Clinical Study Protocol

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: Amendment 5, 29 Jul 2024

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TAKEDA PHARMACEUTICALS

PROTOCOL: TAK-881-3001

Title:	Multicenter, Prospective, Open-label, Randomized, Crossover Study to Evaluate Pharmacokinetics (PK), Safety, and Tolerability of TAK-881 in Primary Immunodeficiency Diseases (PIDD)
Brief Title:	PK, Safety, and Tolerability of TAK-881 in PIDD
Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA
Study Number:	TAK-881-3001
Study Phase:	2/3
IND Number:	027372
Abbreviated EU CT Number:	2022-502095-23
Investigational Product:	Immune Globulin Subcutaneous (Human), 20% Solution (abbreviated as IGSC, 20%) with Recombinant Human Hyaluronidase (abbreviated as rHuPH20) (referred to as TAK-881) Immune Globulin Infusion (Human), 10% Solution (abbreviated as IGI, 10%) with rHuPH20 (referred to as HYQVIA/HyQvia)
Date:	29 July 2024 **Amendment Number:** Amendment 5

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Amendment History:

Date	Amendment Number	Region
29 September 2022	Original protocol	Global
30 January 2023	Amendment 1	Global
25 April 2023	Amendment 2	Global
28 June 2023	Amendment 3	Global
05 March 2024	Amendment 4	Global
29 July 2024	Amendment 5	Global

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APPROVALS

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual subjects in accordance with the following:

- The requirements of this study protocol.
- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) Good Clinical Practice.
- Regulation (EU) No 536/2014 of the European Parliament and of the Council.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES OF THE RESPONSIBLE TAKEDA MEDICAL OFFICER AND OTHER SIGNATORY(IES)

Electronic signatures of the following individuals are provided on the last page of this document.

PPD **MD** Clinical Lead, PPD Global Clinical Sciences/ Plasma-Derived Therapies Business Unit Date
PPD Statistician, PPD Plasma-Derived Therapies and Pharmacometrics, Statistical and Quantitative Sciences Date
PPD PPD Clinical Pharmacology and Early Clinical Development Plasma-Derived Therapies, Clinical and Translational Science Date

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INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the investigator's brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, life, dignity, integrity, confidentiality of personal information, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) as defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator as described in this protocol.

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I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a potential subject to obtain their informed consent to participate.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Summary of Changes Since the Last Version of the Approved Protocol	
Protocol Amendment 5	
Amendment Date: 29 July 2024	**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment The protocol was updated to address requests for information from the European Union Clinical Trial Regulation (EU CTR) submission.	

Description of Each Change and Rationale		Sections Affected by Change
#	**Description of Changes/Rationale for Changes**	**Section**
1	The term “parent(s)/legal guardian(s)” was changed to “legally designated representative” in accordance with EU CTR definitions and to clarify that consent will be obtained of legally designated representatives of minors.	Throughout the document
2	The phrasing of exclusion criterion #5 was rephrased for clarity.	Section 1.1, Section 5.2
3	The description of the timing of statistical analyses was rephrased to improve clarity. There are no changes to the planned analysis.	Section 1.1, Section 9.6

See Section 10.8 for the protocol history.

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ADMINISTRATIVE INFORMATION

CONTACTS

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in the Study Reference Manual and relevant guidelines provided to the site.

Takeda-sponsored investigators will be provided with emergency medical contact information cards to be carried by each subject, per individual country requirements.

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ADDITIONAL INFORMATION

The Study Reference Manual contains additional contact information for:

- Medical monitor, for medical advice on the protocol and the study intervention.
- Sponsor's responsible medical officer.
- Monitor assigned to the study site, for general advice on protocol procedures.
- Serious adverse event reporting.
- Special situation reporting (SSR).
- Pregnancy reporting.
- Product complaints.

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PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product (IP) quality complaints or nonmedical complaints to Takeda within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection, investigation and analysis.

A product quality complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product, device, or combination product after it is released for distribution. Examples of study intervention quality complaints include, but are not limited to, the following:

Unit issues	• Bottle/vial fill shortage or overage • Syringe/vial cracked/broken • Product discoloration	• Syringe leakage • Missing components • Device failure/malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing • Inadequate or faulty closure
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals	• Missing components within package
Foreign material	• Contaminated product • Particulate in packaging	• Particulate in bottle/vial

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Report product complaints using the form called “Clinical Trial Material Complaint Form.”

Send it to the following e-mail address:

ctmcomplaint@takeda.com

Please note that if an adverse event (AE) occurs as a result of a product quality issue, a separate AE reporting form must be completed, in addition to the complaint form.

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1. PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington, MA 02421 USA</td><td colspan="2">Compounds:
TAK-881 - Immune Globulin Subcutaneous (Human), 20% Solution (abbreviated as IGSC, 20%) with Recombinant Human Hyaluronidase (abbreviated as rHuPH20)
HYQVIA/HyQvia - Immune Globulin Infusion (Human), 10% Solution (abbreviated as IGI, 10%) with rHuPH20
(For better readability the names TAK-881 and HYQVIA will be used throughout the document)</td></tr>
<tr><td>Study Number:
TAK-881-3001</td><td>Phase:
2/3</td><td>IND No.:
027372</td><td>Abbreviated EU CT No.:
2022-502095-23</td></tr>
<tr><td colspan="4">Title of Protocol:
Multicenter, Prospective, Open-label, Randomized, Crossover Study to Evaluate Pharmacokinetics (PK), Safety, and Tolerability of TAK-881 in Primary Immunodeficiency Diseases (PIDD)</td></tr>
<tr><td colspan="4">Short title:
PK, Safety, and Tolerability of TAK-881 in PIDD</td></tr>
<tr><td colspan="4">Number of Subjects:
Overall:
• Number of subjects to be screened: anticipated 75.
• Number of subjects to be treated: at least 56.

Subjects aged ≥16 years (TAK-881[A]/HYQVIA[B] AB/BA crossover):
• Number of subjects to be screened: anticipated 51 (assuming 25% screen failure rate).
• Number of subjects to be randomized (treatment schedule) and treated: at least 38 (1:1 randomization; 19 per sequence).
• Number of completed and evaluable subjects: anticipated 30 (assuming 20% drop-out rate; 15 per sequence).

Subjects aged 2 to <16 years (TAK-881 only):
• Number of subjects to be screened: anticipated 24 (assuming 25% screen failure rate).
• Number of subjects to be randomized (sparse PK sampling schedule) and treated: at least 18.
• Number of completed subjects: anticipated 14 (assuming 20% drop-out rate).</td></tr>
<tr><td colspan="4">Investigator(s):
Multicenter study</td></tr>
<tr><td colspan="4">Sites and Regions:
Anticipated regions: United States of America (USA) and Europe
Estimated number of sites planned: Approximately 40</td></tr>
</table>

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Study Period (planned):

Initiation (First subject first visit): October 2023

Enrollment Period: approximately 30 months, from October 2023 to March 2026

Completion (Last subject last visit): approximately September 2026

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate PK comparability of TAK-881 and HYQVIA at steady-state after subcutaneous (SC) administration in subjects aged ≥16 years with PIDD.	• Area under the curve during the dosing interval at steady-state ($AUC_{0-\tau,ss}$) based on total immunoglobulin G (IgG) levels.
Secondary	
• To assess infections in all subjects.	<u>Efficacy</u> • 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.
• To assess healthcare resource utilization (HRU) for subjects using TAK-881/HYQVIA.	• 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.

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• To evaluate PK, safety, tolerability and immunogenicity of TAK-881 in subjects aged ≥16 years with PIDD.	Pharmacokinetics: • 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 and antigen-specific IgG antibodies. Safety: • Occurrence of treatment-emergent adverse events (TEAEs). Tolerability: • Occurrence of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881-related TEAEs. Immunogenicity: • Occurrence of positive binding (defined as titer ≥1:160) and neutralizing antibodies to rHuPH20.
• To characterize the PK of TAK-881 between subjects aged ≥16 years and subjects aged 2 to <16 years with PIDD.	• Pharmacokinetics at steady-state including $AUC_{0-\tau,ss,}$ C_{max}, T_{max}, $t_{1/2}$, CL/F, V_z/F and $AUC_{0-\tau,ss}$/week based on total IgG levels.
• 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.	Pharmacokinetics: • Trough level of total IgG. • Trough level of IgG subclasses. Safety: • Occurrence of TEAEs. Tolerability: • Occurrence of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881-related TEAEs. Immunogenicity: • Occurrence of positive binding (defined as titer ≥1:160) and neutralizing antibodies to rHuPH20.

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• To evaluate infusion parameters at full dose with both TAK-881 and HYQVIA in all subjects.	Infusion Parameters 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).

Estimands:

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 based on 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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Rationale:

TAK-881 is a drug product of IGSC (Human), 20% and rHuPH20 for facilitated SC administration that evolved from the currently licensed HYQVIA (Immune Globulin Infusion [IGI], 10% with rHuPH20) and CUVITRU (IGSC, 20%). Both HYQVIA and CUVITRU have well-established efficacy and safety profiles.

HYQVIA and CUVITRU use the same validated, and approved immunoglobulin manufacturing process except for the additional ultrafiltration step with CUVITRU to achieve the 20% concentration of the Ig component of TAK-881.

Similar to HYQVIA, TAK-881 is administered by sequential SC infusion of rHuPH20 first, followed by SC infusion of IgG. The ratio of rHuPH20 to IgG is the same as for HYQVIA, which is 80 units rHuPH20 per gram of IgG, but due to the higher IgG concentration of TAK-881 (20% IgG) in comparison to HYQVIA (10% IgG), the required infusion volume is reduced by 50% at an equivalent dose level. Following the phase 1 tolerability/safety study with TAK-881 in adult healthy subjects (Study TAK-881-1001), this registrational phase 2/3 study aims to assess the PK, safety, tolerability and immunogenicity of SC administration of TAK-881 compared to HYQVIA in PIDD subjects.

Study Intervention, Dose, and Mode of Administration:

TAK-881: IGSC, 20% (Human) with rHuPH20, **HYQVIA:** IGI, 10% (Human) with rHuPH20

Dosage Form: Solution for infusion

Route of Administration: SC

Dosage Frequency: Study treatment will be administered every 3 or 4 weeks during the study (with the exception of the initial ramp-up epoch, when applicable).

The first study treatment will be administered 1, 2, 3, or 4 weeks after the last prestudy IgG dose, depending on the prestudy IgG treatment interval within the 12 weeks prior to screening. Subjects previously treated with non-HYQVIA/conventional subcutaneous IgG (cIGSC) or intravenous IgG (IGIV) within 12 weeks prior to screening will undergo a ramp-up epoch. For these subjects, the first study infusion, 1-week dose of TAK-881/HYQVIA, will be administered at the first ramp-up visit, 1 or 2 weeks after the last prestudy cIGSC, or 3 or 4 weeks after the last prestudy IGIV dose, depending on the prestudy IgG treatment interval. One week later, these subjects will receive a 2-week dose of study treatment at the second ramp-up visit. Two weeks following the second ramp-up visit, these subjects will receive the first full dose of TAK-881/HYQVIA and thereafter, the study treatment is administered every 3 or 4 weeks. For subjects previously treated with HYQVIA, who do not enter the ramp-up epoch, the first full dose of TAK-881/HYQVIA will be administered 3 or 4 weeks after the last prestudy HYQVIA dose, depending on whether prestudy HYQVIA treatment was administered every 3 or 4 weeks.

Dose: TAK-881/HYQVIA dose (in g/kg body weight [BW]/week) will be the same as the weekly equivalent of last prestudy IgG treatment dose. For subjects who undergo the ramp-up epoch, a 1-week and a 2-week dose based on their last prestudy IGIV/cIGSC treatment dose at screening will be administered at the first and second ramp-up visits, respectively:

Prestudy IgG Treatment	Ramp up (Yes/No)	Treatment Interval Prestudy	Dose in Ramp-up Epoch (in % of Prestudy IgG Treatment Dose)		Treatment Interval During Study	Dose During Study (in % of Prestudy IgG Treatment Dose)
			Ramp-up visit 1	Ramp-up visit 2		
cIGSC	Yes	Every week	100%	200%	Every 3 or 4 weeks, at the discretion of the investigator	1) if transitioning to 3 weeks: 300% of the prestudy IgG dose 2) if transitioning to 4 weeks: 400% of the prestudy IgG dose
	Yes	Every 2 weeks	50%	100%	Every 3 or 4 weeks, at the discretion of the investigator	1) if transitioning to 3 weeks: 150% of the prestudy IgG dose 2) if transitioning to 4 weeks: 200% of the prestudy IgG dose
IGIV	Yes	Every 3 weeks	33%	66%	Every 3 weeks	Same dose as prestudy IgG dose
	Yes	Every 4 weeks	25%	50%	Every 4 weeks	Same dose as prestudy IgG dose
HYQVIA	No	Every 3 weeks	-	-	Every 3 weeks	Same dose as prestudy IgG dose
	No	Every 4 weeks	-	-	Every 4 weeks	Same dose as prestudy IgG dose

TAK-881/HYQVIA doses must not be administered over multiple days. The maximum daily absolute dose of TAK-881/HYQVIA is 120 g.

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Immunoglobulin Infusion Rate:

TAK-881:

- For subjects with a BW of <40 kg: 10 mL/hour/site (at start) to 160 mL/hour/site (maximum, if tolerated).
- For subjects with a BW of ≥40 kg: 30 mL/hour/site (at start) to 300 mL/hour/site (maximum, if tolerated).

HYQVIA:

- For subjects with a BW of <40 kg who were not treated with HYQVIA within 12 weeks of screening: 5 mL/hour/site (at start) to 160 mL/hour/site (maximum, if tolerated).
- For subjects with a BW of ≥40 kg who were not treated with HYQVIA within 12 weeks of screening: 10 mL/hour/site (at start) to 300 mL/hour/site (maximum, if tolerated).
- For subjects regardless of BW who were treated with HYQVIA within 12 weeks of screening: the infusion rate at start and the maximum infusion rate can be the rates they tolerated before screening.

Immunoglobulin Infusion Volume:

TAK-881:

- Administer up to 150 mL per infusion site for subjects with a BW of <40 kg.
- Administer up to 300 mL per infusion site for subjects with a BW of ≥40 kg.

HYQVIA:

- Administer up to 300 mL per infusion site for subjects with a BW of <40 kg.
- Administer up to 600 mL per infusion site for subjects with a BW of ≥40 kg.

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Number and Location of Infusion Sites:

A maximum of 2 infusion sites can be used. If a second site is used for administration, 50% of the total volume of rHuPH20 and IgG of TAK-881/HYQVIA should be delivered into each infusion site. The recommended sites for the infusion of TAK-881/HYQVIA are the middle to upper abdomen and thighs.

Subjects Previously Treated with IGIV

For subjects previously treated with IGIV, the selection of number of infusion sites with TAK-881/HYQVIA during the study will be at the discretion of the investigator. The investigator may base his/her decision on the following:

1. The total calculated volume exceeds the maximum volume per infusion site per protocol.

2. During the escalating rate of infusion the subject exhibits signs of intolerance using 1 infusion site.

3. The investigator knows that the subject may fear tolerating a large volume using only 1 infusion site.

In both cases 1 and 3, the investigator may decide to use 2 infusion sites from the beginning, if feasible, and in case number 2 the investigator may add a second infusion site when the subject exhibits intolerable side effects while ramping up the infusion rate using 1 infusion site.

Subjects Previously Treated with HYQVIA or cIGSC

For subjects previously treated with HYQVIA or cIGSC, a maximum of 2 infusion sites can be used during the study and the number of infusion sites with the prestudy HYQVIA/cIGSC at screening, if they are 1 or 2 infusion sites, should be maintained, if tolerated, during TAK-881/HYQVIA treatment in the study.

Location of Infusion Administration:

TAK-881/HYQVIA infusions will be administered by an appropriately trained healthcare professional (HCP) (eg, infusion nurse) at the study site.

At a number of selected US study sites and only in subjects ≥16 years old willing to participate, digital photographs of the infusion site(s) preinfusion (within 1 hour before infusion), immediately postinfusion (+15 minutes), 24±4 hours and 72±8 hours postinfusion (for both IPs) will be taken. The photograph will be taken of the infusion site only and will be labeled using the subject's identifier. Subjects will be asked to permit photographs of the infusion sites (via an optional informed consent form [ICF]), which will be used for publications, educational and demonstration purposes, both within and external to the study. Subjects who do not provide permission for photographs will still be allowed to participate in the study.

Overall Design and Methodology:

This study is a phase 2/3, multicenter, prospective, open-label, randomized, crossover PK comparability study in PIDD subjects. Subjects must have received regular IgG treatment (HYQVIA, IGIV, or cIGSC) over a period of at least 12 weeks prior to screening.

In the present study, approximately 75 subjects in total (51 subjects aged ≥16 years and 24 subjects aged 2 to <16 years) will be screened. 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.

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All subjects participating in Study TAK-881-3001 must consent for the long-term follow-up Study TAK-881-3002 at the time of consenting to Study TAK-881-3001 participation, if permitted by Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The weekly IgG dose (in g IgG per kg BW/week) should remain stable throughout the study unless clinically indicated by the investigator. In all subjects the dose in g/kg BW/week after the first full dose of the 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 (Physician choice in the Interactive Response Technology [IRT]). 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).
In order to maintain the same dose in g/kg BW when there has been a certain change in kg BW as detailed below, 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 >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. The IRT system is programmed to make these calculations.

Serum trough levels of total IgG >5 g/L must be maintained throughout the study.

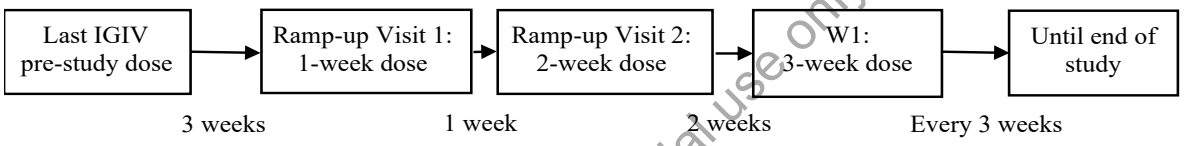
During the study subjects will receive TAK-881/HYQVIA at 3- or 4-week intervals (with the exception of the initial ramp-up epoch, when applicable). Subjects previously treated with IGIV/HYQVIA will continue on their prestudy treatment interval. For subjects previously treated with cIGSC the treatment interval during the study will be decided at the screening visit at the discretion of the investigator, which can be either every 3 or 4 weeks.

Screening and Ramp-up Epochs: The duration of the screening epoch will be up to 4 weeks. All subjects are required to have a serum trough level of IgG >5 g/L at screening to fulfill inclusion criterion #4. This sample must be taken prior to the administration of the prestudy IgG treatment dose that is administered on the same day of the screening visit.

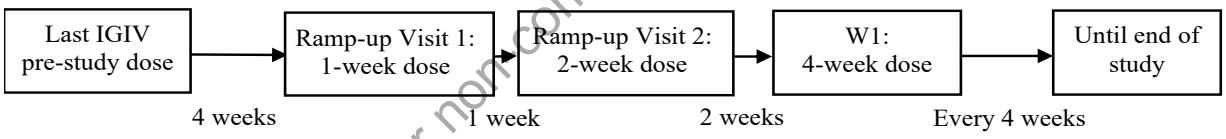
During the screening period no variation in cIGSC doses is allowed for subjects receiving weekly prestudy cIGSC.

For subjects who have been receiving IGIV/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 subject's prestudy IgG 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.

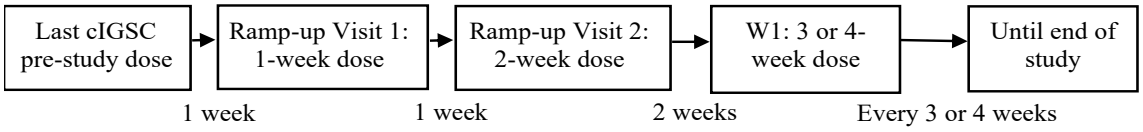
Subjects pre-treated with IGIV every 3 weeks



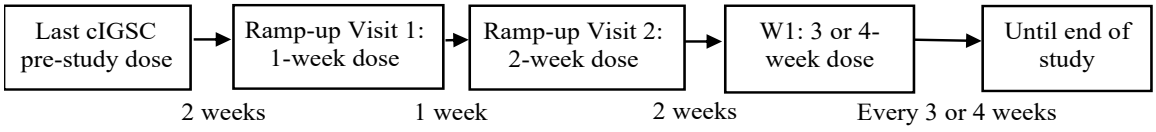
Subjects pre-treated with IGIV every 4 weeks



Subjects pre-treated with cIGSC every 1 week



Subjects pre-treated with cIGSC every 2 weeks



Subjects who have already been receiving HYQVIA treatment will not enter the ramp-up epoch. After screening, these subjects will directly enter the treatment epoch(s), the first full dose of TAK-881/HYQVIA will be administered 3 or 4 weeks after the last prestudy HYQVIA dose, depending on the prestudy HYQVIA treatment interval.

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Treatment Epochs

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 study 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).

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	Crossover Epoch 1	**Crossover Epoch 2**
Sequence 1 (AB)	6 or 8 full doses of TAK-881	6 or 8 full doses of HYQVIA
Sequence 2 (BA)	6 or 8 full doses of HYQVIA	6 or 8 full doses of TAK-881

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).

Single-arm Treatment Epoch (subjects aged 2 to <16 years): 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 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 DMC evaluation will not stop further enrollment of subjects ≥16 years, unless a criterion for premature termination/suspension of the study is met.

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 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. In order to avoid multiple blood drawings in children, subjects will undergo sparse PK sampling. Subjects will be randomized (1:1:1:1:1:1) within 4 days prior to the first planned TAK-881 infusion to 1 of 6 sampling sequences.

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

Inclusion and Exclusion Criteria:

Inclusion Criteria:

Subjects who meet ALL of the following criteria are eligible for this study:

1. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving a defect in antibody formation and requiring IgG replacement, as defined according to the International Union of Immunological Societies (IUIS) Committee (Bousfiha et al., 2020, Tangye et al., 2021).
2. Subject is 2 years to <16 years at the time of signing the ICF for the single-arm treatment part of the study OR 16 years or older at the time of signing the ICF for the crossover part of the study.
3. Subject has received a stable dose of regular treatment with any IGIV OR HYQVIA with a treatment interval of every 21 or 28 days OR any cIGSC with a treatment interval of every 7 or 14 days over a period of at least 12 weeks prior to screening at a minimum prestudy IgG dose equivalent to 0.3 g/kg BW/4 weeks and a maximum dose equivalent to 1 g/kg BW/4 weeks. Over that period, the subject should have been on the same product of IGIV, HYQVIA, or cIGSC. A stable dose is defined as one that deviates less than ±25% from the mean dose for all IgG infusions within this 12-week period prior to screening. Variations in the treatment interval of up to ±5 days for subjects with a 28-day treatment interval and up to ±3 days for subjects with a 7, 14, or 21- day treatment interval are acceptable up to the first IP infusion.
4. Subject has a serum trough level of IgG >5 g/L at the following time points:
   a. At screening (sample taken prior to prestudy IgG infusion after signing the ICF) and
   b. Within 12 weeks prior to screening.
5. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ a highly effective form of contraception for the duration of the study.
6. Subject or, in the case of minors, legally designated representative(s) is/are willing and able to comply with the requirements of the protocol, including PK blood sampling, for the duration of the study.

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Exclusion Criteria:

Subjects who meet ANY of the following criteria are not eligible for this study:

1. Subject has a known history of a positive result or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2. Cured subjects with a history of hepatitis C infection who have a negative PCR test at screening are eligible.
2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
   a. Persistent alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >2.5 × the upper limit of normal (ULN) for the testing laboratory.
   b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] ≤500/mm^3).
3. Known history of chronic kidney disease, or estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 at screening.
4. Subject has anemia that would preclude phlebotomy for laboratory studies, according to standard practice at the site, at the discretion of the investigator.
5. Subject has a known history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IV immunoglobulin, SC immunoglobulin, and/or immune serum globulin infusions.
6. Subjects with a known systemic hypersensitivity to any of the excipients of TAK-881/HYQVIA in accordance with the investigator's brochure/package insert/Summary of Product Characteristics.
7. Known substance or prescription drug abuse within 12 months of screening.
8. Subject has immunoglobulin A (IgA) deficiency (IgA less than 0.07 g/L) associated with known anti-IgA antibodies and a history of hypersensitivity.
9. Subject has a known systemic hypersensitivity to hyaluronidase or rHuPH20.
10. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening.
11. Subject has a bleeding disorder or a platelet count less than 20,000 /µL, or in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of IGSC therapy.
12. Treatment with immunosuppressants including chemotherapeutic agents, immunomodulators, and long-term systemic corticosteroid (defined as a daily dose of >1 mg of prednisone equivalent/kg/day for >30 days) within 12 weeks prior to screening. Short or intermittent courses (≤10 days) of corticosteroids are allowed.
13. Live-attenuated viral vaccination within 12 weeks prior to screening.
14. History or current diagnosis of thrombotic episodes; venous thrombus that occurred in association with a medical device >2 years prior to screening are allowed.
15. Subject has severe dermatitis that would preclude adequate sites for safe product administration in the opinion of the investigator.
16. Subject has a medical condition, laboratory finding, or physical examination finding that precludes participation, or with clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may interfere with successful completion of the study or place the subject at undue medical risk.
17. Subject has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to screening.

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18. Subject is scheduled to participate in another clinical study involving an IP (except for subjects scheduled to enroll in a long-term follow-up study with TAK-881) or investigational device during the course of this study.
19. Subject is a family member or employee of the investigator or the investigator's site staff.
20. If female, subject is pregnant or lactating at the time of screening.

Intervention groups and duration including maximum duration of subject participation in the study:

The total duration of study participation for each subject includes:

- Planned duration of screening epoch: up to 4 weeks prior to first dosing.
- Planned duration of ramp-up (employed in all subjects except for those who have been receiving HYQVIA prior to screening): 3 weeks.
- Planned duration of the AB/BA crossover treatment epochs for subjects aged ≥16 years: 48 weeks and additional maximum of 6 days until the first study treatment with TAK-881 in the long-term follow-up Study TAK-881-3002 if the subject is rolled over.
- Planned duration of single-arm treatment epoch for subjects aged 2 to <16 years: 24 weeks and additional maximum of 6 days until the first study treatment with TAK-881 in the long-term follow-up Study TAK-881-3002 if the subject is rolled over.
- The maximum subject participation period is 56 weeks for subjects aged ≥16 years and 32 weeks for subjects aged 2 to <16 years.

Statistical analysis:

Timing of Statistical 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 statistical analysis plan (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.
    - 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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Irrespective of whether there will be only one formal analysis or two formal analyses, the SAP will be finalized and approved prior to the first visit of the first subject.

Sample Size:

Subjects aged ≥16 years:

The anticipated sample size of 30 completed and evaluable subjects is based on recommendations from the Food and Drug Administration (FDA) 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 2008 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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Analysis Sets:

- Safety Analysis Set (SAS): The 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.
- PK Full-Analysis Set (PKFAS):
  - Subjects aged ≥16 years: The 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.
- PK Per-Protocol Analysis Set (PKPPAS):
  - 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. A list of all deviations that may affect the reliability of the total IgG level time profiles will be provided in the SAP. 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. A list of all deviations that may affect the reliability of the total IgG level time profiles will be provided in the SAP.

All PK analyses will use the actual sampling times (not nominal times) and nonbaseline-corrected total IgG levels. 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, HRU, safety, tolerability, immunogenicity, and infusion endpoints will be presented for the SAS. Analysis of infections will be also based on the SAS.

Primary Endpoint:

For subjects aged ≥16 years, the primary endpoint $AUC_{0\text{-}\tau,ss}$ will be calculated during the dosing interval after the last dose in each crossover epoch by the non-compartmental analysis (NCA) based on total IgG levels for TAK-881 and HYQVIA.

$AUC_{0\text{-}\tau,ss}$ 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. Comparability between TAK-881 and HYQVIA will be assessed based on the 90% CI for the ratio of geometric means for $AUC_{0\text{-}\tau,ss}$ in reference to the acceptance interval of 80.00% to 125.00%.

In addition, geometric means and corresponding two-sided 95% CIs of $AUC_{0\text{-}\tau,ss}$ will be presented separately for TAK-881 and HYQVIA.

Sensitivity Analysis for the primary endpoint:

A sensitivity analysis to assess the robustness of inferences to departures from the MCAR premise in the hypothetical strategy (used to address 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. This sensitivity analysis utilizing the same linear mixed effects model as described above is unbiased under the MAR premise.

Secondary Endpoints:

Pharmacokinetics:

For subjects aged ≥16 years, secondary PK endpoints C_{max}, T_{max}, $t_{1/2}$, CL/F, V_z/F, and $AUC_{0\text{-}\tau,ss}$/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 (data permitting). For total IgG trough levels and trough levels of IgG subclasses and antigen-specific IgG antibodies, the last trough level per subject in each crossover epoch (at the end of the last dosing interval) will be used for analysis. 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).

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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}, for subjects aged ≥16 years. The models will be used to estimate the geometric mean for TAK-881 and HYQVIA and corresponding two-sided 95% CIs.

For pediatric subjects 2 to <16 years, total IgG trough levels and trough levels of IgG subclasses at the end of the last TAK-881 dosing interval and trough levels of IgG subclasses at Week 21 (3-week treatment interval) or Week 22 (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).

PK characterization between subjects aged ≥16 years and subjects aged 2 to <16 years will be assessed according to a population PK model incorporating covariates including allometric scaling of parameters according to BW.

Infections:

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. 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, combined) and for HYQVIA for subjects aged ≥16 years and ≥18 years.

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, combined) and treatment (TAK-881, HYQVIA).

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, combined) and treatment (TAK-881, HYQVIA).

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, combined) and treatment (TAK-881, HYQVIA) with at least one ASBI in the corresponding treatment epoch.

Healthcare resource utilization:

The number and percentage of subjects with at least 1 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).

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The number and percentage of subjects with at least 1 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 will be presented for antibiotics for prophylaxis and treatment of infection separately as well as for all antibiotics combined.

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 <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).

