
5. *The time when the preparation of the IgG component is completed.*
6. *The time at which needle insertion occurs.*
7. *The time the infusion of rHuPH20 is started.*

The duration between time points in minutes (between 1 and 2, between 2 and 3, between 3 and 4, between 4 and 5, between 5 and 6, between 6 and 7, between 1 and 7) will be summarized by infusion preparer (nurse, pharmacist, combined), by infusion interval (3-week, 4-week), study visit, and treatment to be prepared (TAK-881, HYQVIA) using descriptive statistics n, mean, SD, median, minimum, and maximum. These statistics will be provided separately for each administration method (with pooling bag, direct from vial).

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

6.9.3 Semi-Structured Qualitative Interview

A qualitative analysis plan (QAP) will be prepared and finalized to describe the planned elements to be included in the exit interviews.

No listing or statistical summary is planned.

6.10 Interim Analyses

One or two formal analyses will be performed depending on the enrollment status of subjects aged 2 to <16 at the time when all subjects aged ≥16 years completed participation in the study:

1. *Two formal analyses are planned for this study, if not all subjects aged 2 to <16 years have completed the Week 13 visit (or discontinued prematurely from the study) at the time when all subjects aged ≥16 years have completed participation in the study:*

    - *An administrative interim analysis will be performed after all subjects aged ≥16 years have completed participation in the study (ie, after all subjects aged ≥16 years have completed both AB/BA crossover treatment epochs or discontinued prematurely from the study, irrespective of reason for withdrawal). All data for subjects aged ≥16 years will be frozen and analyzed as preplanned in the SAP. This analysis will be considered the final analysis of data for subjects aged ≥16 years. No multiplicity adjustment will be performed as the administrative interim analysis will include all data for all subjects aged ≥16 years who have completed participation in the study.* The analysis has no impact on further study conduct.

    - *A final statistical analysis will be performed after all subjects aged 2 to <16 years have completed participation in the study (ie, after all subjects aged 2 to <16 years have completed the single-arm treatment epoch, or discontinued prematurely from the study, irrespective of reason for withdrawal). This analysis will contain all data for subjects aged 2 to <16 years and will be considered the final analysis of data for subjects aged 2 to <16 years.*

2. *One formal analysis is planned for this study, if all subjects aged 2 to <16 years have already completed the Week 13 visit (or discontinued prematurely from the study) at the time when all subjects aged ≥16 years have completed participation in the study:*

    - *A final statistical analysis will be performed after all subjects aged ≥16 years as well as all subjects aged 2 to <16 years have completed participation in the study or discontinued prematurely from the study, irrespective of reason for withdrawal.*

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6.11 Data Monitoring Committee

A DMC has been appointed for this study. The DMC is a group of independent scientists and/or physicians who are appointed to make recommendations to the sponsor based on the criteria defined in the DMC charter. The enrollment of subjects aged 2 to <16 years for all sites will begin based on recommendation of a DMC after acceptable safety and tolerability have been demonstrated in ≥4 subjects aged ≥16 years who have received all TAK-881 doses (ie, 6 or 8 doses of TAK-881 based on a 4- or 3-week dosing regimen, respectively).

Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of the first IP.

7.0 REFERENCES

FDA. 2008. Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency [Online]. Available: https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/safety-efficacy-and-pharmacokineticstudies-support-marketing-immune-globulin-intravenous-human.

U.S. Department of Health and Human Services. 2017. Common terminology criteria for adverse events (CTCAE), Version 5.0, published Nov 27, 2017. [Online]. Available: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

A) Two additional age groups (18 to <65 years, ≥65 years) were added for the following analyses to evaluate a distinct safety profile for adults and elderly subjects:

- Demographics (Section 6.3.1)
- Baseline Characteristics (Section 6.3.3)
- Infections, ASBIs, and fever episodes (Section 6.5.2.2)
- Adverse Events (Section 6.6.1)
- Tolerability (Section 6.6.3.1)
- Immunogenicity (Section 6.6.3.2)
- Extent of Exposure and Compliance (Section 6.6.4)
- Infusion Parameters at Full Dose (Section 6.9.1)

B) Analyses regarding antibiotics:

- Analyses regarding oral, parenteral or oral plus parenteral antibiotics were added (Section 6.8.2).
- Summaries regarding days, courses and duration of courses on antibiotics will be only presented for antibiotics that were given for treatment of an infection (Section 6.8.2).

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9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Modifications from the earlier version of the SAP that affect the planned statistical analysis methods are outlined below. Additionally, minor changes to improve readability and clarity, which have no substantial effect on the planned statistical analyses, are omitted from the table below.

Changes From Versions	SAP Section	Change	Rationale for Change
Change from SAP v1 to v2	1.1	Secondary objectives were added to assess infections, to assess healthcare resource utilization (HRU), and to characterize the PK of TAK-881 between subjects aged ≥16 years and subjects aged 2 to <16 years with PIDD.	Protocol amendment 2 and 3.
Change from SAP v1 to v2	1.2	Secondary endpoints for infections and HRU were added	Protocol amendment 2 and 3.
Change from SAP v1 to v2	2.0	The ramp-up epoch was revised to include two ramp-up doses. The treatment epochs were extended to 8 full doses for 3-week interval and 6 full doses for 4-week interval. Sparse PK sampling and randomization to sparse PK sampling time points for subjects aged 2 to <16 years was added.	Protocol amendment 2 and 3.
Change from SAP v1 to v2	4.0	Sample size for subjects aged ≥16 years was increased from 30 to 38 subjects to be randomized and treated.	Protocol amendment 2 and 3.
Change from SAP v1 to v2	6.5.2.2	Analysis for infection endpoints was added.	Protocol amendment 2 and 3.
Change from SAP v1 to v2	6.5.3	Analysis for sparse PK of total IgG levels for subjects aged 2 to <16 years was added.	Protocol amendment 2 and 3.
Change from SAP v1 to v2	6.8.1	Pain intensity numeric rating scale was deleted.	Protocol amendment 2 and 3.
Change from SAP v1 to v2	6.8.2	Analysis for HRU endpoints was added.	Protocol amendment 2 and 3.

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Changes From Versions	SAP Section	Change	Rationale for Change
Change from SAP v1 to v2	6.11	The start of enrollment of subjects aged 2 to <16 years was postponed after acceptable safety and tolerability have been demonstrated in ≥4 subjects aged ≥16 years who have received all TAK 881 doses.	Protocol amendment 2 and 3.
Change from SAP v2 to v3	Throughout document	Updates throughout the document to align with changes in protocol amendment 5 – major updates: 1) Updates in secondary endpoints due to adding more clarity & trough levels of antigen-specific IgG antibodies only to be measured for subjects ≥16 years (Section 1.2.2) 2) Addition of conventional subcutaneous IgG as prestudy IgG (Section 2.0) 3) Increase of expected screen failure rate from 20% to 25% (Section 2.0) 4) Changes in allowed visit windows (Section 5.3 and 9.2.3)	Protocol amendment 4 and 5.
Change from SAP v2 to v3	6.3.1 6.3.3 6.5.2.2 6.6.1 6.6.3.1 6.6.3.2 6.6.4	Additional age group (≥65 years) was added for the following analyses: 1) Demographics (Section 6.3.1) 2) Baseline Characteristics (Section 6.3.3) 3) Infections, ASBIs, and fever episodes (Section 6.5.2.2) 4) Adverse Events (Section 6.6.1) 5) Tolerability (Section 6.6.3.1) 6) Immunogenicity (Section 6.6.3.2) 7) Extent of Exposure and Compliance (Section 6.6.4)	Get safety profile for elderly subjects.
Change from SAP v2 to v3	6.8.1	Addition of "Patient Reported Outcomes" analysis by prestudy IgG treatment	Understand whether treatment satisfaction and quality of life may be impacted differentially by pre-treatment IG
Change from SAP v2 to v3	6.9.1	Addition of a second option for calculation of infusion duration	Breaks between the different rate steps should be excluded with the second option
Change from SAP v3 to v4	6.9.1	Additional age group (≥65 years) was added for the infusion parameters at full dose	Get safety profile for elderly subjects.