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Safety, tolerability, immunogenicity:

Descriptive summaries of TEAEs (including and excluding infections), tolerability, and immunogenicity will be presented by 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, combined), by infusion interval (3-week, 4-week, combined), and by prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined), as appropriate. Additional summaries for immunogenicity will be presented by study visit, as appropriate. A TEAE is defined as any AE that started at or after the initiation of the first administration of TAK-881 or HYQVIA.

Clinical laboratory parameters and vital signs do not represent study endpoints but will be also summarized in a descriptive way.

Infusion parameters at full dose:

Descriptive summaries of 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, combined) and treatment (TAK-881, HYQVIA). In addition, the average duration of infusions and the average monthly infusion time will be presented by treatment for the following subgroups:

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

- Subjects aged ≥16 years with 1 infusion site for all HYQVIA infusions and 2 infusion sites for all TAK-881 infusions.

Data Monitoring/Other Committee: Yes

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). The DMC evaluation will not stop further enrollment of subjects ≥16 years, unless a criterion for premature termination/suspension of the study is met.

Benefits and Risks

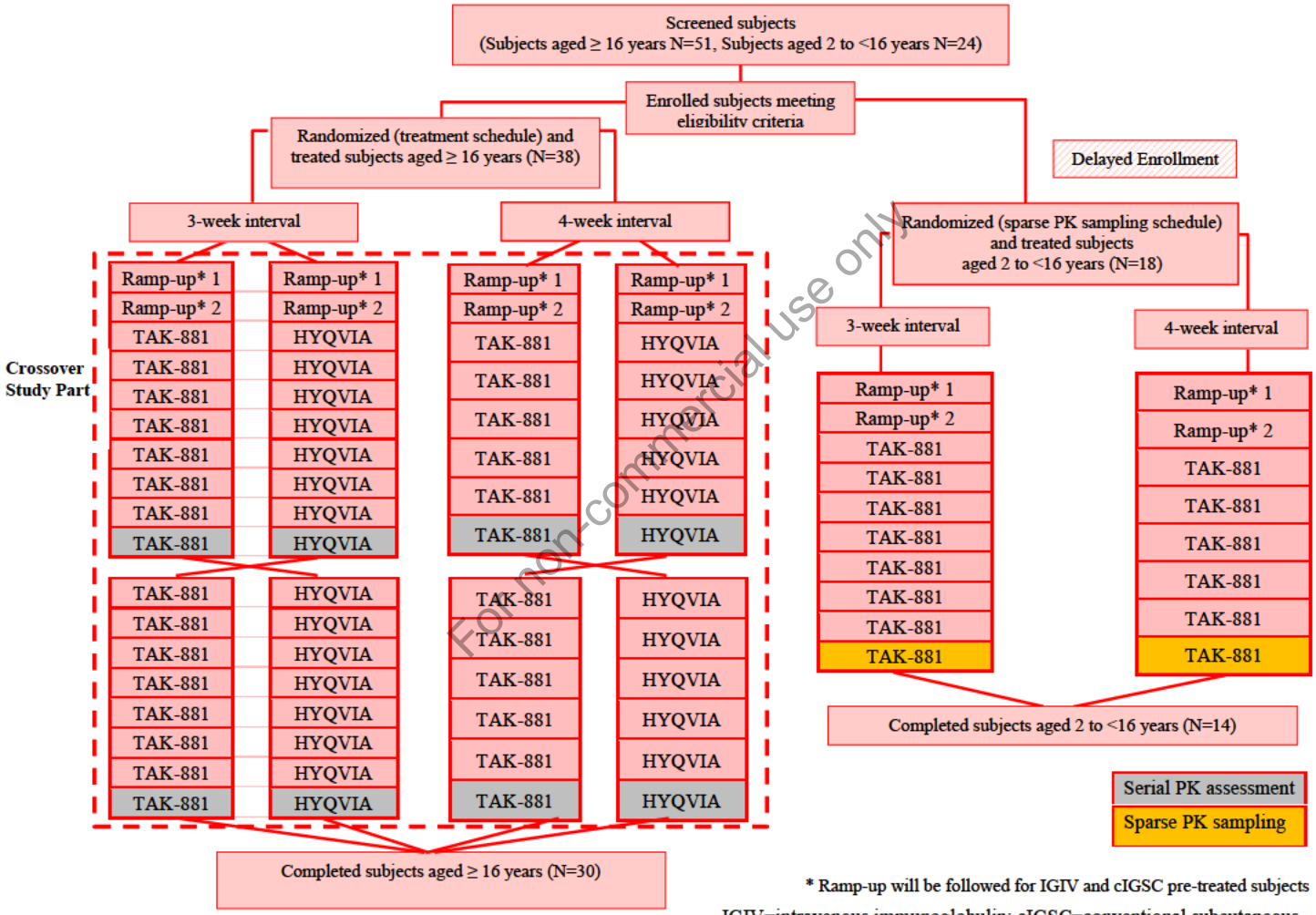
The higher concentration of TAK-881 (20% IgG) in comparison to HYQVIA (10% IgG) allows infusions to occur with a lower volume. This presents an opportunity to improve the PIDD patient's infusion experience.

The risks associated with dosing TAK-881 are anticipated to be similar to those previously documented in the product labels for HYQVIA and CUVITRU. CUVITRU and HYQVIA are licensed products for which the safety profile is well established in hundreds of thousands of patients worldwide, including pediatric patients.

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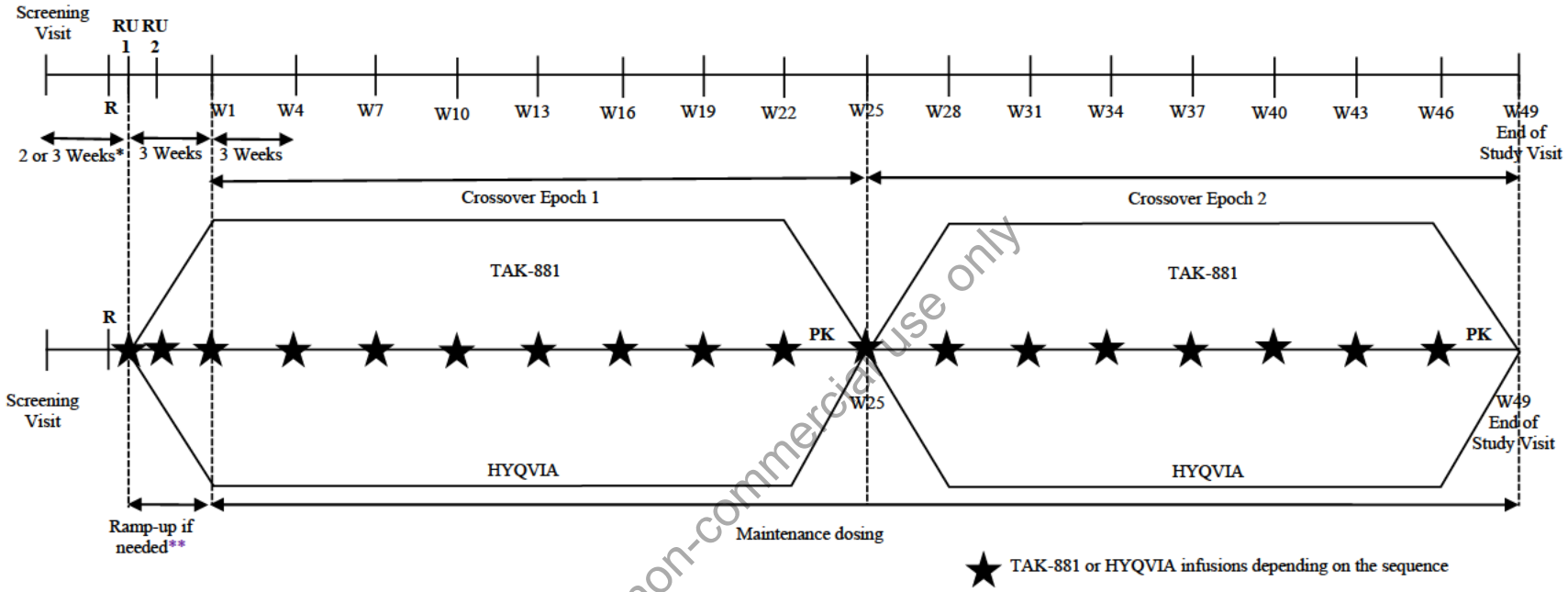
1.2 Schema

Figure 1. Study Schema



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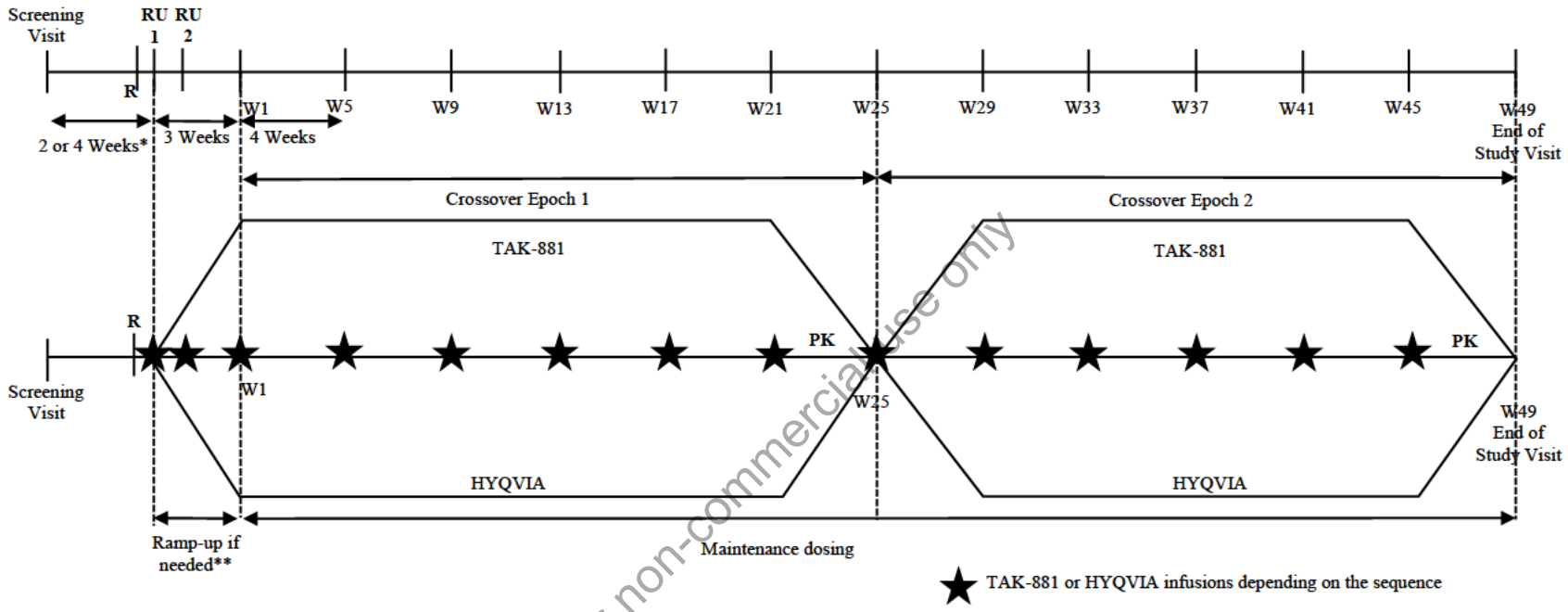
Figure 2. 3-Week Dosing Regimen in Subjects Aged ≥16 years



IGIV=intravenous immunoglobulin; cIGSC=conventional subcutaneous immunoglobulin; PK=pharmacokinetic; R=Randomization; RU 1=Ramp-Up Visit 1; RU 2=Ramp-Up Visit 2; W=Week.
*Screening Period is 2 weeks for cIGSC pre-treated subjects and 3 weeks for IGIV or HYQVIA pre-treated subjects.
** Ramp-up will be followed for IGIV and cIGSC pre-treated subjects.

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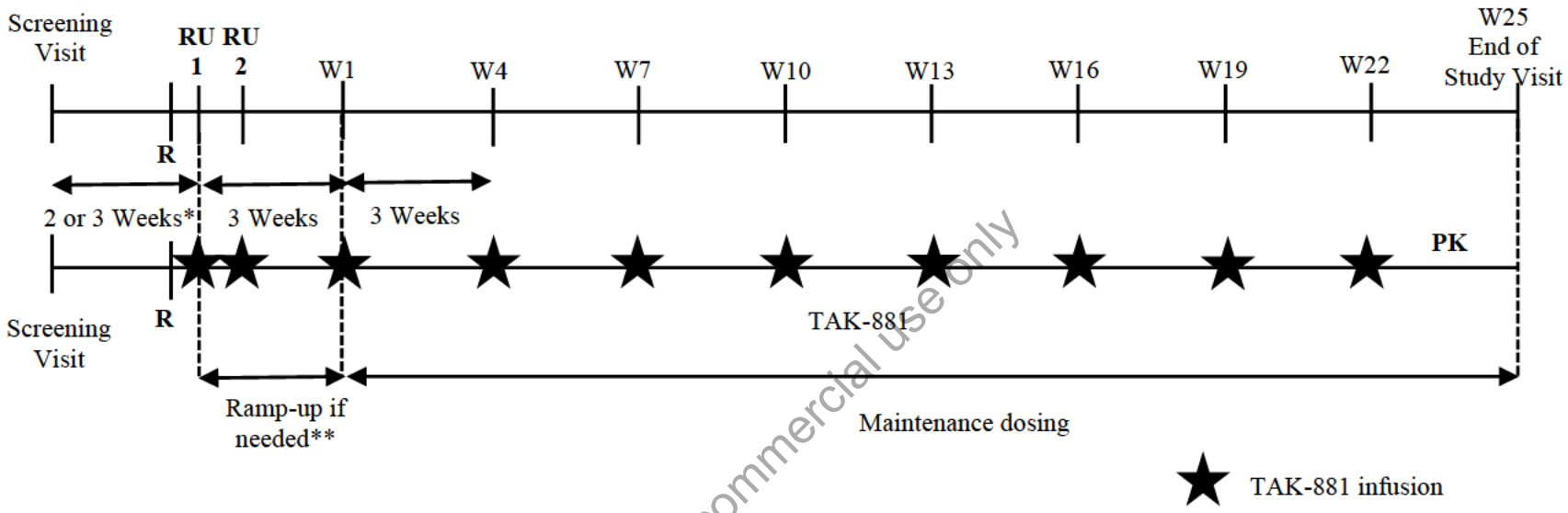
Figure 3. 4-Week Dosing Regimen in Subjects Aged ≥16 Years



IGIV=intravenous immunoglobulin; cIGSC=conventional subcutaneous immunoglobulin; PK=pharmacokinetic; R=Randomization; RU 1=Ramp-Up Visit 1; RU 2=Ramp-Up Visit 2; W=Week.
*Screening Period is 2 weeks for cIGSC pre-treated subjects and 4 weeks for IGIV or HYQVIA pre-treated subjects.
** Ramp-up will be followed for IGIV and cIGSC pre-treated subjects.

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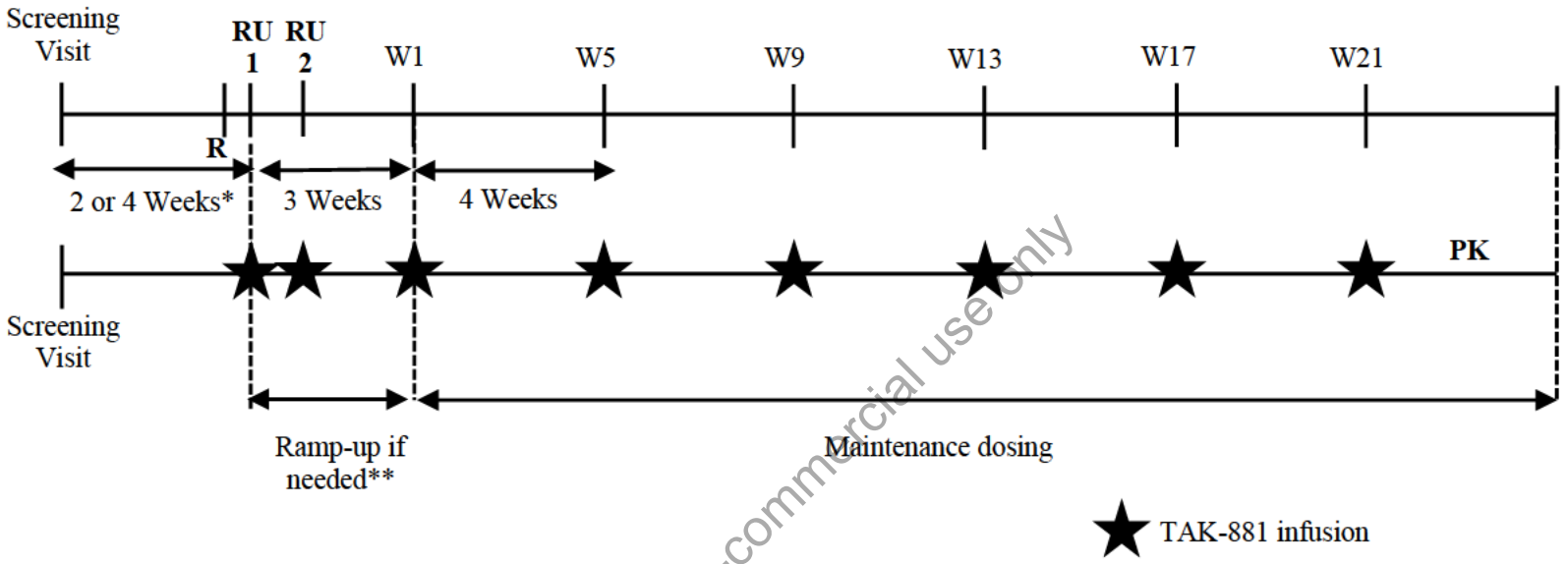
Figure 4. 3-Week Dosing Regimen in Subjects Aged 2 to <16 Years



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IGIV=intravenous immunoglobulin; cIGSC=conventional subcutaneous immunoglobulin; PK=pharmacokinetic; R=Randomization; RU 1=Ramp-Up Visit 1; RU 2=Ramp-Up Visit 2; W=Week.
*Screening Period is 2 weeks for cIGSC pre-treated subjects and 3 weeks for IGIV or HYQVIA pre-treated subjects.
** Ramp-up will be followed for IGIV and cIGSC pre-treated subjects.

Figure 5. 4-Week Dosing Regimen in Subjects Aged 2 to <16 Years



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IGIV=intravenous immunoglobulin; cIGSC=conventional subcutaneous immunoglobulin; PK=pharmacokinetic; R=Randomization; RU 1=Ramp-Up Visit 1; RU 2=Ramp-Up Visit 2; W=Week.
*Screening Period is 2 weeks for cIGSC pre-treated subjects and 4 weeks for IGIV or HYQVIA pre-treated subjects.
** Ramp-up will be followed for IGIV and cIGSC pre-treated subjects.

1.3 Schedule of Activities (SoA)

Table 1. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period: Ramp-up Epoch [b]		AB/BA Crossover Epochs – 3-Week Dosing Interval																EOS / ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8		Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W 13	W 16	W 19	W22		W25	W28	W31	W34	W37	W40	W43	W46	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Administrative Procedures																					
Informed Consent and Assent (if applicable) [e, f, g]	X																				
Inclusion/Exclusion	X																				
Demographics	X																				
Medical History	X																				
Subject's Prestudy IgG Treatment [h, i]	X																				
Concomitant Medications and Nondrug Therapies [j]	←			X							→		←			X				→	
Randomization [k]	X																				
Clinical Procedures																					
Height, weight and BMI [l, m]	X			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Vital Signs [n]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
AEs [j]	←			X							→		←			X				→	
Collection/ Review Diaries [j]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Infusion Preparation Data				X							X		X							X	
IP Administration [o]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	

Crossover

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Table 1. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period		Treatment Period																		
		Ramp-up Epoch [b]		AB/BA Crossover Epochs – 3-Week Dosing Interval																EOS / ET Visit
Visit No.	Screening Visit [a]	Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Crossover	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W 13	W 16	W 19	W22		W25	W28	W31	W34	W37	W40	W43	W46	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Follow-up Call after Infusion (3-5 days postinfusion) [p]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Clinical Laboratory Assessments [q]																					
Hematology Panel	X	X		X									X								X
Clinical Chemistry Panel	X	X		X									X								X
Urinalysis [r]	X												X								X
Pregnancy Test [s]	X																				X
Viral Pathogen Serology	X												X								X
Hemolysis Panel		X		X[t]	← (as applicable) →								← (as applicable) →								
Total IgG Trough Levels [i]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
IgG Subclasses (IgG1, IgG2, IgG3, IgG4) Trough levels		X		X[t]									X								X
Antigen-specific IgG Antibodies Trough levels		X		X[t]									X								X
Anti-rHuPH20 Antibodies (binding/ neutralizing, if applicable)		X		X[t]				X					X				X				X
Serial PK Assessment [u]											X									X	

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Table 1. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period		Treatment Period																		
		Ramp-up Epoch [b]		AB/BA Crossover Epochs – 3-Week Dosing Interval																EOS / ET Visit
Visit No.	Screening Visit [a]	Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Crossover	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W 13	W 16	W 19	W22		W25	W28	W31	W34	W37	W40	W43	W46	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Plasma and Serum Retention Samples		X		X [t]																	X
Clinical Outcome Assessments																					
TSQM-9													X [v]								X
EQ-5D-5L		X [v]		X [t, v]									X [v]								X
HRU [j]	◄				X						►		◄				X			►	
Optional Assessments																					
Photographs of Infusion Site(s) [w]											X									X	
Semi-structured Qualitative Interview [x]										X									X		

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AE=adverse event; BMI=body mass index; BW=body weight; cIGSC=conventional subcutaneous IgG; d=day; eCRF=electronic case report form; EOS=end of study; EQ-5D-5L=EuroQol 5 Dimensions 5 Level Questionnaire; ET=early termination; HRU=healthcare resource utilization; ICF=informed consent form; IEC=Institutional Ethics Committee; IgG=immunoglobulin G; IGI=immune globulin infusion; IGIV=intravenous immunoglobulin; IGSC=immune globulin subcutaneous; IP=investigational product; IRB=Institutional Review Board; IRT=Interactive Response Technology; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous; TSQM-9=Treatment Satisfaction Questionnaire for Medication - 9 Items; w=week.

[a] All subjects switching from cIGSC treatment will have the screening visit at 2 weeks prior to the first IP treatment, on the same day as the second to last prestudy IgG treatment dose for subjects with prestudy treatment interval every 1 week, and on the same day as the last prestudy IgG treatment dose for subjects with prestudy treatment interval every 2 weeks. Subjects switching from IGIV/HYQVIA treatment, with prestudy treatment interval every 3 weeks, will have the Screening Visit at 3 weeks prior to the first IP treatment, on the same day as the last prestudy IgG treatment dose.

[b] Ramp-up epoch is applicable only to those subjects who are on IGIV/cIGSC treatment prior to enrollment and it starts 1, 2, or 3 weeks (±1 day) after last prestudy IGIV/cIGSC dose depending on the prestudy IgG treatment interval. At Ramp-up Visit 1 the subject will receive a 1-week dose, at Ramp-up Visit 2 the subject will receive a 2-week dose.

[c] 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).

[d] Study Visit 1/Week 1 of the AB/BA crossover epochs starts 2 weeks (±1 day) after the second ramp-up dose when ramp-up is applicable OR 3 weeks (±1 day) after last prestudy HYQVIA dose (when ramp-up dose is not applicable).

Table 1. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period																		
		Ramp-up Epoch [b]		AB/BA Crossover Epochs – 3-Week Dosing Interval																EOS / ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8		Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W 13	W 16	W 19	W22		W25	W28	W31	W34	W37	W40	W43	W46	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

[e] Informed consent and assent (if applicable) must be obtained prior to any study procedures (including the prestudy IgG treatment for which the total IgG trough level sample will be taken for screening purposes).

[f] If during the course of the crossover treatment epochs, an adolescent is no longer a minor as defined in national law, then written informed consent is required from these individuals (when required by the local IEC/IRB) at the beginning of the next visit at which they achieve majority or else are to be discontinued from participation in this study. See Section 10.1.3.

[g] Sites must consent subjects for the long-term follow-up Study TAK-881-3002 at the time of consenting to Study TAK-881-3001 participation, if permitted by Institutional Review Board/Institutional Ethics Committee.

[h] For the prestudy IgG treatment dose at screening visit day, variations in the treatment interval of up to ±3 days relative to the prestudy IgG treatment dose before screening, are acceptable for all subjects (with a treatment interval of 7, 14, or 21 days). This applies also to the last prestudy IgG treatment (after screening visit day) for subjects with prestudy cIGSC on a 1-week treatment interval. For subjects with prestudy cIGSC on a 1-week treatment interval, the dose of the last prestudy IgG treatment (after screening visit day) must be the same as the dose of the second to last prestudy IgG treatment at screening visit.

[i] The subject is required to have a serum trough level of IgG >5 g/L at screening. This sample must be taken prior to the prestudy IgG treatment dose that is administered on the same day as the screening visit. The blood drawing for all IgG trough level determinations should take place before the IgG infusion is administered on the same day.

[j] Subjects rolling over to Study TAK-881-3002 will keep the diary for Study TAK-881-3001 until the Study Visit 1/Week 1 of Study TAK-881-3002 and the site will continue reporting concomitant medications, AEs, occurrence of fever and HRU outcomes up to the TAK-881-3002 Study Visit 1/Week 1 in TAK-881-3001 eCRFs.

[k] Randomization should occur within 4 days prior to first IP treatment.

[l] Height will only be measured at screening. All BW measurements are to be taken at the study site using the same scale/instrument throughout the study for that individual subject.

[m] If a subject's BW has increased or decreased by >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. The IRT system is programmed to make these calculations.

[n] Vital signs will be performed at screening and at each IP infusion visit: within 30 min (±10 min) prior to infusion; 30 min (±10 min) after the initiation of infusion; during the infusion if a systemic AE occurs, to be assessed if needed; at least 60 min after the completion of the infusion.

[o] Infusion of rHuPH20 will be administered SC first, followed by SC infusion of IGSC, 20% OR IGI, 10% within 10 minutes of completion of the infusion of rHuPH20 in a sequential order using the same needle set at the same location. TAK-881/HYQVIA doses must not be administered over multiple days.

[p] The investigator/designee will contact the subject 3-5 days after completion of each IP infusion.

[q] Blood/urine samples will be collected before infusion. See Section 10.2 for more detailed information.

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Table 1. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period																		
		Ramp-up Epoch [b]		AB/BA Crossover Epochs – 3-Week Dosing Interval																EOS / ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8		Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W 13	W 16	W 19	W22		W25	W28	W31	W34	W37	W40	W43	W46	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

[r] At the time of the urine sample collection the presence of menstruation must be recorded for female subjects, if applicable, because blood contamination can easily occur.

[s] For females of childbearing potential. Testing will be performed at the specified time points and whenever a pregnancy is suspected. Urine pregnancy tests will be performed at a central laboratory, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

[t] These assessments at study Visit 1 Week 1 of the AB/BA crossover epochs are only to be performed by subjects without a ramp-up epoch.

[u] Starting for serial PK assessment is Week 22 and Week 46. For details of serial PK assessment refer to Section 8.4 and Table 3.

[v] Performed prior to infusion.

[w] Only for selected US study sites. Subjects will be asked to permit photographs of the infusion sites, those who do not provide permission for photographs will still be allowed to participate in the study. Photographs of the infusion site(s) preinfusion (within 1 hour before infusion), immediately postinfusion (+15 minutes), 24±4 hours and 72±8 hours postinfusion will be taken for both IPs. The 24- and 72-hour time points should be coordinated with the PK sampling visit.

[x] Interviews are for English-speaking US subjects only. After the ICF is signed, the subject (for those ≥18 years) or legally designated representative(s) (for those 16 to <18 years) must provide additional consent for interviews and complete a contact order form. Subjects who/subjects for whom legally designated representative(s) do not wish to undergo an interview will still be allowed to participate in the study. The interview should be performed within 2 weeks after the infusion visit.

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Table 2. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period: Ramp-up Epoch [b]		AB/BA Crossover Epochs – 4-Week Dosing Interval												EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21		W25	W29	W33	W37	W41	W45	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Administrative Procedures																	
Informed Consent and Assent (if applicable) [e, f, g]	X																
Inclusion/Exclusion	X																
Demographics	X																
Medical History	X																
Subject's Prestudy IgG Treatment [h, i]	X																
Concomitant Medications and Nondrug Therapies [j]	←			X					→		←			X		→	
Randomization [k]	X																
Clinical Procedures																	
Height, weight and BMI [l, m]	X			X	X	X	X	X	X		X	X	X	X	X	X	X
Vital Signs [n]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
AEs [j]	←			X					→		←			X		→	
Collection/ Review Diaries [j]		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Infusion Preparation Data				X					X		X					X	
IP Administration [o]		X	X	X	X	X	X	X	X		X	X	X	X	X	X	
Follow-up Call after Infusion (3-5 days postinfusion) [p]		X	X	X	X	X	X	X	X		X	X	X	X	X	X	

Crossover

Crossover

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Table 2. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period: Ramp-up Epoch [b]		AB/BA Crossover Epochs – 4-Week Dosing Interval												EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21		W25	W29	W33	W37	W41	W45	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Clinical Laboratory Assessments [q]																	
Hematology Panel	X	X		X							X						X
Clinical Chemistry Panel	X	X		X							X						X
Urinalysis [r]	X										X						X
Pregnancy Test [s]	X																X
Viral Pathogen Serology	X										X						X
Hemolysis Panel		X		X [t]	← (as applicable) →						← (as applicable) →						
Total IgG Trough Levels [i]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
IgG Subclasses (IgG1, IgG2, IgG3, IgG4) Trough levels		X		X [t]							X						X
Antigen-specific IgG Antibodies Trough levels		X		X [t]							X						X
Anti-rHuPH20 Antibodies (binding/ neutralizing, if applicable)		X		X [t]			X				X			X			X
Serial PK Assessment [u]									X							X	
Plasma and Serum Retention Samples		X		X [t]													X
Clinical Outcome Assessments																	
TSQM-9											X [v]						X
EQ-5D-5L		X [v]		X [t, v]							X [v]						X
HRU [j]	←			X →							← X →						

Crossover

Crossover

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Table 2. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period														
		Ramp-up Epoch [b]		AB/BA Crossover Epochs – 4-Week Dosing Interval												EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21		W25	W29	W33	W37	W41	W45	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d		±1 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Optional Assessments																	
Photographs of Infusion Site(s) [w]								X								X	
Semi-structured Qualitative Interview [x]								X							X		

AE=adverse event; BMI=body mass index; BW=body weight; cIGSC=conventional subcutaneous IgG; d=day; eCRF=electronic case report form; EOS=end of study; EQ-5D-5L=EuroQol 5 Dimensions 5 Level Questionnaire; ET=early termination; HRU=healthcare resource utilization; ICF=informed consent form; IEC=Institutional Ethics Committee; IgG=immunoglobulin G; IGI=immune globulin infusion; IGIV=intravenous immunoglobulin; IGSC=immune globulin subcutaneous; IP=investigational product; IRB=Institutional Review Board; IRT=Interactive Response Technology; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous; TSQM-9=Treatment Satisfaction Questionnaire for Medication - 9 Items; w=week.