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Changes From Versions	SAP Section	Change	Rationale for Change
Change from SAP v3 to v4	6.6.3.2 6.6.3.3 6.8.1	The immunogenicity. clinical laboratory and patient reported outcome data will be analyzed by sequence rather than by last treatment prior to the assessment.	Sequence-based analysis accounts for influences carried over from earlier treatments.
Change from SAP v3 to v4	6.8.2	For the analyses regarding antibiotics, analyses regarding oral, parenteral,or oral plus parenteral antibiotics were added. Summaries regarding days, courses and duration of courses on antibiotics will be only presented for antibiotics that were given for treatment of an infection.	To further define antibiotics based on the FDA Guidance on IG development in PID. This definition excludes local antibiotics. Certain prophylactic antibiotics were permitted in the study and those are often used long-term, continuously and not in courses in PID.
Change from SAP v3 to v4	6.8.1	For the visual analogue scale, change from baseline calculation was added. For the score of visual analogue scale and TSQM-9 scores, 95% CIs were added.	Account for difference in starting PRO value, also quantify the confidence of PRO values at each measurement.
Change from SAP v4 to v5	6.3.1 6.3.3 6.5.2.2 6.6.1 6.6.3.1 6.6.3.2 6.6.4	Additional age group (18 to <65 years) was added for the following analyses: 1) Demographics (Section 6.3.1) 2) Baseline Characteristics (Section 6.3.3) 3) Infections, ASBIs, and fever episodes (Section 6.5.2.2) 4) Adverse Events (Section 6.6.1) 5) Tolerability (Section 6.6.3.1) 6) Immunogenicity (Section 6.6.3.2) 7) Extent of Exposure and Compliance (Section 6.6.4)	Get safety profile for adult subjects.
Change from SAP v4 to v5	6.5.1.2	Updated the SAS code for the linear mixed effects models to clarify the method for determining the degrees of freedom, i.e. “Satterthwaite”.	In accordance with Appendix E of the guidance “*Statistical Approaches to Establishing Bioequivalence*” the “Satterthwaite” method will be applied to determine the degrees of freedom in the linear mixed effects model.
Change from SAP v4 to v5	6.5.3	The flag denoting anomalous concentrations for total IgG measurements has been omitted from the listing.	The SAP has been revised to ensure alignment with the CPAP due to the removal of

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Changes From Versions	SAP Section	Change	Rationale for Change
			handling anomalous concentrations from the CPAP (version 2.0, dated 28 Aug 2025, section 4.2).
Change from SAP v4 to v5	6.5	Outlined the process for dealing with unreliable PK parameters.	The SAP has been revised to ensure alignment with the CPAP as a result of adding the definition and handling of unreliable AUC0-τ,ss in the CPAP (version 2.0, dated 28 Aug 2025, section 4.2).
Change from SAP v4 to v5	5.3	Clarified that for the pharmacokinetic per-protocol analysis set (PKPPAS) in subjects aged ⩾16 years, individuals who receive their infusion within ±3 days of the scheduled date at specified visits are eligible for inclusion in the PKPPAS provided that no other protocol deviations that may impact the reliability of the total IgG level time profiles at steady state (as outlined in the PKPPAS definition) are present.	Subjects who receive their infusion within three days before or after the scheduled date at the following specified visits, Ramp-up 1 Visit, Ramp-up 2 Visit, Week 25 Visit – where such deviations do not impact the reliability of total IgG level time profiles at steady state - are still eligible for inclusion in the PK Per-Protocol Set provided that no other protocol deviations, as outlined in section 5.3, are present [redacted]

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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.").

9.2.2 Definition of Baseline

Baseline is defined as the last non-missing value before the first administration of investigational product (IP). The first administration of IP refers to the first ramp-up dose if ramp-up is applicable, or to the first full dose at Week 1 if ramp-up is not applicable. The start date/time of IP administration refers to the start date/time of rHuPH20 administration. If two infusion sites are used, 50% of the total volume of rHuPH20 and IgG will be delivered into each infusion site simultaneously.

9.2.3 Definition of Visit Windows

Visits with IP administration have a visit window of either ±3 days or ±1 day. Deviations of >3 days for visits with IP administration will be considered as a missed dose and the subject will be discontinued from the study. The timing of all study visits is calculated using the last prestudy IgG infusion date as the reference date (not the date of the study visit previous to the one to schedule).