[a] All subjects switching from cIGSC treatment will have the screening visit at 2 weeks prior to the first IP treatment, on the same day as the second to last prestudy IgG treatment dose for subjects with prestudy treatment interval every 1 week, and on the same day as the last prestudy IgG treatment dose for subjects with prestudy treatment interval every 2 weeks. Subjects switching from IGIV/HYQVIA treatment, with prestudy treatment interval every 4 weeks, will have the Screening Visit at 4 weeks prior to the first IP treatment, on the same day as the last prestudy IgG treatment dose.

[b] Ramp-up epoch is applicable only to those subjects who are on IGIV/cIGSC treatment prior to enrollment and it starts 1, 2, or 4 weeks (±1 day) after last prestudy IGIV/cIGSC dose depending on the prestudy IgG treatment interval. At Ramp-up Visit 1 the subject will receive a 1-week dose, at Ramp-up Visit 2 the subject will receive a 2-week dose.

[c] 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).

[d] Study Visit 1/Week 1 of the AB/BA crossover epochs starts 2 weeks (±1 day) after the second ramp-up dose when ramp-up is applicable OR 4 weeks (±1 day) after last prestudy HYQVIA dose (when ramp-up dose is not applicable).

[e] Informed consent and assent (if applicable) must be obtained prior to any study procedures (including the prestudy IgG treatment so that the total IgG trough level sample can be taken for screening purposes).

[f] If during the course of the crossover treatment epochs, an adolescent is no longer a minor as defined in national law, then written informed consent is required from these individuals (when required by the local IEC/IRB) at the beginning of the next visit at which they achieve majority or else are to be discontinued from participation in this study. See Section 10.1.3.

[g] Sites must consent subjects for the long-term follow-up Study TAK-881-3002 at the time of consenting to Study TAK-881-3001 participation, if permitted by Institutional Review Board/Institutional Ethics Committee.

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Table 2. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period													
		Ramp-up Epoch [b]		AB/BA Crossover Epochs – 4-Week Dosing Interval											EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21	W25	W29	W33	W37	W41	W45	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

[h] For the prestudy IgG treatment dose at the screening visit day, variations in the treatment interval of up to ±5 days relative to the prestudy IgG treatment dose before screening, are acceptable for subjects with a treatment interval of 28 days, and variations in the treatment interval of up to ±3 days relative to the prestudy IgG treatment dose before screening, are acceptable for subjects with a treatment interval of 7 or 14 days. This applies also to the last prestudy IgG treatment (after screening visit day) for subjects with prestudy cIGSC on every 1-week interval. For subjects with prestudy cIGSC on a 1-week interval, the dose of the last prestudy IgG treatment (after screening visit day) must be the same as the dose of the second to last prestudy IgG treatment at screening visit.

[i] The subject is required to have a serum trough level of IgG >5 g/L at screening. This sample must be taken prior to the prestudy IgG treatment dose that is administered on the same day as the screening visit. The blood drawing for all IgG trough level determinations should take place before the IgG infusion is administered on the same day.

[j] Subjects rolling over to Study TAK-881-3002 will keep the diary for Study TAK-881-3001 until the Study Visit 1/Week 1 of Study TAK-881-3002 and the site will continue reporting concomitant medications, AEs, occurrence of fever and HRU outcomes up to the TAK-881-3002 Study Visit 1/Week 1 in TAK-881-3001 eCRFs.

[k] Randomization should occur within 4 days prior to first IP treatment.

[l] Height will only be measured at screening. All BW measurements are to be taken at the study site using the same scale/instrument throughout the study for that individual subject.

[m] If a subject's BW has increased or decreased by >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. The IRT system is programmed to make these calculations.

[n] Vital signs will be performed at screening and at each IP infusion visit: within 30 min (±10 min) prior to infusion; 30 min (±10 min) after the initiation of infusion; during the infusion if a systemic AE occurs, to be assessed if needed; at least 60 min after the completion of the infusion.

[o] Infusion of rHuPH20 will be administered SC first, followed by SC infusion of IGSC, 20% OR IGI, 10% within 10 minutes of completion of the infusion of rHuPH20 in a sequential order using the same needle set at the same location. TAK-881/HYQVIA doses must not be administered over multiple days.

[p] The investigator/designee will contact the subject 3-5 days after completion of each IP infusion.

[q] Blood/urine samples will be collected before infusion. See Section 10.2 for more detailed information.

[r] At the time of the urine sample collection the presence of menstruation must be recorded for female subjects, if applicable, because blood contamination can easily occur.

[s] For females of childbearing potential. Testing will be performed at the specified time points and whenever a pregnancy is suspected. Urine pregnancy tests will be performed at a central laboratory, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

[t] These assessments at study Visit 1 Week 1 of the AB/BA crossover epochs are only to be performed by subjects without a ramp-up epoch.

[u] Starting for serial PK assessment is Week 21 and Week 45. For details of serial PK assessment refer to Section 8.4 and Table 4.

[v] Performed prior to infusion.

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Table 2. Schedule of Assessments for Subjects Aged ≥16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period													
		Ramp-up Epoch [b]		AB/BA Crossover Epochs – 4-Week Dosing Interval											EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21	W25	W29	W33	W37	W41	W45	W49
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

[w] Only for selected US study sites. Subjects will be asked to permit photographs of the infusion sites, those who do not provide permission for photographs will still be allowed to participate in the study. Photographs of the infusion site(s) preinfusion (within 1 hour before infusion), immediately postinfusion (+15 minutes), 24±4 hours and 72±8 hours postinfusion will be taken for both IPs. The 24- and 72-hour time points should be coordinated with the PK sampling visit.

[x] Interviews are for English-speaking US subjects only. After the ICF is signed, the subject (for those ≥18 years) or legally designated representative(s) (for those 16 to <18 years) must provide additional consent for interviews and complete a contact order form. Subjects who/subjects for whom legally designated representative(s) do not wish to undergo an interview will still be allowed to participate in the study. The interview should be performed within 2 weeks after the infusion visit.

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Table 3. Pharmacokinetic Assessment Period: 3-Week Dosing Interval (Subjects Aged ≥16 Years)

Clinical Laboratory Assessment	3-Week Dosing Interval							
	Study Visits 8 and 16							Study Visit 9 and EOS
	Weeks 22 and 46					Weeks 23 and 47	Weeks 24 and 48	Weeks 25 and 49
	PREinfusion	POSTinfusion	POSTinfusion (from completion time)					
	PK Day 1 (Infusion Day)		PK Day 2 (24 hours postinfusion)	PK Day 3 (48 hours postinfusion)	PK Day 4 (72 hours postinfusion)	PK Day 8 (7 days postinfusion)	PK Day 15 (14 days postinfusion)	PK Day 22 [a] (21 days postinfusion)
Allowance	**within 1 hour before infusion**	**immediately after infusion**	**±4 hours**	**±4 hours**	**±8 hours**	**±1 day**	**±1 day**	**±1 day**
Serum Total IgG	X	X	X	X	X	X	X	X

EOS=end of study; IgG=immunoglobulin G; PK=pharmacokinetics.

[a] All PK Visits will take as reference the INFUSION Day at PK Day 1 (before and after infusion and 24 hours, 48 hours, 72 hours, 7 days, 14 days, and 21 days POSTINFUSION). However, PK Day 22 needs to coincide with Study Visit 9 and the EOS Visit and for that the window ±1 day may have to be applied.

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Table 4. Pharmacokinetic Assessment Period: 4-Week Dosing Interval (Subjects Aged ≥16 Years)

Clinical Laboratory Assessment	4-Week Dosing Interval								
	Study Visits 6 and 12								Study Visit 7 and EOS
	Weeks 21 and 45					Weeks 22 and 46	Weeks 23 and 47	Weeks 24 and 48	Weeks 25 and 49
	PREinfusion	POSTinfusion	POSTinfusion (from completion time)						
	PK Day 1 (Infusion Day)		PK Day 2 (24 hours postinfusion)	PK Day 3 (48 hours postinfusion)	PK Day 4 (72 hours postinfusion)	PK Day 8 (7 days postinfusion)	PK Day 15 (14 days postinfusion)	PK Day 22 (21 days postinfusion)	PK Day 29 [a] (28 days postinfusion)
Allowance	**within 1 hour before infusion**	**immediately after infusion**	**±4 hours**	**±4 hours**	**±8 hours**	**±1 day**	**±1 day**	**±1 day**	**±1 day**
Serum Total IgG	X	X	X	X	X	X	X	X	X

EOS=end of study; IgG=immunoglobulin G; PK=pharmacokinetics.

[a] All PK Visits will take as reference the INFUSION Day at PK Day 1 (before and after infusion and 24 hours, 48 hours, 72 hours, 7 days, 14 days, 21 days, and 28 days POSTINFUSION). However, PK Day 29 needs to coincide with Study Visit 7 and the EOS Visit and for that the window ±1 day may have to be applied.

Table 5. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period										
		Ramp-up Epoch [b]		3-Week Dosing Interval Epoch								EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W13	W16	W19	W22	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Administrative Procedures												
Informed Consent and Assent (if applicable) [e, f]	X											
Inclusion/Exclusion	X											
Demographics	X											
Medical history	X											
Subject's prestudy IgG treatment [g, h]	X											
Concomitant medications and Nondrug therapies [i]	←	←	←	←	←	X	→	→	→	→	→	→
Randomization [j]	X											
Clinical Procedures												
Height, weight and BMI [k, l]	X			X	X	X	X	X	X	X	X	X
Vital Signs [m]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X
AEs [i]	←	←	←	←	←	X	→	→	→	→	→	→
Collection/Review Diaries [i]		X	X	X	X	X	X	X	X	X	X	X
IP administration [n]		X	X	X	X	X	X	X	X	X	X	
Follow-up call after infusion (3-5 days postinfusion) [o]		X	X	X	X	X	X	X	X	X	X	

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Table 5. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period										
		Ramp-up Epoch [b]		3-Week Dosing Interval Epoch								EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W13	W16	W19	W22	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Clinical Laboratory Assessments [p]												
Hematology Panel	X	X		X								X
Clinical Chemistry (reduced) Panel	X	X		X							X	
Urinalysis [q]	X											X
Pregnancy Test [r]	X											X
Viral Pathogen Serology	X											X
Hemolysis Panel		X		X [s]	←			(as applicable)				→
Total IgG Trough Levels [h]	X	X	X	X	X	X	X	X	X	X	X	X
IgG Subclasses (IgG1, IgG2, IgG3, IgG4) Trough levels		X		X [s]							X	
Anti-rHuPH20 Antibodies (binding/neutralizing, if applicable)		X		X [s]				X			X	
Sparse PK Sampling											X [j]	
Serum Retention Samples		X		X [s]								X
Clinical Outcome Assessments												
EQ-5D-5L [t]		X [u]		X [s, u]								X
HRU [i]	←					X						→
Optional Assessments												
Semi-structured Qualitative Interview [v]											X	

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Table 5. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period									
		Ramp-up Epoch [b]		3-Week Dosing Interval Epoch							EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W13	W16	W19	W22	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

AE=adverse event; BMI=body mass index; BW=body weight; cIGSC=conventional subcutaneous IgG; d=day; eCRF=electronic case report form; EOS=end of study; EQ-5D-5L=EuroQol 5 Dimensions 5 Level Questionnaire; ET=early termination; HRU=healthcare resource utilization; ICF=informed consent form; IEC=Institutional Ethics Committee; IgG=immunoglobulin G; IGIV=intravenous immunoglobulin; IGSC=immune globulin subcutaneous; IP=investigational product; IRB=Institutional Review Board; IRT=Interactive Response Technology; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous; w=week.

[a] All subjects switching from cIGSC treatment will have the screening visit at 2 weeks prior to the first IP treatment, on the same day as the second to last prestudy IgG treatment dose for subjects with prestudy treatment interval every 1 week, and on the same day as the last prestudy IgG treatment dose for subjects with prestudy treatment interval every 2 weeks. Subjects switching from IGIV/HYQVIA treatment, with prestudy treatment interval every 3 weeks, will have the Screening Visit at 3 weeks prior to the first IP treatment, on the same day as the last prestudy IgG treatment dose.

[b] Ramp-up epoch is applicable only to those subjects who are on IGIV/cIGSC treatment prior to enrollment and it starts 1, 2, or 3 weeks (±1 day) after last prestudy IGIV/cIGSC dose depending on the prestudy IgG treatment interval. At Ramp-up Visit 1 the subject will receive a 1-week dose, at Ramp-up Visit 2 the subject will receive a 2-week dose.

[c] 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).

[d] Study Visit 1/Week 1 starts 2 weeks (±1 day) after the second ramp-up dose when ramp-up is applicable OR 3 weeks (±1 day) after last prestudy HYQVIA dose (when ramp-up dose is not applicable).

[e] Legally designated representative(s) informed consent and assent must be obtained prior to any study procedures (including the prestudy IgG treatment so that the total IgG trough level sample can be taken for screening purposes).

[f] Sites must consent subjects for the long-term follow-up Study TAK-881-3002 at the time of consenting to Study TAK-881-3001 participation, if permitted by IEC/IRB.

[g] For the prestudy IgG treatment dose at screening visit day, variations in the treatment interval of up to ±3 days relative to the prestudy IgG treatment dose before screening, are acceptable for all subjects (with a treatment interval of 7, 14, or 21 days). This applies also to the last prestudy IgG treatment (after screening visit day) for subjects with prestudy cIGSC on every 1-week interval. For subjects with prestudy cIGSC on every 1-week interval, the dose of the last prestudy IgG treatment (after screening visit day) must be the same as the dose of the second to last prestudy IgG treatment at screening visit.

[h] The subject is required to have a serum trough level of IgG >5 g/L at screening. This sample must be taken prior to the prestudy IgG treatment dose that is administered on the same day as the screening visit. The blood drawing for all IgG trough level determinations should take place before the IgG infusion is administered on the same day.

[i] Subjects rolling over to Study TAK-881-3002 will keep the diary for Study TAK-881-3001 until the Study Visit 1/Week 1 of Study TAK-881-3002 and the site will continue reporting concomitant medications, AEs, occurrence of fever and HRU outcomes up to the TAK-881-3002 Study Visit 1/Week 1 in TAK-881-3001 eCRFs.

[j] 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 6 PK sampling sequences. Please refer to Table 7.

[k] Height will be only measured at screening. All BW measurements are to be taken at the study site using the same scale/instrument throughout the study for that individual subject.

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Table 5. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 3-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period									
		Ramp-up Epoch [b]		3-Week Dosing Interval Epoch							EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Week [c]	(2 or 3 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W4	W7	W10	W13	W16	W19	W22	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

[l] If a subject's BW has increased or decreased by >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. The IRT system is programmed to make these calculations.

[m] Vital signs will be performed at screening and at each infusion visit: within 30 minutes (±10 min) prior to infusion; 30 min (±10 min) after the initiation of infusion; during the infusion if a systemic AE occurs, to be assessed if needed; at least 60 min after the completion of the infusion.

[n] Infusion of rHuPH20 will be administered SC first, followed by SC infusion of IGSC, 20% within 10 minutes of completion of the infusion of rHuPH20 in a sequential order using the same needle set at the same location. TAK-881 doses must not be administered over multiple days.

[o] The investigator/designee will contact the subject 3-5 days after completion of each IP infusion.

[p] Blood/urine samples will be collected before infusion. See Section 10.2 for more detailed information.

[q] At the time of the urine sample collection the presence of menstruation must be recorded for female subjects, if applicable, because blood contamination can easily occur.

[r] For females of childbearing potential. Testing will be performed at the specified time points and whenever a pregnancy is suspected. Urine pregnancy tests will be performed at a central laboratory, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

[s] These assessments at Study Visit 1 Week 1 are only to be performed by subjects without a ramp-up epoch.

[t] The questionnaire will only be completed by subjects who are ≥12 years of age at the time of signing the ICF. The questionnaire will not be completed by subjects who become 12 years of age during the course of the study.

[u] Performed prior to infusion.

[v] Interviews are for English-speaking US legally designated representative(s) only. After the legally designated representative(s) informed consent and subject assent for the study are signed, the subject's legally designated representative(s) must provide additional consent for interview and complete a contact order form. Subjects for whom legally designated representative(s) do not wish to undergo an interview will still be allowed to participate in the study. The interview should be performed within 2 weeks after the infusion visit.

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Table 6. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period								
		Ramp-up Epoch [b]		4-Week Dosing Interval Epoch						EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Administrative Procedures										
Informed Consent and Assent (if applicable) [e, f]	X									
Inclusion/Exclusion	X									
Demographics	X									
Medical History	X									
Subject's Prestudy IgG Treatment [g, h]	X									
Concomitant Medications and Nondrug Therapies [i]	← X →									
Randomization [j]	X									
Clinical Procedures										
Height, weight and BMI [k, l]	X			X	X	X	X	X	X	X
Vital Signs [m]	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X	X
AEs [i]	← X →									
Collection/Review Diaries [i]		X	X	X	X	X	X	X	X	X
IP Administration [n]		X	X	X	X	X	X	X	X	
Follow-up call after Infusion (3-5 days postinfusion) [o]		X	X	X	X	X	X	X	X	
Clinical Laboratory Assessments [p]										
Hematology Panel	X	X		X						X
Clinical Chemistry (reduced) Panel	X	X		X					X	
Urinalysis [q]	X									X
Pregnancy Test [r]	X									X
Viral Pathogen Serology	X									X

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Table 6. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period								
		Ramp-up Epoch [b]		4-Week Dosing Interval Epoch						EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d
Hemolysis Panel		X		X [s]	← (as applicable) →					
Total IgG Trough Levels [h]	X	X	X	X	X	X	X	X	X	X
IgG Subclasses (IgG1, IgG2, IgG3, IgG4) Trough levels		X		X [s]					X	
Anti-rHuPH20 Antibodies (binding/neutralizing, if applicable)		X		X [s]			X		X	
Sparse PK Sampling									X [j]	
Serum Retention Samples		X		X [s]						X
Clinical Outcome Assessments										
EQ-5D-5L [t]		X [u]		X [s, u]						X
HRU [i]		← X →								
Optional Assessments										
Semi-structured Qualitative Interview [v]									X	

AE=adverse event; BMI=body mass index; BW=body weight; d=day; cIGSC=conventional subcutaneous IgG; eCRF=electronic case report form; EOS=end of study; EQ-5D-5L=EuroQol 5 Dimensions 5 Level Questionnaire; ET=early termination; HRU=healthcare resource utilization; ICF=informed consent form; IEC=Institutional Ethics Committee; IgG=immunoglobulin G; IGIV=intravenous immunoglobulin; IGSC=immune globulin subcutaneous; IP=investigational product; IRB= Institutional Review Board; IRT=Interactive Response Technology; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous; w=week.

[a] All subjects switching from cIGSC treatment will have the screening visit at 2 weeks prior to the first IP treatment, on the same day as the second to last prestudy IgG treatment dose for subjects with prestudy treatment interval every 1 week, and on the same day as the last prestudy IgG treatment dose for subjects with prestudy treatment interval every 2 weeks. Subjects switching from IGIV/HYQVIA treatment, with prestudy treatment interval every 4 weeks, will have the Screening Visit at 4 weeks prior to the first IP treatment, on the same day as the last prestudy IgG treatment dose.

[b] Ramp-up epoch is applicable only to those subjects who are on IGIV/cIGSC treatment prior to enrollment and it starts 1, 2, or 4 weeks (±1 day) after last prestudy IGIV/cIGSC dose depending on the prestudy IgG treatment interval. At Ramp-up Visit 1 the subject will receive a 1-week dose, at Ramp-up Visit 2 the subject will receive a 2-week dose.

[c] 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).

[d] Study Visit 1/Week 1 starts 2 weeks (±1 day) after the second ramp-up dose when ramp-up is applicable OR 4 weeks (±1 day) after last prestudy HYQVIA dose (when ramp-up dose is not applicable).

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Table 6. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period								
		Ramp-up Epoch [b]		4-Week Dosing Interval Epoch						EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

[e] Legally designated representative(s) informed consent and assent must be obtained prior to any study procedures including screening (including the prestudy IgG treatment so that the total IgG trough level sample can be taken for screening purposes).

[f] Sites must consent subjects for the long-term follow-up Study TAK-881-3002 at the time of consenting to Study TAK-881-3001 participation, if permitted by IRB/IEC.

[g] For the prestudy IgG treatment dose at screening visit day, variations in the treatment interval of up to ±5 days relative to the prestudy IgG treatment dose before screening are acceptable for subjects with a treatment interval of 28 days, and variations in the treatment interval of up to ±3 days relative to the prestudy IgG treatment dose before screening, are acceptable for subjects with a treatment interval of 7 or 14 days. This applies also to the last prestudy IgG treatment (after screening visit day) for subjects with prestudy cIGSC on every 1-week interval. For subjects with prestudy cIGSC on a 1-week interval, the dose of the last prestudy IgG treatment (after screening visit day) must be the same as the dose of the second to last prestudy IgG treatment at screening visit.

[h] The subject is required to have a serum trough level of IgG >5 g/L at screening. This sample must be taken prior to the prestudy IgG treatment dose that is administered on the same day as the screening visit. The blood drawing for all IgG trough level determinations should take place before the IgG infusion is administered on the same day.

[i] Subjects rolling over to Study TAK-881-3002 will keep the diary for Study TAK-881-3001 until the Study Visit 1/Week 1 of Study TAK-881-3002 and the site will continue reporting concomitant medications, AEs, occurrence of fever and HRU outcomes up to the TAK-881-3002 Study Visit 1/Week 1 in TAK-881-3001 eCRFs.

[j] 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 6 PK sampling sequences. Please refer to Table 7.

[k] Height will only be measured at screening. All BW measurements are to be taken at the study site using the same scale/instrument throughout the study for that individual subject.

[l] If a subject's BW has increased or decreased by >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. The IRT system is programmed to make these calculations.

[m] Vital signs will be performed at screening and at each infusion visit: within 30 minutes (±10 min) prior to infusion; 30 min (±10 min) after the initiation of infusion; during the infusion if a systemic AE occurs, to be assessed if needed; at least 60 min after the completion of the infusion.

[n] Infusion of rHuPH20 will be administered SC first, followed by SC infusion of IGSC, 20% within 10 minutes of completion of the infusion of rHuPH20 in a sequential order using the same needle set at the same location. TAK-881 doses must not be administered over multiple days.

[o] The investigator/designee will contact the subject 3-5 days after completion of each IP infusion.

[p] Blood/urine samples will be collected before infusion. See Section 10.2 for more detailed information.

[q] At the time of the urine sample collection the presence of menstruation must be recorded for female subjects, if applicable, because blood contamination can easily occur.

[r] For females of childbearing potential. Testing will be performed at the specified time points and whenever a pregnancy is suspected. Urine pregnancy tests will be performed at a central laboratory, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

[s] These assessments at study Visit 1 Week 1 are only to be performed by subjects without a ramp-up epoch.

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Table 6. Schedule of Assessments for Pediatric Subjects Aged 2 to <16 Years Switching from HYQVIA/IGIV/cIGSC Treatment: 4-Week Dosing Interval

Period	Screening Visit [a]	Treatment Period								
		Ramp-up Epoch [b]		4-Week Dosing Interval Epoch						EOS/ ET Visit
Visit No.		Ramp-up Visit 1 (1-week dose)	Ramp-up Visit 2 (2-week dose)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Week [c]	(2 or 4 weeks prior to first IP treatment)	3 weeks prior to first full dose	2 weeks prior to first full dose	W1 [d]	W5	W9	W13	W17	W21	W25
Visit Allowance		±1 d	±1 d	±3 d	±3 d	±3 d	±3 d	±3 d	±1 d	±1 d

[t] The questionnaire can only be completed by subjects who are ≥12 years of age at the time of signing the ICF. The questionnaire will not be completed by subjects who become 12 years of age during the course of the study.

[u] Performed prior to infusion.

[v] Interviews are for English-speaking US legally designated representative(s) only. After the legally designated representative(s) informed consent and subject assent for the study are signed, the subject's legally designated representative(s) must provide additional consent for interview and complete a contact order form. Subjects for whom legally designated representative(s) do not wish to undergo an interview will still be allowed to participate in the study. The interview should be performed within 2 weeks after the infusion visit.

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Table 7. Pharmacokinetic Assessment Period: 3- and 4-Week Dosing Interval (Subjects Aged 2 to <16 Years)

Clinical Laboratory Assessment (Serum Total IgG)										
		3-Week Study Visit 8							EOS (3-Week)	
		4-Week Study Visit 6								EOS (4-Week)
		3-Week Week 22					Week 23	Week 24	Week 25	N/A
		4-Week Week 21					Week 22	N/A	Week 24	Week 25
		PREinfusion	POSTinfusion	POSTinfusion (from completion time)						
		PK Day 1 (Infusion Day)		PK Day 2 (24 hours postinfusion)	PK Day 3 (48 hours postinfusion)	PK Day 4 (72 hours postinfusion)	PK Day 8 (7 days postinfusion)	PK Day 15 (14 days postinfusion)	PK Day 22 [a] (21 days postinfusion)	PK Day 29 [a] (28 days postinfusion)
Allowance		within 1 hour before infusion	immediately after infusion	±4 hours	±4 hours	±8 hours	±1 day	±1 day	±1 day	±1 day
Sequence [b]	Sequence 1, 3-Week	X	X						X	
	Sequence 1, 4-Week									X
	Sequence 2, 3-Week	X		X					X	
	Sequence 2, 4-Week									X
	Sequence 3, 3-Week	X			X				X	
	Sequence 3, 4-Week									X
	Sequence 4, 3-Week	X				X			X	
	Sequence 4, 4-Week									X
	Sequence 5, 3-Week	X					X		X	
	Sequence 5, 4-Week									X
	Sequence 6, 3-Week	X						X	X	
	Sequence 6, 4-Week								X	X

EOS=end of study; IgG=immunoglobulin G; NA=not applicable; PK=pharmacokinetics.

[a] All PK Visits will take as reference the INFUSION Day at PK Day 1 (before and after infusion and 24 hours, 48 hours, 72 hours, 7 days, 14 days, 21 days and 28 days POSTINFUSION). However, PK Day 22 (3-Week Dosing Interval) and Day 29 (4-Week Dosing Interval) need to coincide with the EOS Visit and for that the window ±1 day may have to be applied.

[b] Subjects will be randomized (1:1:1:1:1:1) within 4 days prior to the first planned TAK-881 infusion to one of these sequences for PK sampling times.

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2. INTRODUCTION

2.1 Study Rationale

TAK-881 is a drug product of immune globulin subcutaneous (Human), 20% (IGSC, 20%) and recombinant human hyaluronidase (rHuPH20) for facilitated subcutaneous (SC) administration that evolved from the currently licensed HYQVIA (Immune Globulin Infusion [IGI], 10% with rHuPH20) and CUVITRU (IGSC, 20%). Both HYQVIA and CUVITRU have well-established efficacy and safety profiles.

HYQVIA and CUVITRU use the same validated and approved immunoglobulin manufacturing process except for the additional ultrafiltration step with CUVITRU to achieve the 20% concentration of the IgG component of TAK-881.

Similar to HYQVIA, TAK-881 is administered by sequential SC infusion of rHuPH20 first, followed by SC infusion of IgG. The ratio of rHuPH20 to IgG is the same as for HYQVIA, which is 80 units rHuPH20 per gram of IgG, but due to the higher IgG concentration of TAK-881 (20% IgG) in comparison to HYQVIA (10% IgG), the required infusion volume is reduced by 50% at an equivalent dose level.

Following the phase 1 tolerability/safety study with TAK-881 in adult healthy subjects (Study TAK-881-1001), this registrational phase 2/3 study aims to assess the pharmacokinetics (PK), safety, tolerability and immunogenicity of SC administration of TAK-881 compared to HYQVIA in subjects with Primary Immunodeficiency Disease (PIDD).

For additional information, see the TAK-881 investigator's brochure (IB).

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2.2 Background

Inborn errors of immunity, also referred to as PIDD, manifest as increased susceptibility to infectious diseases, autoimmunity, autoinflammatory diseases, allergy, and/or malignancy (Tangye et al., 2021). Individuals with a defect in antibody formation require lifelong replacement therapy with IgG products, generally in the range of 0.3 to 0.6 g/kg body weight (BW) every 3 to 4 weeks (Gardulf, 2007, Notarangelo, 2010). Administration of these doses is easily achieved by the intravenous (IV) route. However, due to the risk of severe systemic reactions and necessity for venous access, intravenous immune globulin (IGIV) must be administered under the supervision of a medical professional and may require premedication with corticosteroids or antihistamines (Berger, 2004, Bonilla, 2008, Misbah et al., 2009, Tangye et al., 2021).

IgG administered by the SC route is safe and equally efficacious to IGIV, and results in more stable serum levels of IgG (Moore and Quinn, 2008).

As IGSC rarely induces systemic reactions and does not require venous access, self-infusion in the patient's home is possible and can easily be mastered, even by children and elderly patients (Gardulf et al., 1993, Gardulf et al., 1991, Gardulf et al., 1995, Misbah et al., 2009, Moore and Quinn, 2008). Home treatment is associated with reduced costs and is universally reported to be appreciated by patients, who report an improved sense of freedom and independence, less disruption to daily activities and a reduced sense of being sick or disabled (Fasth and Nyström, 2008, Gardulf, 2007, Gardulf and Hammarström, 1996, Gardulf et al., 1995, Nicolay et al., 2006). A number of studies have reported improved health-related quality of life (HRQoL), treatment satisfaction and a distinct preference for IGSC in adult and pediatric patients with PIDD (Berger et al., 2010, Gardulf, 2007, Gardulf et al., 2004).

IGSC is an important alternative to IV treatment in patients with PIDD who cannot tolerate IV infusion due to severe adverse drug reactions (ADRs) or comorbidities (Berger, 2004, Misbah et al., 2009, Moore and Quinn, 2008). These include infants and other patients in whom stable venous access is difficult to maintain (Meth et al., 2010, Skoda-Smith et al., 2010). In these individuals, IGSC precludes the need for surgically implanted devices such as indwelling catheters (Meth et al., 2010, Skoda-Smith et al., 2010).

The primary disadvantage of SC therapy has been the limited volume that can be infused in a single SC site (up to 60 mL), necessitating the use of multiple needle sites on a weekly or biweekly (every-other-week) basis rather than a single IV infusion once every 3 to 4 weeks (Berger, 2004, Misbah et al., 2009, Moore and Quinn, 2008). Furthermore, the bioavailability of IgG after SC administration is substantially lower than after IV administration, necessitating an increased dose of IgG (Ochs et al., 2006). Multiple needle insertions and frequent administration is a major deterrent for patients and has led some physicians to recommend against IGSC (Misbah et al., 2009).

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rHuPH20 acts locally and transiently within the extracellular tissue matrix to increase the dispersion and absorption of other subsequently infused drugs and fluids. rHuPH20 depolymerizes the gel-like hyaluronan, resulting in a transient increase in permeability of the local SC tissue. The increased flow rates and increased delivery volumes of IgG compare favorably with SC administration without rHuPH20 (Misbah et al., 2009).

HYQVIA is the only facilitated SC IGI approved for PIDD both adults and pediatric patients in the US and in the EU, and for select Secondary Immunodeficiencies (SID) in the EU and other countries except the US. HYQVIA offers a unique opportunity for treatment personalization with reduced frequency of infusion (total IgG dose once per month), and a lower number of needle sticks and infusion sites than conventional IGSCs (cIGSC). Moreover, HYQVIA has reduced systemic side effects, demonstrated an efficacy similar to IGIV, and can be a good alternative for patients who have poor venous access, thus combining the benefits of IGSC and IGIV.

CUVITRU, a cIGSC, 20% product, has a high tolerability profile, allowing for infusion of up to 60 mL/hour/site and 60 mL per site, resulting in potentially shorter infusion times and positive patient outcomes as compared to cIGSC products.

With TAK-881, the rHuPH20 component enables SC administration of IGSC, 20% to occur with a lower volume than HYQVIA, with potentially reduced infusion times compared to cIGSC, 20%.

The clinical development of TAK-881 is based on the development of HYQVIA and CUVITRU. The following sections provide an overview of HYQVIA and CUVITRU along with relevant data summarized from HYQVIA and CUVITRU studies.

2.2.1 Overview and Relevant Data of HYQVIA

HYQVIA (also known as TAK-771) is an IGI (Human) 10% solution with a rHuPH20. HYQVIA has been developed to enable the SC administration of large volumes of IgG. HYQVIA is approved in 47 countries, including 31 European countries, and in the US. Licensed indications in each country are detailed in the corresponding national prescribing information. In Europe, IGI, 10% with rHuPH20 is marketed as HyQvia and in the US, IGI, 10% with rHuPH20 is marketed as HYQVIA. Overall, clinical data and postmarketing data for HYQVIA obtained since first licensure are consistent with the known safety profile of IgG preparations and IGI, 10% (Baxalta US Inc., 2020).

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The safety profile of HYQVIA is not considered to be different from the individual components. Since rHuPH20 acts locally with little systemic absorption, no impact on the systemic effects and safety of IGI, 10% is anticipated. Nonclinical studies of HYQVIA showed that rHuPH20 increases the dispersion and absorption of IGI, 10%, while mitigating induration and tissue damage after SC administration of large volumes of IgG. No toxicologically relevant adverse effects on local tolerability were observed with HYQVIA treatment. Endogenous PH20 hyaluronidase is limited to expression in the testes in the human reproductive tract, and nonclinical studies have demonstrated no adverse effects from anti-rHuPH20 antibody exposure from conception through adulthood and no evidence of toxicity during fetal development.

As per May 2023, the clinical program for HYQVIA includes 11 completed interventional clinical studies, 2 completed non-interventional postmarketing safety studies, and 1 completed non-interventional registry study in women exposed to treatment before or during pregnancy (pregnancy registry). Together, these studies demonstrate the efficacy, PK, safety and tolerability of HYQVIA. The rHuPH20 component increased the bioavailability of IGI, 10% administered SC by approximately 20%, thus reducing the clinically effective dose compared to immunoglobulins administered subcutaneously without rHuPH20.

HYQVIA was shown to be effective in preventing infections in patients with PIDD with slightly lower rates of validated acute serious bacterial infections and all infections for HYQVIA compared to IGSC, and protection was maintained with long-term treatment. HYQVIA was more effective than placebo in preventing relapse of neuromuscular disability and impairment in chronic inflammatory demyelinating polyneuropathy (CIDP), irrespective of age, sex, dosing regimen, or geographic location. During the clinical studies, HYQVIA was well tolerated when administered at large volumes and utilizing maximum flow rates significantly higher than those used for IV infusions. The frequency of ADRs per infusion obtained for HYQVIA compares favorably with published data on IGSC, and the frequency of systemic ADRs was lower with HYQVIA than with IGIV treatment, which is in agreement with published data on IGSC treatment. The incidence of treatment-emergent rHuPH20-reactive binding antibodies was within previously published limits, and neutralizing antibodies have been observed in only 1 subject with CIPD. In addition, the presence of anti-rHuPH20 antibodies was not associated with an increased rate of treatment-emergent adverse events (TEAEs). In conclusion, the clinical programs to date have shown that HYQVIA is safe, effective and well tolerated in PIDD and CIDP.

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2.2.2 Overview and Relevant Data of CUVITRU

CUVITRU is an Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) that has been developed with the aim of providing a more concentrated product with a reduced required infusion volume for SC administration. IGSC, 20% is presently approved under the trade name CUVITRU in 37 countries globally, including 16 EU countries, the US, UK, Switzerland, Canada, and Australia.

The safety, tolerability, and efficacy of IGSC, 20% in PIDD have been demonstrated in 2 phase 2/3 studies in Europe (Protocol 170903) and in North America (Protocol 170904), and in 1 phase 3 study in Japan (Protocol TAK-664-3001). A phase 3 extension study assessing long-term safety and tolerability in Japanese subjects (Protocol TAK-664-3002) is currently ongoing.

IGSC, 20% was also administered to healthy volunteers in a phase 1 study (Protocol 170901 Part 1) to investigate the safety and tolerability of IGSC, 20% administered with rHuPH20 as a permeation enhancer and to determine the optimal dose ratio. A total of 14 infusions of IGSC, 20% (12 with and 2 without rHuPH20) were administered in 7 subjects, none of whom experienced serious or severe adverse events (AEs) after administration of IGSC, 20% or withdrew from the study due to AEs.

2.3 Clinical Studies with TAK-881

One phase 1 single-dose, single center, open-label, 3-arm study has been completed (Nagy et al., 2023). The study evaluated the tolerability, safety, and immunogenicity of TAK-881 at various infusion rates in healthy adult subjects aged 19 to 50 years.

This study comprised 3 treatment arms:

- Treatment Arm 1 - Subjects received a single SC infusion of TAK-881 comprising 0.4 g/kg (exterior tubing in-line warming applied) IGSC, 20% at progressively increased infusion rates following a single SC infusion of rHuPH20 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 2 - Subjects received a single SC infusion of TAK-881 comprising 1.0 g/kg (exterior tubing in-line warming applied) IGSC, 20% at progressively increased infusion rates following a single SC infusion of rHuPH20 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 3 - Subjects received a single SC infusion of TAK-881 comprising 1.0 g/kg (unwarmed) IGSC, 20% at progressively increased infusion rates following a single SC infusion of rHuPH20 80 U/g IgG on Day 1 of the study treatment period.

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rHuPH20 was administered first via a peristaltic pump at a rate of 120 mL/h/site and at infusion volumes of up to 30 mL/site. Starting within 10 minutes of completion of rHuPH20 infusion, IGSC, 20% was administered at infusion volumes of up to 300 mL/site. A maximum infusion rate of 300 mL/h was selected to allow comparison with HYQVIA, as well as comparison of this infusion rate between warmed and unwarmed TAK-881. IGSC, 20% infusion required 1 or 2 infusion sites; if 2 infusion sites were needed, the maximum possible volume was administered at the first infusion site, with the remainder of the total dose subsequently administered into a second site.

A total of 24 (100%) healthy adult subjects were enrolled in the study. Eight subjects were enrolled in each of the 3 treatment arms, and a minimum of 3 subjects were enrolled in each of the 2 BMI groups (18 to <25 kg/m^2, ≥25 to 30 kg/m^2) in each treatment arm. Twenty-three (95.8%) subjects completed the study, and 1 (4.2%) subject discontinued the study due to withdrawal of consent.

The primary objective of this study was to assess the tolerability of TAK-881 per infusion site at various SC infusion rates in healthy adult subjects. “Tolerable” infusions were not interrupted, stopped, or reduced in rate owing to TAK-881-related TEAEs. Infusions into the first infusion site (mean total IGSC, 20% volume, 141.3, 291.3, and 293.8 mL in treatment arms 1, 2, and 3, respectively) were tolerable in all participants (n=24).

For participants requiring a second infusion site (n=0, 4, and 7 participants in treatment arms 1, 2, and 3, respectively), all infusions into the second infusion site were also tolerated by all participants (n=11; mean total IGSC, 20% volume, 97.5 and 70.0 mL in treatment arms 2 and 3, respectively).

Secondary endpoints were the occurrence of TEAEs, clinical laboratory parameters, vital signs, and immunogenicity. A total of 107 TEAEs were reported in 24 (100%) subjects during the study. Of these, 105 TEAEs were considered related to TAK-881. Twenty-four (100%) subjects had 102 local TEAEs, 4 (16.7%) subjects had 5 systemic TEAEs, and 1 (4.2%) subject had 1 TEAE (catheter leakage) of special interest. All TEAEs were deemed to be mild in severity and were recovered/resolved by the end of the study. The occurrence of TEAEs was broadly similar between BMI 18 to < 25 and 25 to 30 kg/m^2 groups. In Treatment Arm 1, there were 27 TEAEs in 8 participants (100.0%), of which 25 TEAEs were considered related to TAK-881. In treatment arms 2 and 3, there were 34 TEAEs in 8 participants (100.0%), and 46 TEAEs in 8 participants (100.0%), respectively, all of which were considered related to TAK-881. Most TEAEs were infusion site-related (102 TEAEs reported in 24 participants [100.0%]).

In general, there were no clinically meaningful changes from baseline or apparent differences between the treatment arms in clinical laboratory parameters and vital sign results. No individual clinical laboratory abnormalities or vital sign results were reported as TEAEs by the investigator. All participants tested negative for binding anti-rHuPH20 antibodies (titer < 1:160).

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Warming of IGSC, 20% may potentially reduce the viscosity of concentrated IgG therapies and improve tolerability. In this study, all infusions were tolerated, and a maximum tolerable infusion rate of 300 mL/h/site was achieved in all treatment arms, with and without in-line warming.

In conclusion, TAK-881, warmed and unwarmed, was generally well tolerated at various SC infusion rates in healthy adults. TAK-881, warmed and unwarmed, was safe at various SC infusion rates up to 300 mL/hour with a slightly higher occurrence of TEAEs in the unwarmed TAK-881 treatment arm compared to the warmed TAK-881 treatment arm at the same dose (1.0 g/kg). All TEAEs were mild in severity. Nearly all TEAEs were local infusion site reactions, and all participants experienced local infusion site reactions in this study, most frequently infusion site erythema and swelling, which is consistent with administration of cIGSC. It should also be noted that more subjects used 2 infusion sites in Treatment Arm 3 compared to Treatment Arm 2 (Treatment Arm 2: 4 of 8 subjects vs Treatment Arm 3: 7 of 8 subjects) which contributed to a higher number of TEAEs in Treatment Arm 3. There was no occurrence of binding and neutralizing antibodies to rHuPH20.

As this study did not find a notable difference between warmed and unwarmed TAK-881, and considering the complexity and reduced patient convenience of using a warming device, the current study will infuse unwarmed TAK-881.

2.4 Benefit/Risk Assessment

Refer to the latest version of the TAK-881 IB for the overall benefit/risk assessment and the most current information regarding drug metabolism, PK, efficacy, and safety of TAK-881.

2.4.1 Benefit Assessment

The higher concentration of TAK-881 (20% IgG) in comparison to HYQVIA (10% IgG) allows infusion to occur with a lower volume. This presents an opportunity to improve the PIDD patient's infusion experience.

2.4.2 Risk Assessment

The risks associated with dosing TAK-881 are anticipated to be similar to those previously documented in the product labels for HYQVIA and CUVITRU. CUVITRU and HYQVIA are licensed products for which the safety profile is well established in hundreds of thousands of patients worldwide, including pediatric patients.

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The most common systemic adverse reactions (ARs) observed in PIDD clinical trials with HYQVIA in >5% of subjects were: headache, antibody formation against rHuPH20, fatigue, nausea, pyrexia, and vomiting. The most frequent local ARs observed in ≥5% of subjects were: infusion site pain, infusion site erythema, infusion site swelling, and infusion site pruritus.

The most common systemic ARs observed in clinical trials with CUVITRU in ≥5% of subjects were headache, nausea, fatigue, diarrhea, and vomiting. The most frequent local ARs observed in ≥5% of subjects were: infusion site pain, infusion site erythema, and infusion site pruritus.

Development of non-neutralizing antibodies to the rHuPH20 component has been reported in patients receiving HYQVIA in clinical studies and postmarketing safety studies. However, no neutralizing antibody has been detected to date in studies in PIDD. With regards to antibody formation against rHuPH20, clinical data have shown no temporal association between ARs and the presence of anti-rHuPH20 antibodies, and no increase in incidence or severity of ARs in subjects who developed anti-rHuPH20 antibodies. There is a theoretical potential risk for such antibodies to cross-react with human hyaluronidase which is known to be expressed in the adult male testes, epididymis, and sperm. However, no evidence for cross-reactivity with related hyaluronidase family members Hyal1, Hyal2, and Hyal4 has been detected in studies with HYQVIA to date (Printz et al., 2022). Treatment-emergent antibodies against rHuPH20 (binding and neutralizing antibodies) will be monitored during this clinical study.

2.4.2.1 Pregnancy, Breast Feeding, Fertility

Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy or on the fetus and the neonate are to be expected. Development and reproductive toxicology studies have been conducted with rHuPH20 in mice and rabbits.

No adverse effects on pregnancy and fetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20 were transferred to offspring in utero. The effects of antibodies to the rHuPH20 component on the human embryo or on human fetal development are currently unknown. Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Although the safety of HYQVIA for use in human pregnancy has been investigated, the available data is still limited, and therefore, HYQVIA should only be given with caution to pregnant or breastfeeding women. Study 161301 was a non-interventional, uncontrolled, two-arm, open-label, multicenter postauthorization pregnancy registry that aimed to address safety concerns in women who become pregnant during or after treatment with HYQVIA.

Nine women were enrolled and of the 8 pregnancies with known outcomes, there were 8 live births with normal APGAR scores. There were no specified labor or delivery complications. No AEs were reported as related to HYQVIA. Four mothers were tested for anti-rHuPH20 binding or neutralizing antibodies and no antibodies were detected. The limited sample size of the pregnancy registry precludes any scientific robust conclusion.

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There are currently no clinical safety data for TAK-881 on fertility available. Clinical experience with immunoglobulins suggests that no harmful effects of IgG 10%/20% on fertility are to be expected. Animal studies do not indicate direct or indirect harmful effects of rHuPH20 or anti-rHuPH20 antibodies with respect to reproductive potential at the doses used for facilitating administration.

Subjects who become pregnant during the study must be withdrawn from the study.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The following are the objectives and endpoints of this study:

Objectives	Endpoints
Primary	
• To demonstrate PK comparability of TAK-881 and HYQVIA at steady-state after SC administration in subjects aged ≥16 years with PIDD.	• Area under the curve during the dosing interval at steady-state ($AUC_{0-\tau,ss}$) based on total immunoglobulin G (IgG) levels.
Secondary	
• To assess infections in all subjects.	<u>Efficacy</u> • 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.
• To assess healthcare resource utilization (HRU) for subjects using TAK-881/HYQVIA.	• 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.
• To evaluate PK, safety, tolerability and immunogenicity of TAK-881 in subjects aged ≥16 years with PIDD.	<u>Pharmacokinetics:</u> • 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.

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Objectives	Endpoints
	• Trough level of total IgG. • Trough level of IgG subclasses and antigen-specific IgG antibodies. <u>Safety:</u> • Occurrence of treatment-emergent adverse events (TEAEs). <u>Tolerability:</u> • Occurrence of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881-related TEAEs. <u>Immunogenicity:</u> • Occurrence of positive binding (defined as titer ≥1:160) and neutralizing antibodies to rHuPH20.
• To characterize the PK of TAK-881 between subjects aged ≥16 years and subjects aged 2 to <16 years with PIDD.	• Pharmacokinetics at steady-state including $AUC_{0\text{-}\tau,ss}$, C_{max}, T_{max}, $t_{1/2}$, CL/F, V_z/F and $AUC_{0\text{-}\tau,ss}$/week based on total IgG levels.
• 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.	<u>Pharmacokinetics:</u> • Trough level of total IgG. • Trough level of IgG subclasses. <u>Safety:</u> • Occurrence of TEAEs. <u>Tolerability:</u> • Occurrence of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881-related TEAEs. <u>Immunogenicity:</u> • Occurrence of positive binding (defined as titer ≥1:160) and neutralizing antibodies to rHuPH20.

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Objectives	Endpoints
• To evaluate infusion parameters at full dose with both TAK-881 and HYQVIA in all subjects.	Infusion Parameters 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).
Exploratory	
• To assess subject satisfaction with TAK-881/HYQVIA treatment in subjects aged ≥16 years.	• Subject satisfaction evaluated by subject-reported scores on the Treatment Satisfaction Questionnaire for Medication - 9 items (TSQM-9).
• To assess subject HRQoL while on TAK-881/HYQVIA treatment in subjects aged ≥12 years.	• Subject HRQoL evaluated via the EuroQol 5 Dimension 5 Level Questionnaire (EQ-5D-5L).
• To assess infusion preparation time for TAK-881 and HYQVIA by nurse/pharmacist recordings in subjects aged ≥16 years.	• HCP measured time of infusion preparation.

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3.1 Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

- To assess infections in all subjects.
- To assess 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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3.1.3 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.

3.2 Endpoints

3.2.1 Primary Endpoint

The primary endpoint is $AUC_{0-\tau,ss}$ based on total IgG levels.

3.2.2 Secondary Endpoints

3.2.2.1 Efficacy Endpoints

- Annualized rate of all infections.
- Annualized rate of ASBIs.
- Annualized rate of episodes of fever.
- Time to first ASBI.
- Duration of infections.

3.2.2.2 Health 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.

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3.2.2.3 Pharmacokinetic Endpoints

- Pharmacokinetics at steady-state including C_{max}, T_{max}, $t_{1/2}$, CL/F, 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).

3.2.2.4 Safety Endpoints

- Occurrence of TEAEs.
- Tolerability: occurrence of infusion withdrawals, interruptions, and infusion rate reductions due to TAK-881-related TEAEs.
- Immunogenicity: occurrence of positive binding (defined as titer ≥1:160) and neutralizing antibodies to rHuPH20.

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

3.2.2.5 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).

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3.2.3 Exploratory Endpoints

- Subject satisfaction evaluated by subject-reported scores on TSQM-9.
- Subject HRQoL evaluated via EQ-5D-5L.
- HCP measured time of infusion preparation.

3.3 Estimands

The following are the objectives and associated estimands for this study:

Objective	Estimand
To demonstrate PK comparability of TAK-881 and HYQVIA at steady-state after SC administration in subjects aged ≥16 years with PIDD.	Analysis variable: $AUC_{0\text{-}\tau,ss}$ based on total IgG levels. 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. 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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4. STUDY DESIGN

4.1 Overall 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 1.2. For the Schedule of Assessments, see Section 1.3.

In the present study, approximately 75 subjects in total (51 subjects aged ≥16 years and 24 subjects aged 2 to <16 years) will be screened. 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.

Study visits will occur according to assessment schedules in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6.

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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. Deviations of >1 days but <3 days for IP ramp-up visits and IP visits coinciding with serial/sparse PK sampling will not lead to study discontinuations. 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).

During the study subjects will receive TAK-881/HYQVIA at 3- or 4-week intervals (with the exception of the initial ramp-up epoch, when applicable). Subjects previously treated with IGIV/HYQVIA will continue on their prestudy treatment interval. For subjects previously treated with cIGSC, the treatment interval during the study will be decided at the screening visit at the discretion of the investigator, which can be either every 3 or 4 weeks.

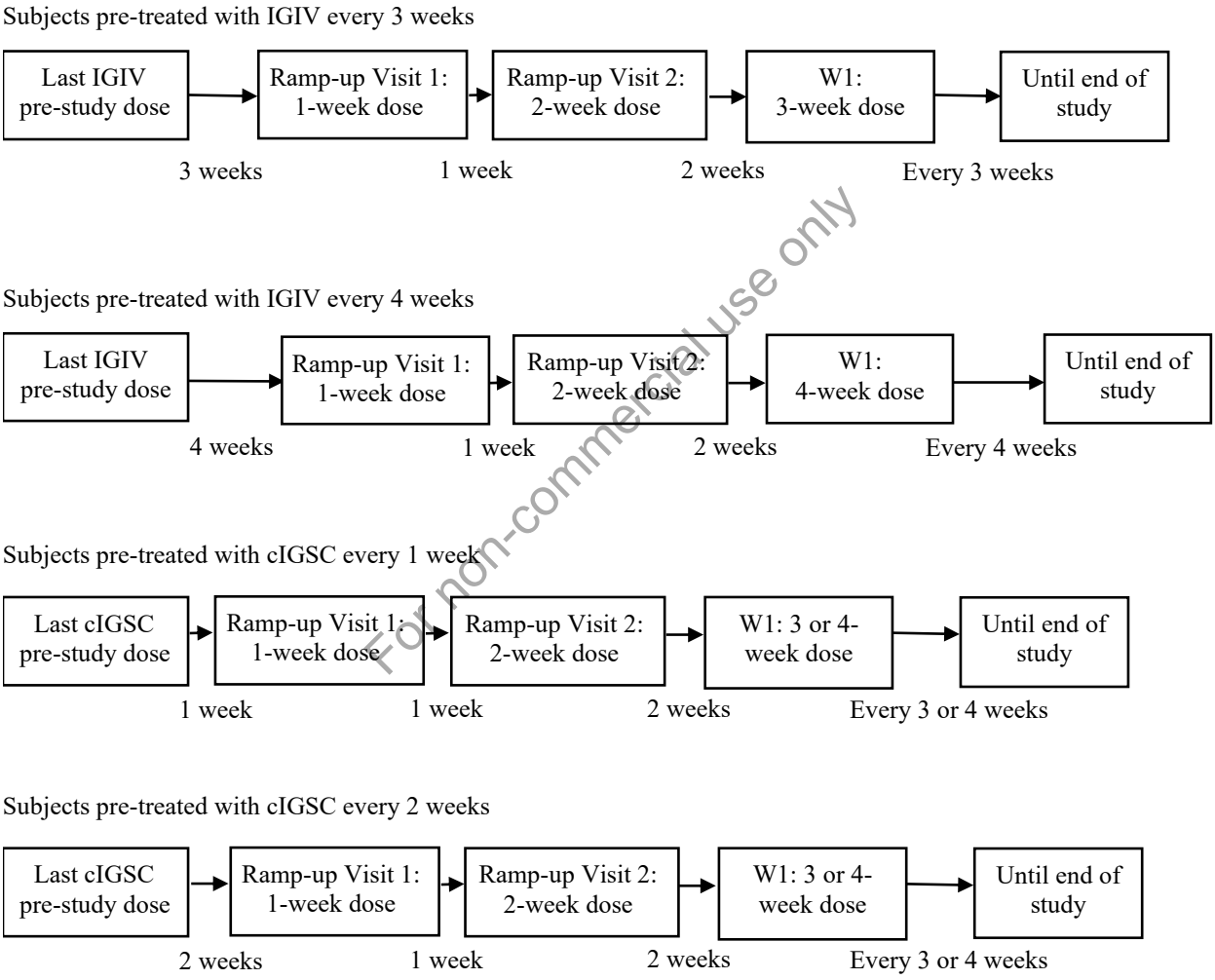
4.1.1 Screening and Ramp-up Epochs

The duration of the screening epoch is up to 4 weeks. All subjects are required to have a serum trough level of IgG >5 g/L at screening to fulfill inclusion criterion #4. This sample must be taken prior to the administration of the prestudy IgG treatment dose that is administered on the same day of the screening visit.

During the screening period no variation in cIGSC doses is allowed.

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 is 2 weeks before the first treatment epoch starts (Figure 6).

Figure 6. Treatment Schedule for Subjects who Enter the Ramp-up Epoch



cIGSC=conventional subcutaneous immunoglobulin G; IGIV=intravenous immunoglobulin; W=Week.

Subjects who have already been receiving HYQVIA treatment, will not enter the ramp-up epoch. After screening, these subjects will directly enter the treatment epoch(s), the first full dose of TAK-881/HYQVIA will be administered 3 or 4 weeks after the last prestudy HYQVIA dose, depending on the prestudy HYQVIA treatment interval.

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4.1.2 Treatment Epochs

4.1.2.1 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). Each crossover epoch is considered as a treatment epoch. 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 (Table 8). 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.

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Table 8. Treatment Sequences in the AB/BA Crossover Epochs

	Crossover Epoch 1	Crossover Epoch 2
Sequence 1 (AB)	6 or 8 full doses of TAK-881	6 or 8 full doses of HYQVIA
Sequence 2 (BA)	6 or 8 full doses of HYQVIA	6 or 8 full doses of TAK-881

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).

Subjects will undergo serial PK sampling at the time points specified in Table 3 and Table 4.

4.1.2.2 Single-Arm Treatment Epoch (Subjects Aged 2 to <16 Years)

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 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 DMC evaluation will not stop further enrollment of subjects ≥16 years, unless a criterion for premature termination/suspension of the study is met (Section 10.1.12.2).

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 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 one 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. In order to avoid multiple blood drawings in children, subjects will undergo sparse PK sampling. 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 6 sampling sequences specified in Table 7.

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4.2 Sites and Regions

This study is planned to be conducted at approximately 40 sites in the United States of America (USA) and Europe.

4.3 Scientific Rationale for Study Design

The primary objective of the study is to demonstrate PK comparability of TAK-881 and HYQVIA at steady-state after SC administration in subjects aged ≥16 years with PIDD.

PK comparability between different formulations has been used to support approval of IgG products using a licensed IgG product as reference (Wasserman, 2020). The crossover design is generally accepted as the design of choice for the analysis of comparative bioavailability data (FDA, 2008).

Because the study will be performed in subjects with PIDD who are already receiving treatment regularly, PK comparability of TAK-881 and HYQVIA will be evaluated by measuring AUC during the dosing interval at steady-state after repeated dosing. Following European Medicines Agency (EMA) and Food and Drug Administration (FDA) regulatory guidelines (FDA, 2008) (EMA, 2015), AUC will be assessed in each crossover epoch after 6 months treatment at full dose, ie, at the eighth infusion if administered every 3 weeks, and at the sixth infusion if administered every 4 weeks.

In accordance with guidelines from the FDA (FDA, 2008) and EMA (EMA, 2015), the study includes a pediatric population with an age distribution representative of PIDD. Both EU and FDA regulatory documents provide guidance on general principles concerning clinical trial design for investigational immunoglobulin products and recommends inclusion of pediatric subjects with PIDD. The FDA guidance document specifies the sample size of 6 to 12 subjects in each pediatric age group. The EU Guideline recommends that approximately 20 children and adolescents with an age distribution representative of this patient population should be included. As the phase 1 study was conducted in healthy adults, in this study 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).

Frequent blood sampling will be performed during the study in accordance with guidelines from the FDA (FDA, 2008) and EMA (EMA, 2015) for evaluation of safety and PK endpoints.

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4.3.1 Subject Input into Design

There was no subject involvement in the design of the clinical study.

4.4 Justification for Dose

All subjects in this study must have received regular IgG treatment (HYQVIA, IGIV, or cIGSC) over a period of at least 12 weeks prior to screening. The TAK-881/HYQVIA dose (in g/kg BW/week) administered in this study will be the same as the weekly equivalent of the prestudy IgG treatment dose at screening. Thus, it is assumed that the subject's treatment regimen has already been optimized in the prestudy period. During the study the dose may be modified only if clinically indicated (eg, increased incidence of infections, low IgG trough level [≤5 g/L]) at the investigator's discretion.

Subjects switching from IGIV or cIGSC treatment will enter a ramp-up epoch. Current HYQVIA dosing guidelines include a 3- or 6-week-long ramp-up period for a 3-week and 4-week dosing schedule, respectively. This allows the subject to become accustomed to the large SC doses. Data from real-world experience settings shows that an accelerated ramp-up period with HYQVIA is common and well tolerated (Hustad et al., 2021, Wasserman, 2020). The studies concluded that a shorter ramp-up period did not appear to increase the number of AEs compared to standard ramp-up schedules. In the phase 1, open-label, randomized study (TAK-771-1001) conducted in healthy volunteers, the tolerability and safety of HYQVIA was evaluated in 3 different ramp-up dosing schedules: the conventional ramp-up dosing schedule, an accelerated ramp-up schedule and without a ramp-up period.