9.3 Analysis Software

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

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9.4 TSQM-9 items

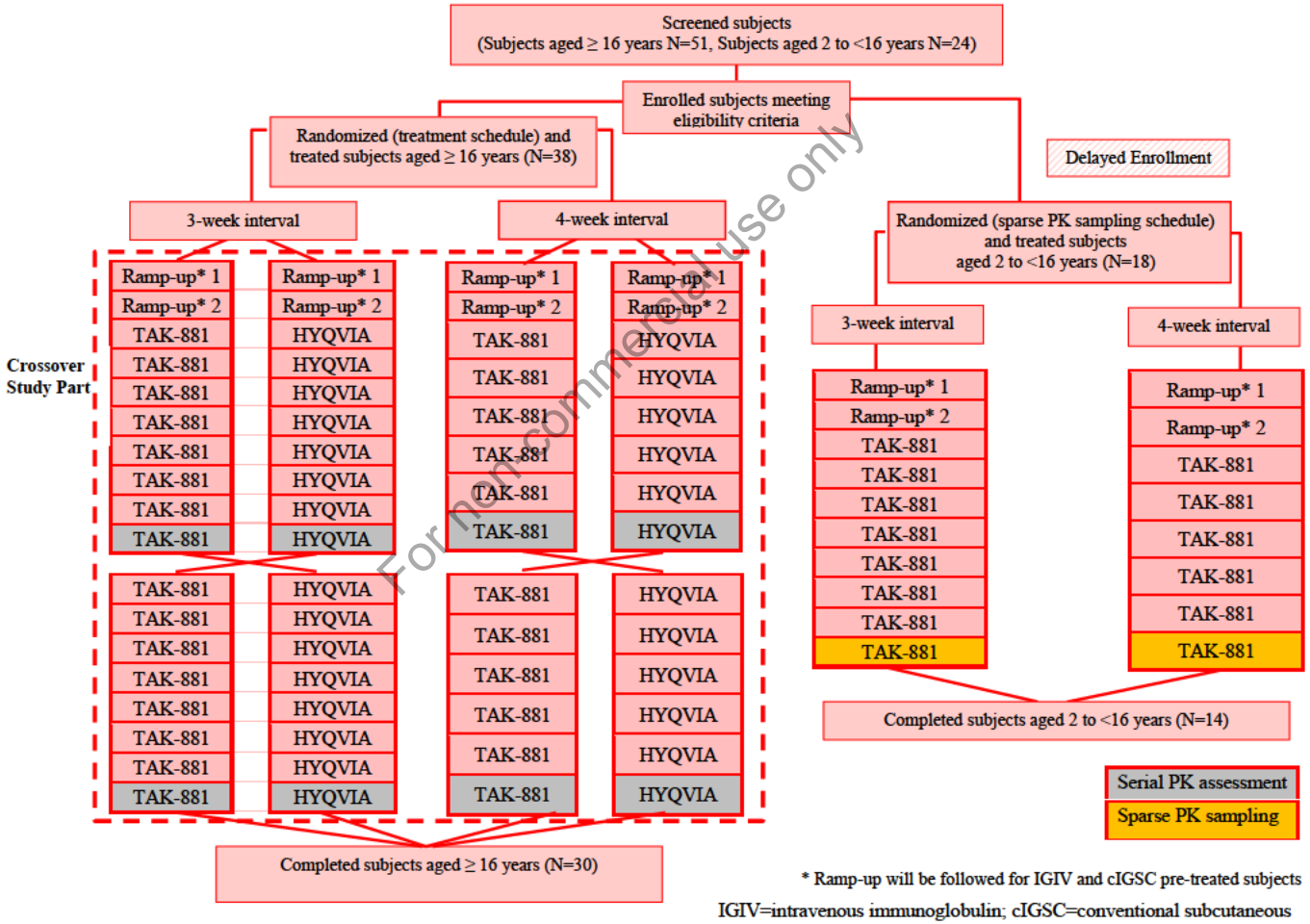
Table 1. TSQM-9 items

TSQM01	How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
TSQM02	How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
TSQM03	How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
TSQM04	How easy or difficult is it to use the medication in its current form?
TSQM05	How easy or difficult is it to plan when you will use the medication each time?
TSQM06	How convenient or inconvenient is it to take the medication as instructed?
TSQM07	Overall, how confident are you that taking this medication is a good thing for you?
TSQM08	How certain are you that the good things about your medication outweigh the bad things?
TSQM09	Taking all things into account, how satisfied or dissatisfied are you with this medication?

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9.5 Study Schema

Figure 1. Overall Study Design



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