The target dose level was either 0.4 g/kg or 1.0 g/kg. All subjects completed all initiated infusions except for one subject who experienced a headache resulting in an infusion rate reduction in the conventional dose ramp-up arm. All subjects experienced local TEAEs, including infusion site swelling, erythema, pain and pruritus. Systemic TEAEs were experienced by 1/8 (12.5%), 2/8 (25.0%) and 2/8 (25.0%) subjects in the conventional, accelerated and no dose ramp-up arms, respectively.

All TEAEs were mild in severity. HYQVIA at a target dose of 0.4 g/kg/infusion, which is a common PIDD dose, showed a favorable safety and tolerability profile in healthy adults, with comparable tolerability and safety outcomes between the dose ramp-up treatment arms. The study concluded that an accelerated and no dose ramp-up schedules could be considered as potential alternatives to the conventional dose ramp-up. Based on all data, in this study an accelerated two-step ramp-up epoch with a 1- week and 2-week dose of TAK-881/HYQVIA will be implemented. This will reduce the number of treatment visits and thus the burden on subjects.

4.5 End of Study/Study Completion Definition

The maximum subject participation period is approximately 56 weeks for subjects aged ≥16 years and approximately 32 weeks for subjects aged 2 to <16 years.

The study completion date is defined as the date on which the last subject in the study completes the final protocol-defined assessments.

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5. STUDY POPULATION

Informed consent must be obtained before any screening procedures, other than activities the Institutional Review Board/Institutional Ethics Committee has specifically approved for use as prescreening procedures. In addition, sites must also consent subjects for the long-term follow-up study (Study TAK-881-3002) at the time of consenting to Study TAK-881-3001 participation, if permitted by Institutional Review Board (IRB)/Institutional Ethics Committee (IEC). Informed consent requirements are described in Section 10.1.3.

All entry criteria, including test results, must be confirmed before randomization/enrollment (Section 5.6). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Investigators must account for all individuals who sign informed consent forms (ICFs) and/or assent forms (as applicable), regardless of the outcome of the screening, by completing the required electronic case report forms (eCRFs).

Rescreening will be allowed under the circumstances described in Section 5.4.2.

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5.1 Inclusion Criteria

Subjects must meet *all* of the following criteria to be eligible for inclusion in the study:

1. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving a defect in antibody formation and requiring IgG replacement, as defined according to the International Union of Immunological Societies (IUIS) Committee (Bousfiha et al., 2020, Tangye et al., 2021).
2. Subject is 2 years to <16 years at the time of signing the ICF for the single-arm treatment part of the study OR 16 years or older at the time of signing the ICF for the crossover part of the study.
3. Subject has received a stable dose of regular treatment with any IGIV OR HYQVIA with a treatment interval of every 21 or 28 days OR any cIGSC with a treatment interval of every 7 or 14 days over a period of at least 12 weeks prior to screening at a minimum prestudy IgG dose equivalent to 0.3 g/kg BW/4 weeks and a maximum dose equivalent to 1 g/kg BW/4 weeks. Over that period, the subject should have been on the same product of IGIV, HYQVIA, or cIGSC. A stable dose is defined as one that deviates less than ±25% from the mean dose for all IgG infusions within this 12-week period prior to screening. Variations in the treatment interval of up to ±5 days for subjects with a 28-day treatment interval and of up to ±3 days for subjects with a 7, 14, or 21-day treatment interval are acceptable up to the first IP infusion.

4. Subject has a serum trough level of IgG >5 g/L at the following time points:
   a. At screening (sample taken prior to prestudy IgG infusion after signing the ICF) and
   b. Within 12 weeks prior to screening.
5. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ a highly effective form of contraception for the duration of the study.
6. Subject or, in the case of minors, legally designated representative(s) is/are willing and able to comply with the requirements of the protocol, including PK blood sampling, for the duration of the study.

Informed Consent

1. The subject or, in the case of minors, legally designated representative(s) is/are willing and able to understand and fully comply with study procedures and requirements, in the opinion of the investigator.
2. The subject or, in the case of minors, legally designated representative(s) has/have provided informed consent/assent, if applicable, (that is, in writing, documented via a signed and dated ICF and/or eConsent, if available), and any required privacy authorization prior to the initiation of any study procedures.

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5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met:

1. Subject has a known history of a positive result or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2. Cured subjects with a history of hepatitis C infection who have a negative PCR test at screening are eligible.
2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
   a. Persistent alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >2.5× the upper limit of normal (ULN) for the testing laboratory.
   b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] $\leq 500/mm^3$).
3. Known history of chronic kidney disease, or estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2 at screening.

4. Subject has anemia that would preclude phlebotomy for laboratory studies, according to standard practice at the site, at the discretion of the investigator.
5. Subject has a known history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IV immunoglobulin, SC immunoglobulin, and/or immune serum globulin infusions.
6. Subjects with a known systemic hypersensitivity to any of the excipients of TAK-881/HYQVIA in accordance with the IB/package insert/Summary of Product Characteristics (SmPC).
7. Known substance or prescription drug abuse within 12 months of screening.
8. Subject has immunoglobulin A (IgA) deficiency (IgA less than 0.07 g/L) associated with known anti-IgA antibodies and a history of hypersensitivity.
9. Subject has a known systemic hypersensitivity to hyaluronidase or rHuPH20.
10. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening.
11. Subject has a bleeding disorder or a platelet count less than 20,000/µL, or in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of IGSC therapy.
12. Treatment with immunosuppressants including chemotherapeutic agents, immunomodulators, and long-term systemic corticosteroid (defined as a daily dose of >1 mg of prednisone equivalent/kg/day for >30 days) within 12 weeks prior to screening. Short or intermittent courses (≤10 days) of corticosteroids are allowed.
13. Live-attenuated viral vaccination within 12 weeks prior to screening.
14. History or current diagnosis of thrombotic episodes; venous thrombus that occurred in association with a medical device >2 years prior to screening are allowed.
15. Subject has severe dermatitis that would preclude adequate sites for safe product administration in the opinion of the investigator.
16. Subject has a medical condition, laboratory finding, or physical examination finding that precludes participation, or with clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may interfere with successful completion of the study or place the subject at undue medical risk.
17. Subject has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to screening.

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18. Subject is scheduled to participate in another clinical study involving an IP (except for subjects scheduled to enroll in a long-term follow-up study with TAK-881) or investigational device during the course of this study.
19. Subject is a family member or employee of the investigator or the investigator's site staff.
20. If female, subject is pregnant or lactating at the time of screening.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no food or drink restrictions for subjects in this study.

5.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions on the consumption of caffeine or alcohol, or the use of tobacco for subjects in this study.

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5.3.3 Activity

There are no restrictions on activity for subjects in this study.

5.3.4 Contraception and Breastfeeding

5.3.4.1 Contraception for Subjects Capable of Producing Viable Ova and/or Becoming Pregnant

Sexually active females of childbearing potential should be using a highly effective form of contraception. Females of childbearing potential must be advised to use highly effective contraceptives throughout the study period and for 30 days following the last dose of IP. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use highly effective contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of IP.

Section 10.4 provides further definitions and lists highly effective methods of contraception.

5.3.4.2 Contraception for Subjects Capable of Producing Viable Sperm

No restrictions are required.

5.3.5 Other Requirements

No further lifestyle restrictions apply.

5.4 Screening

Any subject who provides informed consent (ie, signs and dates the ICF and assent form, if applicable [see Section 10.1.3]), is considered a screened subject in the study.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

The investigator or the investigator's designee will access the Interactive Response Technology (IRT) to screen a subject and obtain the subject identification code (SIC), which will be used to identify the subject throughout the study. The SIC will not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

The investigator is responsible for maintaining a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. After confirming that the subject meets all eligibility criteria, the investigator must complete the Eligibility Review Form and send it to the medical monitor for review. The medical monitor sends the site an e-mail notification regarding their review of the Eligibility Review Form. The responsibility to ensure that the subject is eligible rests with the investigator.

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Please note the following with regards to inclusion criterion #4:

- For all subjects, the last prestudy IgG infusion occurs after signing the ICF so that the samples to assess trough IgG levels must be taken prior to the prestudy IgG at screening.

5.4.1 Screen Failures

Subjects are only considered screen failures if they were not enrolled as per definition in Section 5.6. After enrollment, subjects who are not considered screen failures will be recorded as early terminated subjects and will proceed to the Early Termination (ET) Visit (see Section 7).

An individual who has provided informed consent to participate in the study may be categorized as a screen failure before randomization for any of the following reasons:

- Did not meet eligibility criteria [did not meet at least 1 inclusion criterion and/or met at least 1 exclusion criterion].
- AE.
- Lost to follow-up.
- Pregnancy.
- Withdrawal by subject.

- Met eligibility criteria but not needed.
- Study suspended/terminated by sponsor.
- Other (specify).

Information about screen failures must be collected via the eCRFs, including subject identification, screening disposition (including the reason for screen failure), demography, inclusion/exclusion criteria, and AEs (if applicable). If a potential subject experiences a serious adverse event (SAE) during screening, all of the subject's screening eCRFs must be available for collection.

The IRT must be updated to reflect the status of screen failure.

Subject identification numbers assigned to subjects who fail screening must not be reused.

An individual who has been designated a screen failure may be rescreened under the circumstances described in Section 5.4.2.

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5.4.2 Rescreening

Subjects may be rescreened only once. Subjects who have failed screening based on the following reasons may be rescreened, after the cause underlying the initial screen failure has been resolved and appropriately documented:

- Inclusion criterion #2: Subject is 2 years to <16 years at the time of signing the ICF for the single-arm treatment part of the study OR 16 years or older at the time of signing the ICF for the crossover part of the study.
- Inclusion criterion #3: Subject has received a stable dose of regular treatment with any IGIV OR HYQVIA with a treatment interval of every 21 or 28 days OR any cIGSC with a treatment interval of every 7 or 14 days over a period of at least 12 weeks prior to screening at a minimum prestudy IgG dose equivalent to 0.3 g/kg BW/4 weeks and a maximum dose equivalent to 1 g/kg BW/4 weeks. Over that period, the subject should have been on the same product of IGIV, HYQVIA, or cIGSC. A stable dose is defined as one that deviates less than ±25% from the mean dose for all IgG infusions within this 12-week period prior to screening. Variations in the treatment interval of up to ±5 days for subjects with a 28-day treatment interval and of up to ±3 days for subjects with a 7, 14, or 21-day treatment interval are acceptable up to the first IP infusion.
- Inclusion criterion #4: Subject has a serum trough level of IgG >5 g/L at screening (sample taken prior to prestudy IgG infusion after signing the ICF) and within 12 weeks prior to screening.

- Exclusion criterion #12: Treatment with immunosuppressants including chemotherapeutic agents, immunomodulators, and long-term systemic corticosteroid (defined as a daily dose of >1 mg of prednisone equivalent/kg/day for >30 days) within 12 weeks prior to screening. Short or intermittent courses (≤10 days) of corticosteroids are allowed.
- Exclusion criterion #13: Live-attenuated viral vaccination within 12 weeks prior to screening.
- Exclusion criterion #14: History or current diagnosis of thrombotic episodes; venous thrombus that occurred in association with a medical device >2 years prior to screening are allowed.
- Subject failed screening for an issue related to laboratory sample collection (eg, lack of serum trough level of IgG assessment prior to the last prestudy IgG treatment, difficult venipuncture, received sample was out of stability, received sample had hemolyzed).
- Subject failed screening due to unforeseen circumstances, eg, inclement weather, subject's individual issues related to visit scheduling etc. in the judgement of the investigator, with consultation by the medical monitor as necessary.
- Subject failed screening because the study stopping rules were met and the treatment of new subjects was paused.

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Subjects that are rescreened must sign a new ICF and a new eCRF is required for that subject. A new subject identification number will be assigned at rescreening. All screening laboratory and other assessments will be repeated at rescreening.

5.5 Criteria for Temporarily Delaying Randomization

Randomization may not be delayed for any reason.

5.6 Enrollment

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.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Study Interventions Administered

In this study, the interventions include:

- Investigational products: TAK-881 and HYQVIA.
- Other products required for the study: Not applicable.

Table 9 describes the interventions administered in the study. Further information on TAK-881 is provided in the IB and on HYQVIA in the local package insert and SmPC.

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Table 9. Study Interventions Administered: Biologic

Intervention Name	TAK-881	HYQVIA
Intervention Description	IGSC (Human), 20% solution with rHuPH20	IGI (Human), 10% solution with rHuPH20
Excipients	IGSC, 20%: Glycine. rHuPH20: Sodium chloride, sodium phosphate dibasic dihydrate, human albumin, edetate disodium dihydrate, calcium chloride dihydrate, and sodium hydroxide added for pH adjustment	IGI, 10%: Glycine rHuPH20: Sodium chloride, sodium phosphate dibasic dihydrate, human albumin, edetate disodium dihydrate, calcium chloride dihydrate, and sodium hydroxide added for pH adjustment
Type	Biologic	Biologic
Dose Formulation	Solution for infusion	Solution for infusion
Unit Dose Strength(s)	IGSC, 20% solution is supplied in single-dose glass vials that nominally contain 200 mg/mL protein in a 50 mL or 100 mL vial. rHuPH20 is supplied in single-dose glass vials that nominally contain 160 Units/mL in a 5 mL or 10 mL vial.	IGI, 10% solution is supplied in single-dose glass vials that nominally contain 100 mg/mL protein in a 100 mL or 200 mL vial. rHuPH20 is supplied in single-dose glass vials that nominally contain 160 Units/mL in a 5 mL or 10 mL vial.
Dosage Level(s)	The dose (in g/kg BW/week) will be the same as the weekly equivalent of the last prestudy IgG treatment dose For subjects who undergo the ramp-up epoch, a 1-week and 2-week dose [a] based on their last prestudy IGIV/cIGSC treatment dose will be administered. The first study treatment will be administered 1, 2, 3, or 4 weeks after the last prestudy IgG dose depending on the prestudy IgG treatment interval. Thereafter, - For those subjects who do not enter the ramp-up epoch, the study treatment is administered every 3 or 4 weeks. - For those subjects who enter the ramp-up epoch, subjects first receive a 1-week dose, followed by a 2-week dose [a], and thereafter, treatment will be administered every 3 or 4 weeks. TAK-881 doses must not be administered over multiple days. The maximum daily absolute dose of TAK-881 is 120 g.	The dose (in g/kg BW/week) will be the same as the weekly equivalent of the last prestudy IgG treatment dose For subjects who undergo the ramp-up epoch, a 1-week and 2-week dose [a] based on their last prestudy IGIV/cIGSC treatment dose will be administered. The first study treatment will be administered 1, 2, 3, or 4 weeks after the last prestudy IgG dose depending on the prestudy IgG treatment interval. Thereafter, - For those subjects who do not enter the ramp-up epoch, the study treatment is administered every 3 or 4 weeks. - For those subjects who enter the ramp-up epoch, subjects first receive a 1-week dose, followed by a 2-week dose [a], and thereafter, treatment will be administered every 3 or 4 weeks. HYQVIA doses must not be administered over multiple days. The maximum daily absolute dose of HYQVIA is 120 g.

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Table 9. Study Interventions Administered: Biologic

Intervention Name	TAK-881	HYQVIA
Route of Administration	Subcutaneous	Subcutaneous
Use	Experimental	Experimental
Classification	IP	IP
Authorization Status	Not authorized in any region.	Authorized in specific regions. HYQVIA will be used in the study in accordance with the terms of its marketing authorization.
Sourcing	Provided centrally by Takeda.	Provided centrally by Takeda.
Packaging and Labeling	The separate vials containing IGSC, 20% and rHuPH20 will be labeled then packaged into a DVU. The different sized vials will be contained in the correspondingly sized DVUs. Each DVU will then be packaged into a labeled carton. The study product will be labeled according to the valid regulatory requirements for clinical studies.	The separate vials containing IGI, 10% and rHuPH20 will be labeled then packaged into a DVU. The different sized vials will be contained in the correspondingly sized DVUs. Each DVU will then be packaged into a labeled carton. The study product will be labeled according to the valid regulatory requirements for clinical studies.
Additional Information	Refer to the TAK-881 IB, Pharmacy Manual and Site Infusion Manual	Refer to the local package insert, SmPC, Pharmacy Manual and Site Infusion Manual.

BW=body weight; cIGSC=conventional subcutaneous IgG; DVU=dual-vial unit; IB=investigator's brochure; IgG=immunoglobulin G; IGI, 10%=immune globulin infusion, 10%; IGIV=intravenous immunoglobulin; IGSC, 20%=immune globulin subcutaneous, 20%; IP=investigational product; rHuPH20=recombinant human hyaluronidase; SmPC=Summary of Product Characteristics.

[a] Please see Figure 7 for calculation of doses in relation to a subject's prestudy IgG dose.

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Figure 7. Dose and Treatment Interval

Prestudy IgG Treatment	Ramp up (Yes/No)	Treatment Interval Prestudy	Dose in Ramp-up Epoch (in % of Prestudy IgG Treatment Dose)		Treatment Interval During Study	Dose During Study (in % of Prestudy IgG Treatment Dose)
			Ramp-up Visit 1	Ramp-up Visit 2		
cIGSC	Yes	Every week	100%	200%	Every 3 or 4 weeks, at the discretion of the investigator	1) if transitioning to 3 weeks: 300% of the prestudy IgG dose 2) if transitioning to 4 weeks: 400% of the prestudy IgG dose
	Yes	Every 2 weeks	50%	100%	Every 3 or 4 weeks, at the discretion of the investigator	1) if transitioning to 3 weeks: 150% of the prestudy IgG dose 2) if transitioning to 4 weeks: 200% of the prestudy IgG dose
IGIV	Yes	Every 3 weeks	33%	66%	Every 3 weeks	Same dose as prestudy IgG dose
	Yes	Every 4 weeks	25%	50%	Every 4 weeks	Same dose as prestudy IgG dose
HYQVIA	No	Every 3 weeks	-	-	Every 3 weeks	Same dose as prestudy IgG dose
	No	Every 4 weeks	-	-	Every 4 weeks	Same dose as prestudy IgG dose

cIGSC=conventional subcutaneous IgG; IgG=immunoglobulin G; IGIV=intravenous immunoglobulin.

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6.2 Preparation, Handling, Storage, and Accountability

6.2.1 Accountability Throughout the Study

The investigator or designee must ensure that the sponsor-supplied study product is used in accordance with the protocol and is only dispensed to subjects enrolled in the study.

To document appropriate use of sponsor-supplied study product (Section 6.1), the investigator or designee must maintain 100% accountability for all sponsor-supplied study interventions that the site receives and dispenses during his or her entire participation in the study.

Proper drug accountability includes, but is not limited to:

- The investigator or designee must maintain records of all sponsor-supplied study interventions delivery to the site, current site inventory, dispensing for use by each subject, and final disposition.
- The investigator or designee must record this inventory on a sponsor-approved drug accountability log.

- Based on entries in the log, it must be possible to reconcile study products delivered with those used.
- All study products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.
- If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

6.2.2 Receiving Product at the Site

Investigators will be provided with sufficient quantities of the study intervention to carry out this protocol for the agreed number of subjects.

Upon receipt of sponsor-supplied investigational products, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct and the medication is in good condition.

This will include an examination of temperature-monitoring devices.

If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by recording in the IRT. If there are any discrepancies between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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6.2.3 Handling and Storage at the Site

The investigator bears the overall responsibility for ensuring that the study interventions are stored in an appropriate location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

An appropriate storage location is one that is secure, with access that is limited to the investigator and authorized site staff, and that is environmentally controlled (manually or automated) in accordance with labeled storage requirements.

Study interventions must remain in the original container until dispensed.

The investigator is responsible for ensuring that the study interventions are maintained according to the requirements described in Section 6.2.3.1.

The investigator is responsible for ensuring that the investigational products are maintained within an established temperature range, that the temperature is monitored throughout the duration of the study, and that records are maintained.

A daily temperature log of the drug storage area must be maintained every working day. The temperature should be monitored continuously by using either an in house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording.

The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the study intervention and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the study intervention that could affect the integrity of the product(s), eg, fumigation of a storage room.

The on-site pharmacist (site designee) will receive the Pharmacy Manual created by the sponsor, according to which the site designee will appropriately manage the sponsor/designee-supplied study intervention. The investigator will also receive the Pharmacy Manual from the sponsor. The Pharmacy Manual details the procedures for ensuring appropriate receipt, handling, storage, management, and dispensation of the sponsor/designee-supplied intervention and collection of unused medications from the subject, as well as their final disposition.

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The on-site pharmacist (site designee) will immediately provide final disposition of unused study drugs after the study is closed at the study site.

6.2.3.1 Required Environmental Storage Conditions

Do not freeze the product. Do not use the product if the expiration date is exceeded. Keep the vials in the carton in order to protect from light. Store at a refrigerated temperature of 2° to 8°C (36° to 46°F) for up to 36 months. Do not return the product to the refrigerator if it has been kept at room temperature. Prior to use, the vials must be removed from refrigeration and placed at room temperature for approximately 90 minutes for TAK-881 and approximately 60 minutes for HYQVIA and should be kept at room temperature during administration. More information can be found in the Pharmacy Manual.

6.2.4 Labeling

The product will be labeled according to the regulatory requirements for clinical studies. Space is allocated on the label so that the site representative can record a unique subject identifier.

Changes to sponsor-supplied packaging, including the addition of labels prior to dosing, may not be made without full agreement in advance by the sponsor. Such additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the study intervention in order to satisfy local or institutional requirements, but ***must not*** contradict the clinical study label or obscure the clinical study label.

6.2.5 Preparation

TAK-881

- Visually inspect both vials of TAK-881 for 5 seconds and monitor for discoloration and particulate matter prior to administration.
  - The appearance of the IGSC, 20% (Human) of TAK-881 can vary from clear or pale yellow or light brown.
  - The appearance of the rHuPH20 of TAK-881 should be clear and colorless.
  - Do not use either component of TAK-881 if either solution is cloudy or has particulates.
- Remove product from refrigeration and allow to reach room temperature (approximately 90 minutes) prior to administration. Do not apply heat or place in microwave. If the IGSC, 20% component is pooled into an infusion bag (US only), the infusion must be started after reaching room temperature (ie, approximately 90 minutes out of refrigeration) and within 3 hours of the start of pooling.
  In the EU, a direct-from-the-vial method will be used. Refer to the Pharmacy Manual and Site Infusion Manual for more detailed instructions.
- Do not shake TAK-881.
- Do not mix the rHuPH20 and the IGSC, 20% (Human) of TAK-881 into the same container prior to administration.
- Do not mix or administer components of TAK-881 with other products. Always administer components of TAK-881 sequentially, the rHuPH20 component first. Do not use either component alone.
- Flush the infusion line with normal saline 0.9% (NS) when the IGSC, 20% is completely empty either from the pooling bag or last immunoglobulin vial. The NS will not be administered to the subject, this is to ensure the full dose of the IP is delivered.

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- Discard any remaining unused product (if the seal has been penetrated) according to local standards for biohazard products. TAK-881 contains no preservative and vials are not to be reused.

HYQVIA

- Visually inspect both vials of HYQVIA for 5 seconds and monitor for discoloration and particulate matter prior to administration.
  - The appearance of the IGI, 10% (Human) of HYQVIA can vary from clear or slightly opalescent and colorless or pale yellow.
  - The appearance of the rHuPH20 of HYQVIA should be clear and colorless.
  - Do not use either component of HYQVIA if either solution is cloudy or has particulates.
- Remove product from refrigeration and allow to reach room temperature (approximately 60 minutes) prior to administration. Do not apply heat or place in microwave. If the IGI, 10% component is pooled into an infusion bag, the infusion must be started after reaching room temperature (ie, approximately 60 minutes out of refrigeration) and within 3 hours of the start of pooling.
- Do not shake HYQVIA.
- Do not mix the rHuPH20 and the IGI, 10% (Human) of HYQVIA into the same container prior to administration.
- Do not mix or administer components of HYQVIA with other products. Always administer components of HYQVIA sequentially, the rHuPH20 component first. Do not use either component alone.
- Flush the infusion line with NS when the IGI, 10% is completely empty either from the pooling bag or last immunoglobulin vial. The NS will not be administered to the subject, this is to ensure the full dose of the IP has been delivered.
- Discard any remaining unused product (if the seal has been penetrated) according to local standards for biohazard products. HYQVIA contains no preservative and vials are not to be reused.

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6.2.6 Dispensing/Administration

The investigator has overall responsibility for dispensing the study investigational products.

Where permissible, tasks may be delegated to a qualified designee (for example, a pharmacist, nurse or a home health care representative) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

All study interventions provided to pediatric subjects should be supervised by the study site/investigator.

6.2.6.1 Dispensing

For the single-arm treatment epoch (subjects aged 2 to <16 years) subjects will receive TAK-881 treatment according to the study schedule.

For the AB/BA crossover treatment epochs (subjects aged ≥16 years) subjects will be assigned to receive their treatment (TAK-881/HYQVIA) according to the randomization schedule.

At screening, the investigator or the investigator's designee will access the IRT to obtain the subject's study number.

The investigator or the investigator's designee will subsequently use the IRT to randomize the subject into the study by entering the necessary subject-identifying information, including the SIC assigned at screening.

The IRT will then provide the medication identification (MED ID) number of the study drug to be dispensed. If the sponsor-supplied drug is lost or damaged, the site can request a replacement via the IRT (refer to the IRT manual provided separately).

At subsequent drug-dispensing visits, the investigator or designee will again access the IRT to request additional study drug for a subject via the IRT.

The pharmacist/designee/study nurse will enter the SIC on the study carton labels as they are distributed. All administered/dispensed medication will be documented in the subject's source and/or other study intervention record.

No study intervention stock or returned inventory may be removed from the site to which it was originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer. An IRT system will be used to manage supply and allocation of study intervention to sites and subjects. This includes shipment generation, shipment receipt, temperature excursion tracking, expiry tracking, treatment assignment, and final disposition of unused study interventions.

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Study/sponsor-supplied drug is to remain in its original container until dispensing, unless otherwise agreed upon by the sponsor. Study intervention will be dispensed at the study visits as summarized in the SoA (see Section 1.3). Returned study intervention should not be redispensed to the subjects.

6.2.6.2 Administration

TAK-881/HYQVIA infusions will be administered by an appropriately trained HCP (eg, infusion nurse) at the study site.

TAK-881/HYQVIA infusions will be administered using qualified medical devices commonly used for facilitated immunoglobulin therapy standard of care.

Please refer to the Site Infusion Manual for guidance if a catheter leakage occurs.

TAK-881/HYQVIA doses must not be administered over multiple days.

Please see the Site Infusion Manual for more detailed procedures for the administration of both TAK-881 and HYQVIA.

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Administration of TAK-881

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

The rHuPH20 solution will be administered subcutaneously at an initial rate of approximately 1-2 mL/minute/site or 60-120 mL/hour/site, or as tolerated, and infusion volumes of up to a maximum of 30 mL/site. The rHuPH20 volume is not included in the total volume per infusion site.

The SC infusion of the IGSC, 20% solution will begin within 10 minutes of completion of the SC infusion of the rHuPH20 solution. The infusion rate escalation steps with IGSC, 20% solution from the phase 1 study are applied in subjects with a BW of ≥40 kg. The starting infusion rate in subjects with a BW of <40 kg in this study is the same as in the package insert/SmPC of CUVITRU. The infusion rates and volumes are as follows:

- For subjects with a BW of <40 kg: 10 mL/hour/site (at start) to 160 mL/hour/site (maximum, if tolerated), up to 150 mL per infusion site.
- For subjects with a BW of ≥40 kg: 30 mL/hour/site (at start) to 300 mL/hour/site (maximum, if tolerated), up to 300 mL per infusion site.

A flushing step of NS will be required to ensure the total dose is administered due to the priming volumes of the administration system. NS will not be infused into the subject. For each infusion site, infusion rate ramp-up schedule will be followed as shown in Table 10 and Table 11.

Most immunoglobulin infusion reactions are infusion rate-related, mild, and occur within the first 30 minutes to 1 hour of the infusion (Perez et al., 2017). In addition, published evidence indicates that the most common ARs to IGSC are local infusion site reactions (Gardulf et al., 2006, Perez et al., 2017), although systemic reactions may occur.

In the event of the following Grade 2 clinical signs/symptoms and vital sign changes such as localized infusion site reaction (pain, warmth, edema, pruritus etc.), fever, chills, flushing, nausea, headache, abdominal pain, back pain, anxiety, arthralgia, myalgia, and Grade 1 or Grade 2 isolated urticaria as defined by CTCAE v.5.0, the infusion will be interrupted briefly, and the infusion rate will be reduced to the rate immediately below that at which no Grade 2 infusion rate-related signs and symptoms or Grade 1 or Grade 2 isolated urticaria occurred.

If clinical signs and symptoms resolve in response to the intervention described above, the infusion will continue at the adjusted rate for the remainder of the infusion (eg, if the maximum infusion rate is 300 mL/hour/site and it is not tolerable, the infusion rate will be decreased to the previous infusion rate of 180 mL/hour/site assuming it was well tolerated). In the event of an AE other than the infusion rate-related AEs above, the management of the infusion and the appropriate medical approach should be decided based on the investigator's discretion.

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If the subject develops Grade 1 (Urticarial lesions covering <10% body surface area [BSA]; topical intervention indicated) or Grade 2 urticaria (Urticarial lesions covering 10-30% BSA; oral intervention indicated) as defined by NCI CTCAE v5.0, without any other signs or symptoms from another organ system, the infusion will be interrupted briefly, and the subject will be observed for approximately 1 hour while vital signs are being monitored. If the urticaria resolves on its own or with one dose of oral antihistamine without any other intervention, the subject is stable, and does not have any additional symptoms, the infusion rate will be reduced to the rate immediately below that at which no Grade 1 or Grade 2 occurred. If urticaria returns after the infusion is restarted, the infusion will immediately be stopped completely regardless of the urticaria grading, and appropriate medical intervention will be implemented, and the subject will be permanently withdrawn from the study.

A step-wise infusion rate escalation regimen as shown below will be followed for the study based on tolerability of each incremental infusion rate increase:

Table 10. TAK-881 Infusion Rates for Subjects with a Body Weight of <40 kg

		First 2 infusions	Subsequent infusions
Administration		**Rate Per Infusion Site**	**Rate Per Infusion Site**
rHuPH20	To be infused first	approximately 1-2 mL/min/site or 60-120 mL/hour/site	Approximately 2 mL/min/site or 60-120 mL/hour/site
IGSC, 20%	5-15 min	10 mL/hour	20 mL/hour
	5-15 min	20 mL/hour	40 mL/hour
	5-15 min	40 mL/hour	80 mL/hour
	5-15 min	80 mL/hour	NA
	Remainder of infusion	160 mL/hour	160 mL/hour

IGSC, 20%=immune globulin subcutaneous; 20%; NA=not applicable; rHuPH20=recombinant human hyaluronidase.

Table 11. TAK-881 Infusion Rates for Subjects with a Body Weight of ≥40 kg

		First 2 infusions	Subsequent infusions
Administration		**Rate Per Infusion Site**	**Rate Per Infusion Site**
rHuPH20	To be infused first	approximately 1-2 mL/min/site or 60-120 mL/hour/site	approximately 2 mL/min/site or 60-120 mL/hour/site
IGSC, 20%	5-15 min	30 mL/hour	60 mL/hour
	5-15 min	60 mL/hour	120 mL/hour
	5-15 min	120 mL/hour	180 mL/hour
	5-15 min	180 mL/hour	NA
	Remainder of infusion	300 mL/hour	300 mL/hour

IGSC, 20% =immune globulin subcutaneous; 20%; NA=not applicable; rHuPH20=recombinant human hyaluronidase.

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Administration of HYQVIA

HYQVIA will be administered via a SC route of administration using a SC needle set. The rHuPH20 solution will be administered first, followed by IGI, 10% using the same needle set.

The rHuPH20 solution will be administered via SC at an initial rate of approximately 1-2 mL/minute/site or 60-120 mL/hour/site, or as tolerated, and infusion volumes of up to a maximum of 30 mL/site. The rHuPH20 volume is not included in the total volume per infusion site.

The SC infusion of the IGI, 10% solution will begin within 10 minutes of completion of the SC infusion of the rHuPH20 solution. The infusion rate escalation steps with IGI, 10% solution in this study are the same as in the package insert/SmPC of HYQVIA. The infusion rates and volumes are as follows:

- For subjects with a BW of <40 kg who were not treated with HYQVIA within 12 weeks of screening: 5 mL/hour/site (at start) to 160 mL/hour/site (maximum, if tolerated), up to 300 mL per infusion site.
- For subjects with a BW of ≥40 kg who were not treated with HYQVIA within 12 weeks of screening: 10 mL/hour/site (at start) to 300 mL/hour/site (maximum, if tolerated), up to 600 mL per infusion site.
- For subjects regardless of BW who were treated with HYQVIA within 12 weeks of screening: the infusion rate at start and the maximum infusion rate can be the rates they tolerated before screening.

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A flushing step of NS will be required to ensure the total dose is administered due to the priming volumes of the administration system. NS will not be infused into the subject. For each infusion site, infusion rate ramp-up schedule will be followed as shown in Table 12 and Table 13.

In the event of the following Grade 2 clinical signs/symptoms and vital sign changes such as localized infusion site reaction (pain, warmth, edema, pruritus etc.), fever, chills, flushing, nausea, headache, abdominal pain, back pain, anxiety, arthralgia, myalgia, and Grade 1 or Grade 2 isolated urticaria as defined by CTCAE v.5.0, the infusion will be interrupted briefly, and the infusion rate will be reduced to the rate immediately below that at which no Grade 2 infusion rate-related signs and symptoms or Grade 1 or Grade 2 isolated urticaria occurred.

If clinical signs and symptoms resolve in response to the intervention described above, the infusion will continue at the adjusted rate for the remainder of the infusion. (eg, if the maximum infusion rate is 300 mL/hour/site and it is not tolerable, the infusion rate will be decreased to the previous infusion rate of 240 mL/hour/site assuming it was well tolerated). In the event of an AE other than the infusion rate-related AEs above, the management of the infusion and the appropriate medical approach should be decided based on the investigator's discretion.

If the subject develops Grade 1 (Urticarial lesions covering <10% BSA; topical intervention indicated) or Grade 2 urticaria (Urticarial lesions covering 10-30% BSA; oral intervention indicated) as defined by NCI CTCAE v5.0, without any other signs or symptoms from another organ system, the infusion will be interrupted briefly, and the subject will be observed for approximately 1 hour while vital signs are being monitored.

If the urticaria resolves on its own or with one dose of oral antihistamine without any other intervention, the subject is stable, and does not have any additional symptoms, the infusion rate will be reduced to the rate immediately below that at which no Grade 1 or Grade 2 occurred. If urticaria returns after the infusion is restarted, the infusion will immediately be stopped completely regardless of the urticaria grading, and appropriate medical intervention will be implemented, and the subject will be permanently withdrawn from the study.

A step-wise infusion rate escalation regimen as shown below will be followed for the study based on tolerability of each incremental infusion rate increase:

Table 12. HYQVIA Infusion Rates for Subjects Who Were not Treated With HYQVIA Within 12 Weeks of Screening With a Body Weight of <40 kg

		First 2 infusions	Subsequent infusions
Administration		**Rate Per Infusion Site**	**Rate Per Infusion Site**
rHuPH20	To be infused first	approximately 1-2 mL/min/site or 60-120 mL/hour/site	approximately 2 mL/min/site or 60-120 mL/hour/site
IGI, 10%	5-15 min	5 mL/hour	10 mL/hour
	5-15 min	10 mL/hour	20 mL/hour
	5-15 min	20 mL/hour	40 mL/hour
	5-15 min	40 mL/hour	80 mL/hour
	Remainder of infusion	80 mL/hour	160 mL/hour

IGI, 10% =immune globulin infusion; 10%; rHuPH20=recombinant human hyaluronidase.

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Table 13. HYQVIA Infusion Rates for Subjects Who Were not Treated With HYQVIA Within 12 Weeks of Screening With a Body Weight of ≥40 kg

		First 2 infusions	Subsequent infusions
Administration		**Rate Per Infusion Site**	**Rate Per Infusion Site**
rHuPH20	To be infused first	approximately 1-2 mL/min/site or 60-120 mL/hour/site	approximately 2 mL/min/site or 60-120 mL/hour/site
IGI, 10%	5-15 min	10 mL/hour	10 mL/hour
	5-15 min	30 mL/hour	30 mL/hour
	5-15 min	60 mL/hour	120 mL/hour
	5-15 min	120 mL/hour	240 mL/hour
	Remainder of infusion	240 mL/hour	300 mL/hour

IGI, 10%=immune globulin infusion; 10%; rHuPH20=recombinant human hyaluronidase.

For subjects who have been on HYQVIA within 12 weeks prior to screening, HYQVIA is permitted to be infused at previously tolerated maximum infusion rates, both the time intervals and number of rate changes of the infusion rate escalation in Table 12 and Table 13 can be adjusted for HYQVIA infusions at the discretion of the investigator and subject.

For subjects who have not received HYQVIA within 12 weeks prior to screening, HYQVIA administration must follow a step-wise infusion rate escalation as described above.

Number and Location of Infusion Sites

A maximum of 2 infusion sites can be used. If a second site is used for administration, 50% of the total volume of rHuPH20 and IgG of TAK-881/HYQVIA should be delivered into each infusion site. The recommended sites for the infusion of TAK-881/HYQVIA are the middle to upper abdomen and thighs.

Subjects Previously Treated with IGIV

For subjects previously treated with IGIV, the selection of number of infusion sites with TAK-881/HYQVIA during the study will be at the discretion of the investigator. The investigator may base his/her decision on the following:

1. The total calculated volume exceeds the maximum volume per infusion site per protocol.
2. During the escalating rate of infusion the subject exhibits signs of intolerance using 1 infusion site.
3. The investigator knows that the subject may fear tolerating a large volume using only 1 infusion site.

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In both cases 1 and 3, the investigator may decide to use 2 infusion sites from the beginning, if feasible, and in case number 2 the investigator may add a second infusion site when the subject exhibits intolerable side effects while ramping up the infusion rate using 1 infusion site.

Subjects Previously Treated with HYQVIA or cIGSC

For subjects previously treated with HYQVIA or cIGSC, a maximum of 2 infusion sites can be used during the study and the number of infusion sites with the prestudy HYQVIA/cIGSC at screening, if they are 1 or 2 infusion sites, should be maintained, if tolerated, during TAK-881/HYQVIA treatment in the study.

6.2.7 Destruction or Return

Prior to site closure and at appropriate intervals, the sponsor or its designee will perform accountability and reconciliation of sponsor-supplied product before final disposition. Sponsor-supplied study interventions should be destroyed locally, unless prohibited by local regulations.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

Further instructions regarding the destruction or return of used, partially used, and unused study interventions are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The contract research organization will be responsible for the generation of the randomization schedules.

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AB/BA Crossover Treatment Epochs (Subjects Aged ≥16 Years)

The AB/BA crossover epochs are randomized. The actual treatment given to individual subjects is determined by a randomization schedule. Individual subject treatment assignment is automatically assigned using the IRT.

The randomization to Sequence 1 (TAK-881 followed by HYQVIA) or Sequence 2 (HYQVIA followed by TAK-881) will be performed at a 1:1 ratio. Randomization will be stratified by IgG treatment interval during the study (every 3 or 4 weeks).

Single-arm Treatment Epoch (Subjects Aged 2 to <16 Years)

Subjects in this treatment epoch will not be randomized with respect to treatment allocation as all subjects will receive TAK-881.

Subjects will be randomized with regards to sparse PK sampling. The randomization to 1 of the 6 sampling sequences (see Table 7) will be performed at a 1:1:1:1:1:1 ratio and will be assigned using the IRT. Randomization will be stratified by pediatric age cohort (2 to <6, ≥6 to <12, ≥12 to <16).

6.3.2 Blinding the Treatment Assignment

Neither the subject nor the site staff will be blinded to the treatment assignment. The laboratory analysts that process samples for PK measurements will be blinded to treatment assignment.

The master randomization list will be stored in a secure system accessible only to authorized staff. Site personnel have no access to the master randomization list and the randomization block size. Sites do not have access to treatment assignment information from other sites.

6.3.3 Unblinding

Not applicable.

6.4 Study Intervention Compliance

Compliance must be assessed by observation of dosing by the investigator or designee. The investigator/designee will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time, date, total grams dosed) will be captured in the appropriate CRF.

Drug accountability must be assessed at the container/packaging level for unused IP that is contained within the original tamper-evident sealed container (eg, DVU's in cartons) or at the individual count for opened containers/packaging. The pharmacist/designee will record details on the drug accountability form.

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6.5 Dose Modification

Modification due to Clinical Need

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 the 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 (Physician choice in the IRT). 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 file, and it should be entered in the CRFs.

Modification due to Body Weight Changes (>5%)

In all subjects 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 >5% relative to the subject's BW used for the most recent dose calculation, the absolute dose should be calculated using the current BW as follows:

new absolute IgG dose (g) =
previous absolute IgG dose (g) * (current BW/BW used for the most recent dose calculation).

To allow for sufficient infusion preparation time, the new absolute IgG dose will be administered at the subsequent visit. Subjects with dose modifications due to BW changes will still undergo serial PK (if ≥ 16 years) or sparse PK (if 2 to <16 years) of total IgG measurements. The IRT system is programmed to make these calculations.

6.6 Continued Access to Study Intervention After the End of the Study

A multicenter, prospective open-label, long-term follow-up study (Study TAK-881-3002) in subjects completing this study is planned. The objective of Study TAK-881-3002 will be to assess long-term safety, tolerability, immunogenicity, all infections, ASBIs, infusion preparation time, treatment preference, treatment satisfaction, HRQoL, and HRU associated with TAK-881 administration.

All subjects participating in Study TAK-881-3001 must consent for the long-term follow-up Study TAK-881-3002 at the time of consenting to Study TAK-881-3001 participation, if permitted by the IRB/IEC. A separate informed consent will be provided to the subjects. The treatment with TAK-881 in the long-term follow-up study will start once Study TAK-881-3001 is completed and the eligibility for the long-term follow-up study is confirmed.

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No aftercare is planned for subjects that do not continue to the long-term follow-up study. The study drugs will not be available upon completion of the subject's participation in the Study TAK-881-3001. The subject should be returned to the care of a physician and standard therapies as required.

6.7 Treatment of Overdose

In this study, an overdose is defined as a known deliberate or accidental administration of the study intervention, either to or by a study subject, at a dose above that assigned to that individual subject.

Takeda does not recommend specific treatment for an overdose.

In addition, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the subject to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities.

The categories below are not mutually exclusive; the event can meet more than 1 category:

- **Abuse** – Persistent or sporadic intentional intake of IP when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of IP other than as directed or indicated at any dose (Note: this includes a situation where the IP is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Intentional or unintentional intake of a dose of IP higher than the protocol-prescribed dose.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an IP. For studies, medication errors are reportable to the sponsor only as defined below.

All cases of overdose, abuse, misuse, medication error, or other uses not foreseen in the protocol must be documented. Because these events are not, in and of themselves, AEs, they should be reported regardless of whether any manifested signs or symptoms are considered AEs. If there are signs and symptoms meeting the criteria for reporting as AEs or SAEs, they should also be reported, as described in Section 10.3.

Overdose, abuse, misuse, medication error, or other uses not foreseen in the protocol must be reported to the sponsor *whether or not it resulted in an AE/SAE* via a paper form (see the Study Reference Manual for SSR) within 7 days of awareness. If the event resulted in an SAE, the 24-hour reporting requirement for SAEs will apply.

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Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired IP should be considered as a reportable medication error.

6.8 Concomitant Therapy

6.8.1 Rescue Medicine

The use of rescue medications is not allowed at any time during the study. If the use of rescue medication is deemed medically necessary, the medical monitor should be contacted.

6.8.2 Excluded Procedures and Treatments

Table 14. Prohibited Concomitant Medications and Therapies

Prohibited Concomitant Medication or Therapy	Circumstance Under Which the Drug is Prohibited and Exceptions
Prophylactic treatment with systemic antibacterial antibiotics	Throughout the study The use of systemic prophylactic antibacterial antibiotics by a subject will be considered a protocol deviation except: - Trimethoprim-Sulfamethoxazole for pneumocystis prophylaxis, which is acceptable in doses typical for pneumocystis pneumonia, but not low-dose daily therapy that can also be used for antibacterial prophylaxis - Low-dose continuous administration of macrolides which are used for anti-inflammatory effects (eg, for subjects ≥15 years old): erythromycin 400 mg/day; clarithromycin 200 mg/day, for subjects (<15 years old): erythromycin 10 mg/kg/day; clarithromycin 5 mg/kg/day) - Brief (less than 72 hours), prophylaxis for surgery (including dental procedures) or injury is permitted but treatment and indication must be recorded
Other IGIV or IGSC products or hyperimmune serum or other IgG products (both monoclonal and polyclonal antibodies)	Throughout the study (with the exception of prestudy IgG treatment during screening and Evusheld® [tixagevimab and cilgavimab]. It is required to refer to package insert with dosage and administration)
Live-attenuated viral vaccination	Throughout the study.
Immunosuppressants including chemotherapeutic agents, immunomodulators, and long-term systemic corticosteroid (defined as a daily dose >1 mg of prednisone equivalent/kg/day for >30 days)	Throughout the study Short or intermittent courses (≤10 days) of corticosteroids are allowed.
Premedication with antipyretics or antihistamines	Throughout the study. Premedication on the day of IP administration during the study can be administered for both IPs at the investigator's discretion and per institutional standards in the following exceptional cases: - Subjects who had HYQVIA or any cIGSC as prestudy IgG treatment and experienced a documented moderate HYQVIA-related or cIGSC-related AE during or after at least 2 prestudy HYQVIA infusions that did not resolve with a reduction in the infusion rate. - Subjects who, regardless of prestudy IgG treatment, experience a TAK-881/HYQVIA-related Grade 2 AE (NCI CTCAE v5.0) during or after at least 2 infusions during the study that does not resolve with a reduction in the infusion rate.

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Table 14. Prohibited Concomitant Medications and Therapies

Prohibited Concomitant Medication or Therapy	Circumstance Under Which the Drug is Prohibited and Exceptions
	- Topical anesthetics (eg, EMLA) may be used if the needle insertion was intolerable in prestudy IgG infusions. Subjects who have a history of using topical anesthetics (eg, EMLA) may use these topical anesthetics for TAK-881/HYQVIA infusions during the study. - Intravenous hydration with crystalloid solutions (Normal saline, 5% dextrose in water, Lactated Ringer's) is allowed.

AE=adverse event; cIGSC= conventional subcutaneous IgG; CTCAE=Common Terminology Criteria for Adverse Events; IgG=immunoglobulin G; IGIV=intravenous immune globulin; IGSC=subcutaneous immune globulin; IP=investigational product; NCI=National Cancer Institute.

6.8.2.1 Justification of Excluded Procedures

The exclusion of polyclonal and monoclonal IgG antibodies except the prestudy IgG treatment and the IPs was selected for their potential to interfere with the PK comparability assessment based on AUC of total IgG levels.

Live-attenuated viral vaccination is excluded because patients with PIDD have a severe impairment in antibody production and are at a higher risk to develop severe, potentially lethal ARs after vaccination with live-attenuated vaccines. In patients with severe antibody deficiency, IV or SC administered immunoglobulin replacement therapy remains the mainstay of treatment. In addition, the passive transfer of antibodies through the IP administration can transiently impair the immune responses to live-attenuated virus vaccines.

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The exclusion of prophylactic treatment with systemic antibacterial antibiotics, and immunosuppressants including chemotherapeutic agents, immunomodulators, and long-term systemic corticosteroid were selected for their potential to interfere with the evaluation of AEs including infections.

The exclusion of premedication on the day of the IP administration was selected for its potential to interfere with the evaluation of safety endpoints.

6.8.3 Permitted Concomitant Medications and Procedures

Treatments for common ailments (eg, cold and allergy remedies) and other supportive care medications are permitted, as are medications that are considered necessary for the welfare of the recipient (eg, thyroid medication, bronchodilators, etc.). This list is not intended to be exhaustive. The administration of all medications (including IPs) must be listed on the appropriate CRF page.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

This section describes the circumstances under which individual subjects would withdraw or be discontinued from the study intervention or from the study itself.

Section 10.1.9.2 describes circumstances in which specific sites or the study itself would be discontinued.

7.1 Discontinuation of Study Intervention

The administration of the IP infusion will be stopped, that will preclude a subject from receiving subsequent treatments with TAK-881/HYQVIA and the subject will be discontinued permanently from the study if the subject experiences:

- Any Grade 2 or higher systemic allergic reaction (SAR) graded by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) (Appendix 2) or anaphylaxis defined by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) (Sampson et al., 2006) (Appendix 3) OR
- Any grade of urticaria returns after the interventions related to Grade 1 or Grade 2 isolated urticaria detailed in Section 6.2.6.2 OR
- Any Grade 3 or higher urticaria OR
- Any Grade 3 or higher infusion-related reactions/general disorders and administration site conditions — other, specify OR
- Any Grade 4 or higher AE other than infusion-related reactions/general disorders and administration site conditions — other, specify.

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All AEs and clinically significant laboratory abnormalities, excluding SARs, will be graded according to National Cancer Institute (NCI) CTCAE, Version 5.0, dated November 27, 2017 (U.S. Department of Health and Human Services, 2017). SARs will be graded by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) (Appendix 2). Anaphylaxis will be reported as defined per NIAID/FAAN (Sampson et al., 2006) (Appendix 3).

The reason for discontinuation must be recorded on the appropriate CRF.

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. If a subject discontinued for more than 1 reason, each reason must be documented in the source document and the most clinically relevant reason must be indicated. Whenever possible, all discontinued subjects must also undergo the protocol-specified evaluations at ET Visit.

Reasons for discontinuation include but are not limited to:

- **Adverse event.** In addition to the above criteria for discontinuation of study intervention, if the subject has experienced an AE that may require early termination if continued participation would impose an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
- **Death.**
- **Selected protocol deviations.** The discovery that the subject did not meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the subject's health (as per the investigator's discretion). Subjects that deviate from the study visit window for IP administration by >3 days will be discontinued from the study.
- **Lost to follow-up.** The subject did not attend visits and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents (refer to Section 7.3).
- **Withdrawal by subject.** The subject (or, in the case of minors, legally designated representative[s]) wishes to withdraw from the study. The reason for withdrawal, if provided, must be recorded in the eCRF. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason must be recorded (for example, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
- **Study termination:** the sponsor, IRB, IEC, or Regulatory Agency terminates the study.
- **Investigator's discretion.**
- **Pregnancy:** A positive pregnancy test for female.
- **Other.**

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7.1.1 Liver Chemistry Stopping Criteria

Not applicable.

7.1.2 Rechallenge

7.1.2.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Not applicable.

7.1.2.2 Permanent Discontinuation of the Study Product

Please see Section 7.1.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.1.

At the time of discontinuing from the study, if possible, an ET Visit should be conducted, as shown in the SoA (Section 1.3). The primary criterion for termination must be recorded by the investigator. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Subjects who discontinue or withdraw will not be replaced.

7.3 Lost to Follow-up

A minimum of 3 documented attempts must be made to contact any subject (or, in the case of minors, their legally designated representative[s]) who is lost to follow-up at any time point prior to the last scheduled contact (in person or by phone or video). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgment of receipt request) asking that the subject be assessed for final safety evaluations and return any unused study intervention.

8. STUDY ASSESSMENTS AND PROCEDURES

Written or electronic informed consent must be obtained (signed and dated) before study assessments and procedures can be performed, as described in Section 10.1.3.

The following sections describe the study procedures and data to be collected at planned time points per the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Whenever possible, the same person should perform each assessment.

8.1 Demographics, Medical History, and Medication History

8.1.1 Demographics

Subject demographic information will be collected prior to the subject receiving the first dose of study intervention.

Demographic information to be obtained will include:

- Date of birth/Age (in Europe).
- Sex.
- Race and ethnicity (if allowed by local regulations).

The race and ethnicity will be self-identified by the subject and should not be assigned by the study team conducting the study. Collection of race and ethnicity will be used as covariates for population PK analysis.

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8.1.2 Medical History

Medical history, including concurrent medical conditions, will be collected and recorded in the subject's source documents and in the eCRF. The date of PIDD diagnosis, the date of first symptoms associated with PIDD, and the PIDD type will also be collected.

Medical history to be obtained will include determining whether the subject meets eligibility criteria and/or has any significant conditions or diseases relevant to the disease under study that resolved before, or at the time when the subject provided informed consent. Ongoing conditions are considered concurrent medical conditions. A complete medical history includes a more in-depth inquiry into the subject's medical issues which includes all current and prior diseases and illnesses (eg, allergies). The surgical history includes all invasive procedures the subject has undergone. Once medical history information has been obtained it will be treated with care for the subjects' privacy under laws such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States and EU General Data Protection Regulation (GDPR).

Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant physical examination, and/or vital signs abnormalities noted at the screening examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

8.1.3 Prior and Concomitant Treatments/Medications

Prior and concomitant treatments and medications will be collected and recorded in the subject's source document.

Such treatments/medications include but are not limited to:

- Medications or vaccines.
- Over-the-counter (OTC) or prescription medicines.
- Recreational drugs.
- Vitamins.
- Herbal supplements.
- Medications relevant to the eligibility criteria.
- Other specific categories of interest.

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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. Prior treatment information must be recorded on the appropriate CRF page.

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. Concomitant treatment information must be recorded on the appropriate CRF page.

Concomitant medications may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor.

At the time of the medical history, any available prior medication/treatment information will be collected.

At each study visit, subjects will be asked whether they have taken any medication or received any treatment other than the study intervention.

Information to be recorded will include:

- Identification of the medication or treatment.
- Reason for use.
- Dates of treatment/medication administration: start and end dates.
- Dosage information including dose, route and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.1.4 Diagnostic Criteria/Disease Classification

Subjects must have a documented diagnosis of a form of primary humoral immunodeficiency involving a defect in antibody formation and requiring IgG replacement, as defined according to the IUIS Committee (Bousfiha et al., 2020, Tangye et al., 2021).

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8.2 Efficacy Assessments

Infections will be assessed through AE reporting as described in Section 8.3.8 and Section 8.3.10. ASBIs will be defined as per FDA guidelines (FDA, 2008) (see Appendix 1).

The pharmacokinetic assessments described in Section 8.4 are considered as surrogate assessments for efficacy in this study.

8.3 Safety Assessments

Planned time points for all safety assessments (eg, immunogenicity by measurement of anti-rHuPH20 antibodies) are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

A baseline physical examination (defined as the assessment prior to first dose of IP) will consist of the following body parts and systems: ears, eyes, nose, throat, extremities, lymph nodes and cardiovascular, respiratory, gastrointestinal, dermatologic, musculoskeletal, and nervous systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

All subsequent physical examinations should assess clinically significant changes from the baseline physical examination.

At screening if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal preexisting condition is detected, the condition will be described on the AE CRF.

If the abnormal condition was not deemed an AE because it was due to an error, due to a preexisting disease, not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

8.3.2 Vital Signs

At study visits with infusions, vital signs will be performed within 30 minutes (±10 min) prior to infusion; 30 min (±10 min) after the initiation of infusion; during the infusion if a systemic AE occurs (to be assessed if needed) and at least 60 min after the completion of the infusion. The administration of both components of TAK-881/HYQVIA (ie, the rHuPH20 and IgG components) is defined as one infusion.

At the End-of-Study (EOS) Visit, vital signs will be measured once.

Vital sign values are to be recorded on the eCRF. For each abnormal vital sign value, the investigator will determine whether to report an AE (see definition in Section 10.3.1) and record the medical diagnosis (preferably), symptom, or sign on the AE CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

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Vital signs will include:

- Body temperature (°C).
- Respiratory rate (breaths per minute).
- Blood pressure (mmHg).
- Pulse rate (beats per minute).

8.3.2.1 Weight and Height, and Body Mass Index

Weight and height will be measured and recorded. Height will only be measured at the screening visit.

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Weight is collected in kilograms (kg). All BW measurements are to be taken at the study site using the same scale/instrument throughout the study for that individual subject.

Height is recorded in centimeters (cm).

Please consider that weight changes may require dose adjustments (see Section 6.5).

8.3.3 Clinical Safety Laboratory Tests

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3). Details about these procedures and required safety monitoring will be given in the Laboratory Manual.

The central laboratory (and subcontracted specialty laboratories) will perform all laboratory tests.

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator must assess out-of-range clinical laboratory values for clinical significance. If the value(s) is/are clinically significant this must be recorded as an AE (Section 10.3.1). Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

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Clinical safety laboratory test will be performed as outlined in the Schedule of Study Procedures (Section 1.3). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the investigator or designee.

Samples for hematology and clinical chemistry assessments will be collected in the appropriate matrix as specified in the Laboratory Manual. At any time during the study, unscheduled hematology and/or hemolytic panel and/or clinical chemistry test(s) may be performed as part of AE/safety investigation or may be repeated once in the event of abnormalities in test results due to errors.

Abnormal laboratory findings associated with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

Clinically significant abnormal laboratory values obtained during participation in the study should be repeated until the values return to normal or the baseline value (defined as the value prior to first dose of IP) or are no longer considered clinically significant by the investigator or medical monitor. The investigator should evaluate whether the laboratory result meets the AE criteria in Section 10.3.1.

For subjects with treatment-emergent ALT elevations ≥3× ULN, see Section 10.5 for additional monitoring, evaluation, and follow-up recommendations.

Abnormal clinical laboratory values that are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

8.3.3.1 Hematology

The hematology panel will consist of complete blood count (hemoglobin [Hgb], hematocrit, erythrocytes [ie, red blood cell, RBC, count], and leukocytes [ie, white blood cell count, WBC] with differential [ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils]) and platelet counts.

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8.3.3.2 Clinical Chemistry

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate amino transferase (AST), total bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), serum creatinine, lactate dehydrogenase (LDH) and glucose. If the LDH is ≥ 2× ULN, the sample should reflexively be sent for isoenzyme analysis.

For subjects aged 2 to <16 years a reduced clinical chemistry panel will be performed, which will not include chloride, bicarbonate, total protein, and albumin. In addition, no isoenzyme analysis will be performed if LDH is ≥ 2× ULN in subjects aged 2 to <16 years.

8.3.3.3 Urine Test

Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination. Urinalysis tests will be conducted at the central laboratory.

At the time of the urine sample collection the presence of menstruation must be recorded for female subjects, if applicable, because blood contamination can easily occur.

8.3.3.4 Hemolysis Test

The hemolytic anemia panel will consist of hemoglobin, LDH, serum haptoglobin, plasma-free (unbound) hemoglobin, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), the number and percentage of reticulocytes, as well as urine hemosiderin.

For subjects aged 2 to <16 years the blood sample for the antibody elution test is only to be taken if the direct Coombs test is positive and will be collected in an unscheduled visit within 72 hours after the positive result.

If the LDH is ≥2× ULN, the sample should reflexively be sent for isoenzyme analysis (unless the subject is <16 years). If clinical hematology/clinical chemistry testing coincides with hemolysis tests, overlapping tests need to be performed only once.

If there is a reduction in hemoglobin of ≥2 g/dL compared to baseline hemoglobin (defined as the value prior to first dose of IP), every effort is to be made to perform a repeat test consisting of the hemolysis tests described above within 72 hours; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible.

It is not necessary to repeat the hemolytic panel if the drop of ≥2 g/dL hemoglobin remains constant at or after an unscheduled visit blood draw, unless it drops further. It is recommended that the investigator uses good medical judgment in assessing subjects with an unexplained decrease in serum hemoglobin as other medical conditions beside hemolysis can cause this, and therefore may require additional investigations. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

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8.3.3.5 Viral Pathogen Serology

Tests for viral pathogen serology include: HBsAg by enzyme-linked immunosorbent assay, PCR for HCV, and PCR for HIV-1/2. These assessments will be performed at the central laboratory at the time points specified in SoA (Section 1.3).

8.3.3.6 Back-up Samples

Back-up serum/plasma samples will be taken and stored for the duration of the study if re-testing is needed (eg, further evaluation of an abnormal test, investigation of an AE, or suspected development of antibodies in your blood as a result of infection), with limited collection in subjects aged <16 years to minimize blood drawing in this population. Upon finalization of the study, back-up serum and plasma samples will be stored and may be used at a later time point for future research. Subjects can still participate in the study even if they do not agree with the use of their samples for future research.

Takeda Future Research is defined as analyses that are not stated in the main study protocol endpoints; protocol endpoints include primary, secondary, and exploratory endpoints. The purpose of the future research is to advance medical science and improve patient care. The ICFs will define the allowable use of the samples in future scientific research, which is generally in the area of disease and/or drug under the main study. Future research samples may be stored for up to but not longer than 15 years or as required by applicable law (Section 10.2.2).

8.3.3.7 Retention Samples

Retention serum/plasma samples will be taken and stored at -70°C for possible future testing with respect to transmissible agents as per regulatory guidelines. Retention samples may be stored for up to but not longer than 15 years or as required by applicable law.

Both serum and plasma retention samples will be collected for subjects ≥16 years. Only serum retention samples will be collected for subjects aged 2 to <16 years.

8.3.4 Immunogenicity Assessments

8.3.4.1 Anti-rHuPH20 Antibodies

In all subjects, immunogenicity assessment for binding anti-rHuPH20 antibodies will occur as described in the SoA (Section 1.3). For subjects with a binding anti-rHuPH20 antibody titer ≥1:160, neutralizing antibodies will also be measured.

8.3.5 Pregnancy Testing

Pregnancy tests will be done for all females of childbearing age. Urine pregnancy tests will be performed at a central laboratory, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

If a subject becomes pregnant during the study, the pregnancy must be followed as described in Section 10.4.3.

8.3.6 Clinical Outcome Assessments

8.3.6.1 EuroQol 5 Dimension 5 Level Questionnaire

The EQ-5D-5L will be used to assess subject HRQoL. The EQ-5D-5L is a validated, self-administered assessment of overall health designed by the EuroQol Group (Rabin and de Charro, 2001). It is a descriptive system of HRQoL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Subjects are asked to describe their health state that day by choosing one of 5 responses that reflect the levels of severity for each of the 5 dimensions: no problems, slight problems, some or moderate problems, severe problems, or extreme problems. The EQ-5D-5L also includes a standard vertical 20-cm visual analog scale (similar to a thermometer) for recording a subject's rating of their current HRQoL state.

The EQ-5D-5L will be administered to subjects who are ≥12 years at the time of signing the ICF at the study site using a validated translated version, as applicable. It is recommended that the subject completes the assessment using the same translated version throughout the course of the study. In the event that the appropriate language is not available, the questionnaire will not be administered for that subject.

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8.3.6.2 Semi-structured Qualitative Interviews

English-speaking subjects (≥16 years)/subjects' (<16 years) legally designated representative(s) based in the US will be asked for their permission to participate in semi-structured qualitative interviews. Subjects who/subjects for whom legally designated representative(s) do not wish to undergo an interview will still be allowed to participate in the study.

Two interviews will be completed for subjects ≥16 years, responded by the subject (target sample size of up to 10 subjects, n=20 interviews) and 1 interview for subjects <16 years, responded by legally designated representative(s) (target sample size is up to 5 legally designated representative[s]). Interviews will follow a semi-structured interview guide designed to explore the following objectives: (1) subject's experiences while on TAK-881/HYQVIA, (2) general preferences for a PIDD treatment, and (3) meaningful change in their condition. Trained interviewers experienced in qualitative data collection will conduct the interviews following a semi-structured interview guide developed specifically for this study. Interviews may be conducted in the English language only and via telephone or video-conference, according to the subject's preference. Interviews will last up to 60 minutes and will be audio-recorded for verbatim transcription and qualitative analysis.

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8.3.6.3 Treatment Satisfaction Questionnaire for Medication – 9 Items

Subject satisfaction with TAK-881/HYQVIA treatment will be assessed by the TSQM-9 in subjects aged ≥16 years at the time of signing the ICF. The TSQM-9 is a reliable and validated 9-item questionnaire designed to measure subjects' satisfaction with medication across 3 domains: effectiveness, convenience, and global satisfaction (Bharmal et al., 2009). The recall period is the past 2 to 3 weeks, or since the last medication use, and the item response options include 5- or 7-point Likert-type scales. Higher scores indicate higher satisfaction with treatment.

The questionnaire will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject completes the assessment using the same translated version throughout the course of the study. In the event that the appropriate language is not available, the questionnaire will not be administered for that subject.

8.3.6.4 Healthcare Resource Utilization

The following information will be collected in subject diaries:

- 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.

8.3.7 Duration of Infusion Preparation

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 as described in the SoA (Section 1.3). Seven time points will be recorded, please refer to the Site Infusion Manual and Pharmacy Manual for detailed instructions.

- Time point 1 (start time): The time at which the DVUs of TAK-881/HYQVIA are removed from refrigeration.
- Time point 2: The time at which the preparation of the rHuPH20 component into a syringe begins.
- Time point 3: The time at which the preparation of the rHuPH20 component is completed.
- Time point 4: The time at which the preparation of the IGI, 10% or IGSC, 20% component begins (ie, into a pooling bag [US only] or direct from the vial using a vented pump tubing set [Europe]).
- Time point 5: The time when the preparation of the IgG component is completed.
- Time point 6: The time at which needle insertion occurs.
- Time point 7: (end time): The time the infusion of rHuPH20 is started.

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8.3.8 Diaries

A paper subject diary will be provided to each subject or, in case of minors, legally designated representative(s) at the screening visit to record the following information:

- Occurrence of AEs (including infections). The investigator will provide guidance for the subject or, in case of minors, legally designated representative(s) regarding identification and documentation of AEs.
- Occurrence of fever.

  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 (U.S. Department of Health and Human Services, 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.
- Concomitant medication use that includes antibiotics.
- HRU outcomes as described in Section 8.3.6.4.

Subjects or, in case of minors, legally designated representative(s) will be trained in the use of the diary. The diary will be provided in paper format and will be taken home by the subject and will remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

The paper subject diary will serve as a source record and remain at the study site after the study completion visit. Entries in the subject paper diary will be transcribed onto eCRFs. Any entry in the eCRF that does not correspond with an entry in the subject diary will be explained by the investigator in source documentation.

Subjects rolling over to the long-term follow-up Study TAK-881-3002 (Section 6.6), will continue recording AEs, concomitant medication, occurrence of fever and HRU outcomes in the Study TAK-881-3001 diary until the Study Visit 1/Week 1 of Study TAK-881-3002 and these entries will be transcribed onto TAK-881-3001 eCRFs. The TAK-881-3001 diary will remain at the site after this visit and a new diary for Study TAK-881-3002 will be provided to each subject or, in case of minors, legally designated representative(s) during this visit.

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8.3.9 Other

No further assessments are planned.

8.3.10 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided in Section 10.3.

The investigator and any qualified designees are responsible for collecting, detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for follow-up of these events (see Section 10.3.4).

Subject diaries will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with these instruments, then proper follow-up with the subject for medical evaluation should be undertaken. If it is determined through this follow-up that an AE not previously reported has been identified, normal reporting requirements should be applied.

8.3.10.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs will be collected from the signing of the ICF until EOS/ET Visit at the time points specified in the SoA (Section 1.3). For subjects rolling over to the long-term follow-up Study TAK-881-3002 (Section 6.6), AEs that occur until the Study Visit 1/Week 1 of Study TAK-881-3002 will be collected under Study TAK-881-3001.

All SAEs will be recorded and reported to the sponsor or designee immediately. Under no circumstance should this exceed 24 hours. The investigator will also submit any updated SAE data within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor via the reporting method described in Section 10.3.5.

8.3.10.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit specified in Section 1.3 and during the follow-up call after each infusion visit, subject or, in case of minors, legally designated representative(s), will be questioned in a general way to ascertain if AEs have occurred since the previous visit. The follow-up call will provide yet another window for collection or confirmation of AEs within 3-5 days following the infusion to mitigate recall lapses, error, or bias. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences without introducing bias. Subjects may report AEs occurring at any time during the study.

Additionally, the investigator will review the subject diary at each visit to identify AEs.

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8.3.10.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All subjects experiencing AEs, whether considered associated with the use of the study drug or not, will be documented in the AE page of the eCRF.

AEs must be monitored until the end of the study or until the event resolves, stabilizes, is otherwise explained, or the subject is lost to follow-up as defined in Section 7.3.

SAEs must be monitored until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Information to be documented for each event is defined in Section 10.3.4.

Further information on follow-up procedures is provided in Section 10.3.

8.3.10.4 Regulatory Reporting Requirements for Serious Adverse Events

All SAEs must be recorded and reported to the sponsor or designee immediately, via the procedure described in Section 10.3.5. Under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation.

The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/independent IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or package insert/SmPC (as applicable) and will notify the IRB/IEC, if appropriate according to local requirements.

The sponsor or designee must prepare safety reports for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forward them to investigators as necessary.

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Reporting of Abnormal Liver-associated Test Results

For any subject with ALT ≥3× ULN **and** total bilirubin >2× ULN for which an alternative etiology has not been found, report the event as an SAE, contact the medical monitor and Takeda trial clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Section 10.5.

8.3.10.5 Pregnancy During the Study

All subject pregnancies are to be reported from the time informed consent is signed until the defined follow-up period.

Any report of pregnancy for any female study subject must be reported within 24 hours to the Takeda Pharmacovigilance (PV) Operations Department using the Takeda Pregnancy Report Form. A copy of the Takeda Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the contract research organization (CRO)/Takeda Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study subject must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification (for the pregnancy outcome) and at approximately 30 calendar days and at approximately 1-year postpartum (for the condition of the infant).

Pregnancy complications such as spontaneous abortion/miscarriage, or congenital abnormality are considered SAEs and must be reported using the Takeda Safety Report Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Takeda Safety Report Form as well as the Takeda Pregnancy Report Form. The test date of the first positive serum/urine beta-human chorionic gonadotropin (β-hCG) test or ultrasound result will determine the pregnancy onset date.

8.3.10.6 Deaths

Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another IP action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the IP should be recorded as "dose not changed" or "not applicable" (if the subject never received IP). The IP action of withdrawn should not be selected solely as a result of the subject's death.

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8.3.10.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All disease-related events (DREs) and/or disease-related outcomes need to be reported as AEs or SAEs.

8.3.10.8 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical concern specific to the compound/program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. If the AE of special interest is serious, Takeda PV Operations team will send the appropriate Targeted Questionnaire (TQ) to the reporter and the list of Preferred Terms (PTs) or a Standard Medical Dictionary for Regulatory Activities Query (SMQ) associated with certain Takeda compound/program.

The following AESIs apply to this compound/program:

- Allergy.
- Catheter leakage (at the infusion site).
- Thromboembolic events.

If an AESI occurs during the study and is considered clinically significant, it must be recorded as an AESI in the AE eCRF form. In the event the AESI is serious, the eCRF SAE form must be completed within 24 hours which will be reported to Takeda Global Patient Safety Evaluation (GPSE).

8.4 Pharmacokinetics

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).

8.4.1 Pharmacokinetic Profiles

On a case-by-case basis, PK sampling may be performed at home by a home healthcare representative for PK visits.

All PK analyses will use the actual sampling times (not nominal times) and nonbaseline-corrected total IgG levels.

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AB/BA Crossover Treatment Epochs (Subjects Aged ≥16 Years)

The following PK metrics at steady-state 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 and details regarding the calculation of PK metrics using NCA will be described in a separate CPAP.

Serial PK of total IgG measurements will be performed at the time points specified in Table 3 and Table 4.

Single-Arm Treatment Epoch (subjects aged 2 to <16 years)

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.

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 6 sampling sequences specified in Table 7.

In general, study infusion visits are calculated based on the last prestudy IgG infusion date and that serial PK assessments may fall onto weekends and/or public holidays. If sites and/or subjects cannot accommodate weekend visits, the site is advised to review the best day for study visits prior to planning the last prestudy IgG infusion date. A ±5 days window is permitted for the last prestudy IgG infusion for subjects with a treatment interval of 28 days, and a ±3 days window is permitted for the last prestudy IgG infusion for subjects with a treatment interval of 7, 14, or 21 days.

Last prestudy IgG infusions on Mondays and Tuesdays will avoid weekend PK draws. The -1 day window can additionally be used on PK Day 1 scheduled on Wednesdays to bring PK visits forward.

8.4.2 Serum IgG Trough Levels

Trough levels of IgG total, IgG subclasses (total serum levels of IgG and IgG subclasses: IgG1, IgG2, IgG3, and IgG4) will be determined in all subjects at visits specified in the SoA (Section 1.3) by using standard assay methods.

Specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and hepatitis B) will only be determined in subjects ≥16 years at visits specified in the SoA (Section 1.3) by using standard assay methods. The blood drawing for the IgG trough level determination will always take place before the infusion is administered on the same day. PK measurements will be performed at the specialty laboratory and by using validated bioanalytical methods. For serial PK (≥16 years) and sparse PK (2 to <16 years) assessments, only total IgG will be measured.

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8.4.3 Pharmacokinetic Sample Collection and Analysis

8.4.3.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples will be collected to measure serum concentrations of total IgG and IgG subclasses.

Blood samples will be drawn according to the time points specified in Section 1.3 and processed as described in the Laboratory Manual. The actual time that the sample was obtained will be recorded in the subject's source document and on the appropriate CRF page. In instances where more than 1 blood collection tube is used, the time of the initial blood draw will be recorded for all tubes collected at that time point on the appropriate CRF page. After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

Serum sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the specialty laboratory. The labels will contain the following information:

- Study number.
- Subject identifier.
- Treatment.
- Epoch.
- Nominal day.

- Nominal time.
- Actual day.
- Actual time.
- Matrix identifier (serum).
- Split (primary or back-up).

Incurred sample reanalysis will be performed to confirm that IgG assay results are reproducible.

8.4.3.2 Collection of Urine for Pharmacokinetic Sampling

Not applicable.

8.5 Pharmacodynamics

Not applicable.

8.6 Genetics

Genetics will not be evaluated in this study.

8.7 Biomarkers

Biomarkers will not be evaluated in this study.

8.8 Immunogenicity Assessments

Please refer to Section 8.3.4.

8.9 Photographs of Infusion Sites

At a number of selected US study sites and only in subjects ≥16 years old willing to participate, digital photographs of the infusion site(s) preinfusion (within 1 hour before infusion), immediately postinfusion (+15 minutes), 24±4 hours and 72±8 hours postinfusion (for both IPs) will be taken. The photographs will be taken of the infusion site only and will be labeled using the subject's identifier. Subjects will be asked to permit photographs of the infusion sites (via an optional ICF), which will be used for publications, educational and demonstration purposes, both within and external to the study. Subjects who do not provide permission for photographs will still be allowed to participate in the study.

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8.10 End of Study Visit/Early Termination Visit

All subjects completing or exiting the study must complete the EOS/ET procedures.

The EOS Visit will be 21 days (±1 day) after the last dose for 3-week dosing intervals and 28 days (±1 day) after the last dose for 4-week dosing intervals.

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9. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be prepared and finalized before the first visit of the first subject. The SAP will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all study objectives (except the objective to characterize the PK of TAK-881 between subjects aged ≥16 years and subjects aged 2 to <16 years which will be addressed in a separate population PK analysis plan). In addition, a qualitative analysis plan (QAP) will be prepared and finalized to describe the planned elements to be included in the exit interviews.

All statistical analyses will be performed using Statistical Analysis Software, SAS® (SAS Institute, Cary, NC 27513), Version 9.4 or higher. Qualitative interviews will be analyzed using MAXQDA qualitative analysis software.

9.1 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 $\alpha=0.05$ (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%.

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No other hypotheses will be tested in this study.

9.2 Analysis Sets

9.2.1 Safety Analysis

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.

9.2.2 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.

9.2.3 Pharmacokinetic Per-Protocol Analysis Set

Subjects aged ≥16 years:

The Pharmacokinetic Per-Protocol Analysis Set (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. A list of all deviations that may affect the reliability of the total IgG level time profiles will be provided in the SAP. 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. A list of all deviations that may affect the reliability of the total IgG level time profiles will be provided in the SAP.

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9.3 Efficacy Analyses

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 will be presented for the SAS. Infections are considered efficacy endpoints and will be analyzed based on the SAS.

9.3.1 Primary Efficacy Endpoint

Subjects aged ≥16 years:

The primary endpoint $AUC_{0\text{-}\tau,ss}$ 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, see Section 8.4.1.

$AUC_{0-\tau,ss}$ 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.

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%, see Section 9.1.

In addition, geometric means and corresponding two-sided 95% CIs of $AUC_{0-\tau,ss}$ will be presented separately for TAK-881 and HYQVIA.

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).

Sensitivity Analysis for the Primary Endpoint:

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. This sensitivity analysis utilizing the same linear mixed effects model as described above is unbiased under the MAR premise.

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9.3.2 Secondary Efficacy Endpoints

9.3.2.1 Pharmacokinetics

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 (data permitting), see Section 8.4.1.

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).

The same linear mixed effects model as for the primary endpoint $AUC_{0\text{-}\tau,ss}$, see Section 9.3.1, 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.

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). In addition, trough levels will be also summarized by study visit.

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 21 (3-week treatment interval) or Week 22 (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).

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). In addition, trough levels will be also summarized by study visit.

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9.3.2.2 Infections

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. 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, combined) and for HYQVIA for subjects aged ≥16 years and ≥18 years.

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, combined) and treatment (TAK-881, HYQVIA).

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, combined) and treatment (TAK-881, HYQVIA).

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, combined) and treatment (TAK-881, HYQVIA) for subjects with at least one ASBI in the corresponding treatment epoch.

9.3.3 Multiplicity Adjustment

No adjustments for multiplicity will be performed.

9.4 Safety Analyses

Safety analyses will be presented for the SAS.

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Occurrence of TEAEs:

AEs will be coded using the Medical Dictionary for Regulatory Activities. TEAEs are defined as AEs that started at or after the initiation of the first administration of TAK-881 or HYQVIA.

The severity of AEs (except SARs) will be assessed by the investigator using the CTCAE, version 5.0, consisting of 5 grades:

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

The severity of SARs will be assessed by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017), consisting also of 5 grades.

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:

- Any TEAE.
- Serious TEAEs.

- TEAEs considered related to TAK-881/HYQVIA.
- Local TEAEs.
- Systemic TEAEs.
- Temporally associated TEAEs within 72 hours.
- TEAEs by maximum severity (CTCAE grades 1-5).
- TEAEs leading to study discontinuation.
- TEAEs of special interest (allergy, catheter leakage, and thromboembolic events).

The 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, combined), by infusion interval (3-week, 4-week, combined), and by prestudy IgG treatment (HYQVIA, IGIV, cIGSC, combined).

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, combined), SOC and PT.

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

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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 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, 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.

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, 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.

9.5 Other Analyses

Other Analyses will be presented for the SAS.

9.5.1 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, 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.
- 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 duration of infusions per subject will be summarized using descriptive statistics.
- Average monthly infusion time (minutes/month) will be calculated per subject as total duration of infusions divided by the total time in months on treatment and will be summarized using descriptive statistics.
- Maximum infusion rate per site (mL/hour/site) will be summarized using the following descriptive statistics: n, minimum, median, and maximum across infusions and subjects.
- Infusion volume per site (mL/site) as well as total infusion volume (mL) will be summarized using descriptive statistics for the average infusion volume per subject.

In addition, the average duration of infusions and the average monthly infusion time will be presented by treatment (TAK-881, HYQVIA) for the following subgroups:

- All subjects.
- Subjects aged 2 to <16 years with 1 infusion site for all TAK-881 infusions.

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

9.5.2 Clinical Outcome Assessments

Subject satisfaction evaluated by TSQM-9, subject HRQoL evaluated by EQ-5D-5L, and HCP measured time of infusion preparation will be summarized descriptively at each assessment and, if applicable, by item and domain. Further details will be provided in the SAP.

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9.5.3 Healthcare Resource Utilization

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).

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 will be presented for antibiotics for prophylaxis and treatment of infection separately as well as for all antibiotics combined.

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 <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).

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9.6 Interim Analysis and Data Monitoring Committee

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.
    - 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.

Irrespective of whether there will be only one formal analysis or two formal analyses, the SAP will be finalized and approved prior to the first visit of the first subject.

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). The DMC evaluation will not stop further enrollment of subjects ≥16 years, unless a criterion for premature termination/suspension of the study is met (Section 10.1.12.2).

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

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9.7 Determination of Sample Size

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" (FDA, 2008).

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Section 10.1.11.2. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

10.1.2 Financial Disclosure

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and sub-investigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor prior to the start of the study at their site.

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All institutional affiliations of the investigator and sub-investigator should be declared on their curriculum vitae, which must be provided to the sponsor prior to the start of the study.

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor.

The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in study intervention; any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations (CFR) 54 2(b) (1998).

10.1.3 Informed Consent Process

10.1.3.1 Informed Consent Requirements in This Study

The goal of the informed consent process is to provide a potential subject or, in the case of minors, their legally designated representative(s) with sufficient information about the research to allow for an informed decision about their voluntary participation in the research study. The informed consent process must facilitate the subject's comprehension of the information and allow adequate opportunity for the subject to ask questions and consider whether or not to participate. This process may extend beyond a subject's initial consent due to changing circumstances within the study, the therapeutic landscape, or the subject's situation.

When a subject or, in the case of minors, their legally designated representative(s) consents to participate in the study, their informed consent must be documented in writing via a signed and dated ICF or via an eConsent system (if available). The date of the informed consent will also be collected in the eCRF along with the most recent approved protocol version.

The study includes subjects who are incapable of providing informed consent (see Section 4.3).

In this study, informed consent will be required from all subjects or, in the case of minors, their legally designated representative(s).

The definition of those persons who are able to act as legally designated representative(s) should be checked against national laws.

In addition, assent will be required from subjects who are too young to fully consent and are considered capable of providing assent.

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If, during the course of the crossover treatment epochs, an adolescent is no longer a minor as defined in national law, or is an "emancipated minor", then written informed consent is required from these individuals (when required by the local IEC/IRB) and must be sought directly from the individual and as soon as possible. Under these conditions, informed consent is no longer required from the legally designated representative(s).

In this study, informed consent will be obtained using paper forms and eConsent (if available).

10.1.3.2 Standards the Informed Consent Follows

Informed consent documents, regardless of whether they are presented on paper or electronically, must embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations.

The ICF and related materials, information form, and assent form (for minors capable of assent):

- Explain the nature of the study, its objectives, potential risks and benefits.
- Describe the subject's rights and responsibilities, including what the study will require of the subject.
- Describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies, if applicable.
- State the fact the subject is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

More specifically, in seeking informed consent, the following information shall be provided to each subject:

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- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the subject's participation.
- A description of the procedures to be followed, including invasive procedures.
- The identification of any procedures that are experimental.
- The estimated number of subjects involved in the study.
- A description of the subject's responsibilities.
- A description of the conduct of the study.
- A statement describing the treatment(s) and the probability for random assignment to each treatment.
- A description of the possible side effects of the treatment that the subject may receive.
- A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- A description of any required restrictions related to contraception, pregnancy, and breastfeeding.
- Contraception requirements for subjects of childbearing potential.
- Definition of relevant terms such as "childbearing potential".

- Statement that female subjects of childbearing potential will undergo regular pregnancy tests during the study.
- Explanation of required actions (such as discontinuation or treatment or from the study) if a subject becomes pregnant during study.
- Statement that the subject must avoid breastfeeding during the study.
- A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
- A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing an ICF, the subject or, in case of minors, legally designated representative(s) is authorizing such access.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
- The anticipated prorated payment(s), if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled.
- A statement that the subject or, in case of minors, legally designated representative(s) may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that the subject or, in case of minors, legally designated representative(s) will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

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- The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
- A subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
  - That de-identified personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs.
  - That is possible that de-identified personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law.
  - That de-identified personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies.
  - That subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research.
  - That the subject's identity will remain confidential in the event that study results are published.
  - A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.
  - A description of the electronic devices and associated technology and its usage in the study.

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10.1.3.3 Additional Optional Consent Forms

In addition to the standard informed consent materials, there are additional optional consent forms for specific assessments in the study; photographs of infusion sites and qualitative interviews (US only). Subjects will be informed that they are free to refuse permission for these specific assessments and will still be allowed to participate in the study.

10.1.3.4 Who Creates the Informed Consent Materials

The sponsor will provide sample ICFs, information forms, and assent forms (for minors capable of assent) to the investigator.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF, information forms, and assent forms (for minors capable of assent).

The principal investigator will provide the sponsor with a copy of the ICF, information forms, and assent forms (for minors capable of assent) that were reviewed by the IRB/IEC and received their favorable opinion/approval. A copy of the IRB/IEC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/IEC requires modification of the sample documents that the sponsor provided, the documentation supporting this requirement must be provided to the sponsor. Both the IRB or IEC and the sponsor must approve the ICF, information forms, and assent forms (for minors capable of assent) before use.

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The sponsor will provide the IRB-approved version of the ICF to the site in an electronic form with 21CFR compliant eConsent functionality, if applicable.

10.1.3.5 Who Conducts the Informed Consent Process

It is the responsibility of the investigator and the study personnel to:

- Explain the detailed elements of the ICF, information forms, and assent forms (for minors capable of assent) to the subject or, in case of minors, legally designated representative(s).
- Answer all of the subject's or, in case of minors, legally designated representative(s)'s questions about the study.
- Provide the subject or, in case of minors, legally designated representative(s) ample time to decide whether or not to participate in the study.
- Obtain written and/or electronic informed consent and assent, where applicable from all subjects or, in case of minors, legally designated representative(s) prior to any study-related procedures including screening assessments.

Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. (Oral and written information may be provided via remote or virtual visits, eg, via telehealth [video, phone] and eConsent systems).

If the subject or, in case of minors, legally designated representative(s), determines they will participate in the study, then they must sign and date the ICF at the time of consent and prior to entering into the study.

Subjects or, in case of minors, legally designated representative(s) will sign paper consent forms. The subject or, in case of minors, legally designated representative(s) should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink in the case of written informed consent.

Subjects or, in case of minors, legally designated representative(s) may electronically sign consent forms. eConsent provides the same information as written consent forms, but in an electronic format that may include multimedia components. eConsent does not replace the important discussion between the study subject and site staff or investigator. Regardless of the consent format – written or eConsent – the investigational site is responsible for the consenting process.

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A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be provided to the subject or, in case of minors, legally designated representative(s).

The investigator must also sign and date the ICF/eConsent at the time of consent or after receipt of subject signature (in the case of eConsent) and before the subject enters the study. However, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law and as described on the Site Delegation Log.

The investigator's copy of the signed consent forms or certified copies of electronic signatures must remain in each subject's study file at the site and must be available for verification at any time.

The investigator must document the date the subject signs the ICF in the subject's source documents.

10.1.3.6 Reconsent

Subjects or, in case of minors, legally designated representative(s) are required to re-consent/re-assent if changes are made to the protocol or if new information is made available that may affect the willingness of current subjects (those who are already enrolled and actively participating) to continue in the clinical investigation. Re-consent/assent must be obtained as described in Section 10.1.3.1.

Updated ICFs, individual consents, individual assents, individual re-consents and re-assents will be placed in the Trial Master File. Re-consent information including the protocol version and re-consent date will also be recorded in the eCRFs.

10.1.4 Data Protection

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects or, in case of minors, legally designated representative(s) have consented to take part in the study, the sponsor and/or its representatives reviews their source documents and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market TAK-881/HYQVIA; national or local regulatory authorities; and the IRBs/IECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their date of birth may also be collected, if permitted under local laws governing privacy. The process of assigning a unique identifying number (see Section 5.4) refers to pseudonymization. Pseudonymization is defined as the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

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The results of studies containing subjects' unique identifying number, relevant source documents, and possibly dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the ICF.

- The subject must be informed that their source documents may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject data.

The sponsor or its designee uses access-controlled systems to house, review, and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The sponsor or its designee has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed.

The contracts between the responsible CRO and the study sites specify the responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented and the relevant regulatory agency/agencies will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

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Coded personal information collected during the study may be used by or sent to other parties, in other countries, for clinical research, safety reporting, and any other study-related uses. The sponsor or designee will do everything possible to keep coded personal information confidential.

With respect to transfers to its affiliates and business partner, the sponsor has put in place appropriate contractual provisions, or is otherwise satisfied that there are measures in place to achieve the level of protection of coded personal information equivalent to that under European law.

Retention of data will be according to ICH GCP requirements or applicable regulatory requirements.

10.1.4.1 Notice Regarding the Use and Transfer of the Investigator's Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and telephone number, and other personally identifiable information such as education and professional details, payment-related details (if applicable), identity information (eg, medical registration number) and information relating to his or her interactions and activities with or involving Takeda. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world, including the following:

- Takeda, its affiliates, and their licensing partners.
- Business partners assisting Takeda, its affiliates, and their licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

In addition, where required by law or industry codes of practice, Takeda and/or its affiliates may have to report or publicly disclose any payments or transfers of value made in connection with the study by or on behalf of Takeda and/or its affiliates or their service providers to the investigator or their institution.

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The legal basis on which Takeda and its affiliates will process the Investigator's personal information for the above purposes are in order to comply with a legal obligation; or to perform any contract in place with the investigator (if applicable); or to meet the legitimate research, scientific and business interests of Takeda and its affiliates, including ensuring the proper performance of this study to the applicable standards, appropriate reporting of study results and archiving of study-related records and information, and further development and registration of the study drug or other compounds. The investigator may not be able to opt-out of this processing, or the investigator's choice to opt-out may impact his or her ability to continue to participate in this study and/or future studies involving Takeda and/or its affiliates.

Takeda and its affiliates will maintain physical, administrative and technical safeguards to protect the Investigator's personal information from loss, misuse, unauthorized access, disclosure, alteration or destruction. Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

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However, where Investigator's personal information is transferred to Takeda affiliates, licensing partners, business partners or service providers in such countries, Takeda will ensure that all adequate safeguards are in place and that all applicable laws and regulations are complied with in connection with such transfers.

The Investigator's personal information will only be stored as long as necessary for the purposes for which it was collected subject to local laws and regulations and legitimate scientific, research and business needs.

Individuals located in the European Economic Area (EEA) and in certain other countries have certain data subject rights which may be subject to limitations and/or restrictions.

These rights include the right to: (i) request access to and rectification or erasure of their personal data; (ii) obtain restriction of processing or to object to processing of their personal data; (iii) the right to data portability; and (iv) obtain additional information regarding the safeguards Takeda has in place for cross-border transfers of their personal data. If the Investigator wishes to exercise one of these rights, the Investigator may use the contact information below.

Individuals located in the EEA and in certain other countries may also have the right to lodge a complaint about the processing of their personal data with their local data protection authority.

The Investigator can contact Takeda in order to exercise his or her rights, make inquiries or submit complaints concerning Takeda's processing of his or her personal information. Takeda will take appropriate steps to address requests, inquiries and complaints. Takeda will respond to such requests within thirty (30) business days.

Contact Details:

Mailing Address: Attn: Data Protection Officer, Legal Department, Takeda Pharmaceuticals International AG, Thurgauerstrasse 130, CH-8152 Glattpark-Opfikon (Zurich), Switzerland.

E-mail Address: dataprivacy@takeda.com

Investigator acknowledges and authorizes the use of his or her personal information by Takeda and other parties for the purposes described above.

10.1.5 Committees Structure

10.1.5.1 IRB and/or IEC Approval

IRBs/IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRBs/IECs. If any member of the IRBs/IECs has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federalwide Assurance Number or comparable number assigned by the Department of Health and Human Services.

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The sponsor or designee will supply relevant documents for submission to the respective IRBs/ IECs for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRBs/IECs for approval.

The IRB's/IEC's written approval of the protocol and subject ICF must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity).

The IRBs/IECs approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date.
If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify sites once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB/IEC. This may include notification to the IRBs/IECs regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRBs/IECs, and submission of the investigator's final status report to IRBs/IECs. All IRBs/IECs approvals and relevant documentation for these items must be provided to the sponsor or designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRBs/IECs and sponsor.

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed eConsent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/IEC for review, and all must be approved prior to site initiation.

The applicant for an ethics committee opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

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Responsibility for coordinating with IRBs/IECs is defined in the investigator agreement. Study intervention supplies will not be released until CRO has received written IRB/IEC approval.

Prior to implementing changes in the study, the sponsor and the IRB/IEC must approve any revisions of all informed eConsent documents and amendments to the protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/IEC informed of any serious and significant AEs as required by IRB/IEC procedures.

Safety Review

Subject safety will be continuously monitored by the external DMC (Section 10.1.5.2), which includes safety signal detection at any time during the study.

10.1.5.2 Other Committees

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). The DMC evaluation will not stop further enrollment of subjects ≥16 years, unless a criterion for premature termination/suspension of the study is met (Section 10.1.12.2).

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

10.1.6 Dissemination of Clinical Study Data

10.1.6.1 Study Results Disclosure

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials before study start and disclose the results of those trials in a manner and timeframe compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on ClinicalTrials.gov, other clinical trial registries/databases as required by law, and on Takeda's corporate website(s).

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10.1.7 Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Guidelines (CCGs).

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) will be predefined in the Takeda Risk Assessment and Oversight Plan and Evaluation to identify systematic issues that can impact subject safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report (CSR).

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as specified in Section 10.1.8.4. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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10.1.7.1 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The sponsor will assess any protocol deviation. If it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The site must document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

Protocol deviations will be captured in a Part 11 compliant clinical trial management system (CTMS).

10.1.7.2 Study Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site head guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB/IEC.

Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review/source data verification via phone or video) as permitted by regional and local regulations. See the monitoring plan for additional details.

10.1.7.3 Audits

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately.

The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 10.1.8.

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10.1.8 Source Documents

All key data must be recorded in the subject's source documents unless otherwise noted in the protocol. Source documents may be paper or electronic, including data obtained using electronic devices and associated technologies. Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, appointment books, diaries, clinical outcome assessments (COAs), original clinical laboratory reports, histology reports, pathology reports, X-rays. The investigator (for the US: as listed on the US FDA Form 1572) is responsible for maintaining adequate and accurate source documents.

The investigator must provide direct access to inspect facilities, including original source records relevant to this study (regardless of media), to: the sponsor or its authorized representatives; the respective national, local, or foreign regulatory authorities; the IRB/IEC; and auditors. These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, Pharmaceutical and Medical Devices Agency [PMDA]) or an auditor. The eConsent form includes a statement granting this access to source data.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.1.8.1 Electronic Case Report Forms

Completed eCRFs are required for each subject who has completed the consent process. The eCRFs are designed to record all observations and other data pertinent to the clinical investigation unless otherwise noted in the protocol.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

The sponsor or its designee will supply study sites with access to eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. eCRFs must be completed in English.

The investigator or the investigator's designee (ie, authorized site personnel, as stated in the Site Delegation Log) must enter data from the source documents (Section 10.1.8) into the eCRF with guidance from the study CCGs.

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The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

A study monitor from the sponsor or its designee will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Auditors, IRB/IEC members, or regulatory inspectors may also check the eCRF entries against the source documents.

Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should also be included.

The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values.

The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data. Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

The CRFs should be approved by the investigator per study specifications and the sponsor's data delivery requirements.

Once the CRA/study monitor has verified the contents of the completed CRF pages against the source data, the duplicate pages are retrieved and forwarded to the study sponsor (or designee) for data entry. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

The investigator's signature constitutes their attestation to the integrity of the data transmitted to the sponsor.

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10.1.8.2 Documentation and Retention of Records

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. A definition of what constitutes source data and its origin can be found in the monitoring guidelines.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous source documents or transfer records, depending on the study. Also, current source documents must be available.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8.3 Data Handling

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

Data are to be entered into a clinical database as specified in the CRO's Data Management Plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

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10.1.8.4 Record Retention

The investigator agrees to keep records and documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, source documents, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed (e)Consent forms (including consent to use digital tools and applications, if applicable), subject authorization forms regarding the use of personal health information (if separate from informed (e)Consent forms), query responses/electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6(R2) Section 5.5.11 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

10.1.9 Study and Site Start and Closure

10.1.9.1 First Act of Recruitment

The first act of recruitment is the signing of the ICF by the first subject.

For clinical trial disclosure purposes, the study start date is the date when the first subject signed the ICF.

10.1.9.2 Study/Site Termination

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. The sponsor reserves the right to close the study site at its sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/IECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- For study termination:
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
  - Total number of subjects included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

The sponsor will make an end of study declaration to the relevant competent authority.

10.1.10 Publication Policy

During this study, until the open access period, only Takeda may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation.

Both during and after this study, all public disclosures containing data/information from this study must undergo ***review and receive written approval*** by the appropriate Takeda representative(s) ***before*** any public disclosure (including but not limited to submission, presentation, posting on online platforms for archiving, and distribution of unpublished preprints).

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This policy applies to all publication types, including: abstracts and presentations (oral and poster, including invited presentations) for scientific congresses; articles (original research manuscripts, review articles, invited articles), letters to the editor, and editorials, in scientific peer-reviewed journals; print, electronic and enhanced multimedia publications associated with traditional congress and journal publishing (such as, but not limited to, audio, visual/graphical or video abstracts or manuscript summaries; video or animated posters; augmented reality, etc.); books and book chapters.

Authorship will be determined in line with the requirements of the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals, unless otherwise required by the journal or forum where the publication appears.

All publications must be developed with a dataset (such as statistical tables and listings, CSR, and/or final report) that has been verified by a qualified Takeda employee per Takeda's internal standards. Data relevant to the development of Takeda publications must be shared with all authors via a secure site.

Publications derived from this study may never contain subjects' direct identifiers (such as SIC) but may contain indirect/quasi identifiers (for example sex/gender, age/birth date, geographic indicators). Publications derived from this study may not include products' direct identifiers (lot numbers or batch numbers) unless specifically required by the journal or conference guidelines and if approved by Takeda.

Takeda requires the submission of all manuscripts resulting from this study, regardless of the intended audience or language, to journals that offer public availability via an Open Access platform.

The following types of information are required by ICH to be in the protocol if not addressed in another document (such as the site contracts):

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

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10.1.11 Responsibilities of the Sponsor and the Investigator

10.1.11.1 Sponsor Responsibilities

10.1.11.1.1 Study-related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform these activities either in full or in partnership with the sponsor.

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and sub-investigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their site.

All institutional affiliations of the investigator and sub-investigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.

10.1.11.1.2 Insurance

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

10.1.11.2 Investigator Responsibilities

Clinical research studies sponsored by the sponsor are subject to ICH GCP, FDA, EMA, PDMA and all other applicable local laws and regulations.

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The investigator agrees to assume the following responsibilities:

- Conduct the study in accordance with the protocol.
- Personally conduct or supervise the staff who will assist in the protocol.
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
- Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
- Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
- Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to local regulatory requirements.
- Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.

- Ensure that requirements for informed eConsent, as outlined in ICH and local regulations, are met.
- Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. A valid ICF is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or, in case of minors, legally designated representative(s).
- Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
- Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
- Maintain current records of the receipt, administration, and disposition of sponsor-supplied materials.
- Report ARs to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
- It is the investigator's responsibility to ensure that adequate time, appropriately trained personnel, and resources are available prior to commitment to participate in this study.
- The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.
- The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
- If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

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- The investigator (for the US: listed on the Form FDA 1572) will verify by signature the integrity of the data transmitted to the sponsor.
- The investigator will be responsible for reviewing data, reports, and inter-laboratory/reader standardization methods (if applicable); facilitating monitoring and auditing activities.

10.1.11.2.1 Protocol Adherence and Investigator Agreement

The investigator and any subinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRBs/IECs and provide them with a detailed written explanation. The investigator will also provide final disposition of all study intervention, containers, and other study materials per sponsor instructions. Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

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Communication with local IRBs/IECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.1.11.2.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study.

Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research, as well as study participation.

The principal investigator/coordinating principal investigator will be required to review and sign the final CSR and by doing so agrees that it accurately describes the results of the study, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.1.11.2.3 Compliance With all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances, biohazardous material, or substances for infectious diseases, the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

10.1.12 Site Termination or Suspension

10.1.12.1 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement; is unable to ensure adequate performance of the study; or as otherwise permitted by the contractual agreement.

10.1.12.2 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require suspension (temporary cessation of some or all research activities) or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the IPs, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- The DMC recommends that the study should be suspended or terminated.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.
- If any of the following criteria are met, it will trigger a pause of enrollment and treatment with TAK-881 in all subjects. Upon further DMC evaluation and recommendation, the protocol and/or informed consent may be modified, or the study may be fully stopped. The ad-hoc DMC meeting will be initiated as soon as possible to minimize the time between any event triggering these criteria and the DMC recommendation:
  - Two or more subjects with Grade 3 or higher SAR graded by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) (Appendix 2) or anaphylaxis defined by NIAID/FAAN (Sampson et al., 2006) (Appendix 3) OR
  - Two or more subjects with Grade 3 adverse events occurring in the same system organ class, with the exception of infections, OR
  - Any Grade 4 or higher adverse event.

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All AEs and clinically significant laboratory abnormalities, excluding SARs, will be graded according to National Cancer Institute (NCI) CTCAE, Version 5.0, dated November 27, 2017 (U.S. Department of Health and Human Services, 2017).

SARs will be graded by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) (Appendix 2). Anaphylaxis will be reported as defined per NIAID/FAAN (Sampson et al., 2006) (Appendix 3).

10.1.12.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an IRB/IEC, or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

10.2 Clinical Laboratory Tests

Table 15 lists the tests that will be obtained for each laboratory specimen. These tests will be performed by the central laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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Table 15. Protocol-required Laboratory Tests

Laboratory Tests	Parameters			
Hematology [a]	Platelet count Hemoglobin Hematocrit	RBC count		White blood cell count with differential Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry [a, b, c]	Albumin* BUN Serum Creatinine Glucose	Potassium Sodium Chloride* Bicarbonate*	AST ALT ALP LDH [e]	Total bilirubin Total protein*
Routine Urinalysis	Color Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	For females of childbearing potential only: Urine human chorionic gonadotropin pregnancy test (to be performed by the central laboratory)			
Other screening tests	HIV [HIV-1/2], HBsAg, and HCV)			
Hemolysis [d]	Hemoglobin, LDH [e], serum haptoglobin, plasma-free (unbound) hemoglobin, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive)[f], the number and percentage of reticulocytes, urine hemosiderin			
Trough Levels of total IgG, IgG Subclasses and Specific Antibodies	Trough levels of total IgG, IgG subclasses and specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and HBV)[g]			
Anti-rHuPH20 antibodies	Binding anti-rHuPH20 antibodies, neutralizing anti-rHuPH20 antibodies (for subjects with a binding anti-rHuPH20 antibody titer ≥ 1:160)			
eGFR	Subjects ≥18 years: Calculated using the CKD-EPI creatinine age sex equation (Inker et al, 2021) Subjects <18 years: Calculated using the revised bedside Schartz equation (Schwartz et al., 2009)			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI= CKD Epidemiology Collaboration; eGFR=estimated Glomerular Filtration Rate; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IgG=immunoglobulin G; LDH: lactate dehydrogenase; RBC=red blood cell; rHuPH20=recombinant human hyaluronidase; ULN=upper limit of normal.

[a] Hematology and clinical chemistry assessments will be performed on Ethylenediamine tetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively.

[b] Details of required actions and follow-up are given in Section 10.5 Abnormal Liver-Associated Test Result Monitoring and Follow-Up Assessments.

[c] For subjects aged 2 to <16 years a reduced clinical chemistry panel excluding the parameters indicated with "*" will be performed.

[d] If there is a reduction in hemoglobin of 2 g/dL or more compared to baseline hemoglobin, every effort is to be made to perform a repeat test consisting of the hemolysis tests described above within 72 hours; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

[e] If the LDH is ≥2× ULN, the sample should reflexively be sent for isoenzyme analysis unless the subject is <16 years old.

[f] For subjects aged 2 to <16 years, the blood sample for antibody elution test is only to be taken if the direct Coombs test is positive, and will be collected in an unscheduled visit within 72 hours after the positive result.

[g] Specific antibodies to clinically relevant pathogens will only be determined for subjects ≥16 years.

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10.2.1 Clinical Laboratory Assessments and Other Safety Assessments

A change in the value of a clinical laboratory parameter, physical examination finding, or vital sign measure can represent an AE if the change is clinically relevant or if, during administration of study intervention, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further worsening of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the study intervention, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), physical examination, or vital sign values that were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator must assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, physical examination, or vital sign is clinically significant and represents an AE (in which case, it must be recorded on the AE eCRF page).

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10.2.2 Biological Sample Retention and Destruction

In this study, back-up serum/plasma samples will be stored and may be used for future research studies, which could help the study sponsor understand PIDD or the effects of the study drug at a later time (Section 8.3.3.6).

In general, the samples may be stored for up to but not longer than 15 years or as required by applicable law. Samples for future research will be stored by the long-term storage vendor, Azenta, 2910 Fortune Circle West, Suite E, Indianapolis, IN 46241 USA. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

Subjects who consented for future research can withdraw their consent and request disposal of a stored sample at any time. The sponsor should be notified of the consent withdrawal. When subjects request disposal of a stored sample during the retention period, the site will ask the vendor to destroy the sample via the sponsor according to the procedure.

The vendor will destroy the sample in accordance with the procedure and notify the site and sponsor. The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

10.3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Table 16. Adverse Event Subtypes Defined in this Section

Type	Nested Subtypes	Report Within[1]	Sponsor reports[2]
AE – collection timing per SoA—Section 1.3		--	--
	AESI - Section 8.3.10.8, Section 10.3.3.2	24 hours	See Footnote 3
	Pretreatment emergent	--	--
	TEAE - Section 10.3.4.9	--	--
	SAE - Section 8.3.10.4	24 hours	See Footnote 3
	Related AE - any study intervention (whether the IP or another intervention) – Section 6.1, Section 10.3.4.3	--	--
	Related AE (ADR) (related to the IP)	--	--
	Expected adverse event—Section 10.3.4.7	--	--
	Unexpected adverse event—Section 10.3.4.8	--	--
	SUSAR (ie, related to IP)—Section 10.3.5.3		
	• Fatal/Life-threatening	24 hours	7 days
	• Nonfatal/Non–life-threatening	24 hours	15 days

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ADR=adverse drug reaction; AE=adverse event; AESI=adverse event of special interest; CRO=contract research organization; eCRF=electronic case report form; IP=investigational product; SAE=serious adverse event; SoA=schedule of assessments; SUSAR=suspected unexpected serious adverse reaction; TEAE=treatment-emergent adverse event.

The specific timeframes on this chart apply to expedited AE/SAE reporting periods and procedures for which this protocol provides additional instructions. Reporting via the eCRF is *required but is not sufficient* to expedite a report.

(--)=not expedited

[1] This is the required, expedited reporting period for the site to report the event to the sponsor/CRO.

[2] This is the required, expedited reporting period for the sponsor to notify other parties including but not limited to regulatory agencies. For some studies, partner agreements may exist that have different reporting timelines, as specified in the individual pharmacovigilance agreement.

[3] To be evaluated at the sponsor. Reporting requirements vary.

10.3.1 Definition of Adverse Event

Adverse Event Definition
An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of the study intervention, whether or not the occurrence is considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study intervention. An untoward finding generally may necessitate therapeutic intervention, require an invasive diagnostic procedure, or require discontinuation or a change in dose of study drug or a concomitant medication. (Repeated or additional noninvasive testing [eg, laboratory or electrocardiogram (ECG) retests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.)
Note: AEs associated with medical devices are subject to additional specialized definitions and requirements.

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Events Meeting the AE Definition
• New condition detected or diagnosed after the use of the study intervention(s), even though it may have been present before the start of the study. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency or intensity of the condition. • Event that is of greater intensity, frequency, or duration than expected for the individual subject or an event with a reasonable possibility that it was related to the study intervention (See Section 8.3.10.7 for guidance). • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, physical examinations, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease), including those that worsen from baseline (defined as the result/assessment prior to first dose of study drug).

Events NOT Meeting the AE Definition

- Situations in which an untoward medical occurrence did not occur (eg, preplanned or elective surgery [a]).
- Presence or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition (See Section 8.3.10.7).
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen[b].
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Cases of overdose with any medication without manifested side effects [c].

[a] Preplanned and elective surgeries are defined as those that were scheduled prior to signing of the ICF. See exceptions in Section 10.3.3.1. While these procedures are not considered AEs, they must be documented in the subject's source documents as described in Section 8.1.3.

[b] Preexisting conditions (present at the time of signing of informed (e)Consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Likewise, baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless they are related to study procedures.

[c] Overdoses must be documented in the subject's source documents.

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AE onset and resolution dates are defined as follows:

- Start date: the date when the first signs/symptoms were noted by the subject and/or investigator.
- End date: the date when the subject recovered, the event resolved but with sequelae, or the subject died.

10.3.2 Definition of Serious Adverse Event

SAEs are events that meet BOTH the AE criteria described in Section 10.3.1 AND the criteria for seriousness below.

SAE Definition
a. Results in death.
b. Is life-threatening. The term *life-threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect.
f. Other situations: • Is an important medical event. • May require intervention to prevent one of the outcomes listed above. • May expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.

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SAE Definition
• Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.3 Additional Considerations in Identifying and Defining Adverse Events

10.3.3.1 Defining Discrete Adverse Events

Each reported AE should represent a single diagnosis, if the diagnosis is known. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs UNLESS the diagnosis is unknown. Specific examples are as follows:

Laboratory values and ECG findings:

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis should be reported as the AE.

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Worsening of a condition:

If the subject experiences a worsening or complication of a medical condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…"). This includes:

- Preexisting conditions present at the time of signing of informed (e)Consent.
- Preexisting episodic concurrent medical conditions (eg, asthma, epilepsy): An episode should only be recorded as an AE if the condition becomes more frequent, serious, or severe in nature.
- A degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis): Worsening of the condition should only be recorded as an AE if it occurs to a greater extent than expected.
- Worsening or complication of an AE after any change in study drug: The worsening or complication should be recorded as a new AE.

Complications associated with preplanned procedures:

- Changes in plan and surgical complications associated with preplanned or elective surgeries, therapies, or procedures should be recorded as AEs.
- If a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the preexisting condition, the worsening of the condition should be recorded as an AE.
- Complications resulting from an elective surgery should be recorded as AEs.

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be recorded once with the maximum intensity recorded.

10.3.3.2 Adverse Events of Special Interest

An AE of special interest (AESI) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. If the AESI is serious, Takeda PV Operations team will send the appropriate TQ to the reporter and the list of PTs or a SMQ associated with certain Takeda compound/program.

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The following AESIs apply to this compound/program:

- Allergy.
- Catheter leakage (at the infusion site).
- Thromboembolic events.

If an AESI occurs during the study and is considered clinically significant, it must be recorded as an AESI in the AE eCRF form. In the event the AESI is serious, the eCRF SAE form must be completed within 24 hours which will be reported to Takeda GPSE.

10.3.4 Recording and Follow-up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information. Each event must be categorized in terms of the attributes below, over the entire course of the event, including the start and stop dates. It is not acceptable for the investigator to send photocopies of the subject's source documents to the sponsor in lieu of completion of the AE/SAE required form. There may be instances when copies of source documents for certain cases are requested by the sponsor. In this case, all subject identifiers, with the exception of the SIC, will be redacted on the copies of the source documents before submission to the sponsor. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

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10.3.4.1 Frequency

Assessment of Frequency
The investigator must assess and record the frequency of the event. Episodic AEs (eg, vomiting) or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.3.4.2 Intensity

Assessment of Intensity
The investigator will assess the intensity for each AE and SAE (including any laboratory abnormality) reported during the study and assign it to 1 of the following categories: All AEs and clinically significant laboratory abnormalities excluding SARs will be graded according to NCI CTCAE, Version 5.0, dated November 27, 2017 (U.S. Department of Health and Human Services, 2017). For any term that is not specifically listed on the CTCAE scale, intensity will be assigned a Grade of 1 through 5 using the following CTCAE guidelines:

Assessment of Intensity

Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences.

Grade 5: Death related to AE.

Assessment of Intensity of Infusion Site-related Adverse Events

Infusion site-related AEs, except catheter leakage, must be graded under the CTCAE term of General disorders and administration site conditions, Other, specify in order to capture details of the infusion site-related AEs. The following CTCAE terms, but not limited, can be considered as infusion site-related AEs: infusion site swelling, infusion site bruising, infusion site discomfort, infusion site erythema, infusion site pruritus, infusion site hematoma, infusion site hemorrhage, infusion site discoloration, infusion site induration, infusion site irritation, infusion site mass, infusion site pain etc.

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Catheter leakage at an infusion site will be evaluated by the investigator/designee based on the following scoring system:

Score 1: Minimal leakage (ie, transient/barely observable leakage). Score 1 will be considered equivalent to Grade 1 of CTCAE v5.0 evaluation scale.

Score 2: Readily observable leakage (ie, continuous/inability to complete infusion at that site). Score 2 will be considered equivalent to Grade 2 of CTCAE v5.0 evaluation scale. No higher grading above Grade 2 will be applied to catheter leakage.

Please note: Infusion-related systemic AEs (eg, infusion-related headache or chills or fever or malaise or nausea etc.) must be graded under the specific CTCAE term in the dictionary. Infusion-related systemic AEs excluding SARs that can not be found in dictionary must be graded under the term of Infusion-related reaction.

Assessment of Systemic Allergic Reactions

See Appendix 2.

Assessment of Intensity
Please note: Intensity and seriousness are separate concepts. The terms "severe" and "serious" are not synonymous. Because serious events usually pose a threat to a subject's life or ability to function, seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.3.4.3 Causality/Relatedness

Assessment of Causality	
The investigator must assess the relationship to both IPs and each occurrence of each AE/SAE based on the criteria below:	
Related:	An AE that follows a reasonable temporal sequence from administration of the investigational products (including the course after withdrawal of the intervention), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications, and concurrent treatments, may also be responsible. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
Not Related:	An AE that does *not* follow a reasonable temporal sequence from administration of the investigational products and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.
The investigator will also consult the IB and/or product information, for marketed products, in their assessment. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.	

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10.3.4.4 Action Taken

Action Taken Concerning Intervention(s)
The investigator must make note of the action taken concerning the study drug: • Dose not changed. • Dose increased. • Dose reduced. • Drug infusion interrupted. • Drug withdrawn. • Infusion rate reduced. • Not applicable: a study drug was stopped for a reason other than the particular AE (eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE). For any AE that was ongoing at the time of a subject's death, the study intervention action should reflect the most recent action that had been taken at the time of death (eg, drug interrupted, reduced, withdrawn). If the subject had never received the study intervention, the action taken should be recorded as "dose not changed" or "not applicable." The study intervention action of "withdrawn" should not be selected solely as a result of the subject's death.

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10.3.4.5 Outcome

Outcome
The investigator must make note of the outcome of any AEs that occur during the course of the study: Recovered/resolved: The subject returned to first assessment status with respect to the AE. Recovered/resolved with sequelae: The subject recovered from an acute AE but was left with permanent/significant impairment. Recovering/resolving: The intensity has decreased by 1 or more stages; the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value has improved, but has not returned to the normal range or to baseline; the subject died from a cause *other than* this particular AE. Not recovered/not resolved: There is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period is now worse than when it started; is an irreversible congenital anomaly; the subject died from another cause. Fatal: The AE is considered to be the cause of death or contributed to the subject's death. Unknown: The course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

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10.3.4.6 Follow-up

Follow-up of AEs and SAEs
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. New or updated information will be recorded in the originally submitted documents. The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4.7 Reference Safety Information/Risk Analysis Report

The reference safety information (RSI) for TAK-881 in this study is the IB, which the sponsor has provided under separate cover to all investigators.

The RSI for HYQVIA is the local package insert and SmPC, which the sponsor has provided under separate cover to all investigators.

10.3.4.8 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the RSI. “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB for TAK-881 and the local package insert/SmPC for HYQVIA as the RSI. This determination will include considerations such as the number of AEs previously observed, but will not be based on what might be anticipated based on the pharmacological properties of a product.

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10.3.4.9 Treatment-emergent Adverse Events

As described in Section 1.3, all AEs will be collected from the time when the ICF is signed. For reporting purposes in the study, a TEAE is defined as any event emerging or manifesting at or after the initiation of treatment with a study intervention or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the study intervention or medicinal product.

10.3.5 Expedited Reporting of Serious Adverse Events

This section describes the expedited reporting required for certain types of events, in addition to eCRF completion, sites must report SAEs immediately, and in no case in more than 24 hours.

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data form and report to Takeda Pharmacovigilance within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form to Takeda Pharmacovigilance Contacts for SAE reporting can be found in the Study Reference Manual.

10.3.5.1 Serious Adverse Events that do not Require Immediate Reporting

Not applicable.

10.3.5.2 Reporting of Abnormal Liver-Associated Test Results

For any subject with ALT ≥3× ULN ***and*** total bilirubin >2× ULN for which an alternative etiology has not been found, report the event as an SAE, contact the medical monitor and Takeda trial clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Section 10.5.

10.3.5.3 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor will be responsible for identifying and reporting all SUSARs and any other applicable SAEs to regulatory authorities including the specific regulatory authority(ies), investigators, and IRB/IEC in accordance with national regulations in the countries where the study is conducted.

Timelines and format of reporting SUSARs to EudraVigilance are as follows:

- SUSARs will be submitted to Eudravigilance Clinical Trial Module in E2B
- Initial fatal and/or life-threatening SUSARs will be reported in 7 days and all other SUSARs will be reported in 15 days.

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10.4 Contraceptive and Barrier Guidance

10.4.1 Definitions

For the purposes of this study, reproductive status is defined as follows:

- **Nonpregnant:** Negative urine and/or serum beta-human chorionic gonadotropin pregnancy test result.
- Person who **is <u>not</u> of childbearing potential**:
  - Premenarchal and 1 of the following:
    - Tanner stage 1.
    - Less than 9 years of age.
  - Surgically sterile for at least 6 weeks at screening (defined as having undergone one of the following procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy).
  - Postmenopausal at screening (defined as no menses for 12 months without an alternative medical cause). A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Person who ***is*** **of childbearing potential**: following menarche and until becoming postmenopausal unless permanently sterile by the definition above.
- Male who **is <u>not</u> fertile**: Vasectomized male with absence of sperm has confirmed OR prepuberty OR post puberty but permanently sterile by bilateral orchidectomy.
- Male who ***is*** **fertile**: post puberty, unless permanently sterile by the definition above.

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10.4.2 Contraception Guidance

In this study, the use of highly effective forms of contraception is generally required unless otherwise noted. In addition, contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

The failure rates of contraceptives that are used consistently and correctly may differ in typical use. Therefore, when study participation requires any of these methods of contraception to be used, subjects must commit to using them:

- Consistently throughout the required period.
- Correctly, as described below and in any labeling associated with the method.

Contraception requirements depend in part on the reproductive status of the subject and the subject's partner.

Female subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years).
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks poststerilization, or
- Of childbearing potential with a negative urine and/or serum β-hCG pregnancy test at screening and prior to dosing. Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use highly effective methods of contraception listed below:
  - i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral.
    - Intravaginal.
    - Transdermal.
  - ii. Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral.
    - Injectable.
    - Implantable*.
  - iii. Intrauterine device* plus condom
    - Intrauterine hormone-releasing system*.
  - iv. Bilateral tubal occlusion*.
  - v. Vasectomized partner(s)*.
  - vi. Sexual abstinence during the entire study period.
  - vii. Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the first dose of IP, plus condoms. NOTE: if subject becomes sexually active during the study, they should use one of the other highly effective methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

* Contraception methods that are considered to have low user dependency.

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Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condoms and male condoms should not be used together.

10.4.3 Pregnancy

If any subject is found to be pregnant during the study, the subject must be withdrawn and any sponsor-supplied intervention(s) must be immediately discontinued.

If the pregnant subject agrees, the investigator should notify their primary care physician that the subject was participating in a clinical study when they became pregnant and provide details about the intervention the subject received.

If the pregnancy occurs from the time informed consent is signed until 30 days after the last dose of active study drug in TAK-881-3001 (if the subject is not participating in the long-term follow-up Study TAK-881-3002) or until the first infusion in Study TAK-881-3002 (if applicable), the pregnancy should be reported immediately, using the Takeda Pregnancy Report Form to the contact listed in the Study Reference Manual.

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Pregnancies for which regulatory reporting is not required include:

- Pregnancies that occurred during the pretreatment phase

All pregnancies in subjects on study intervention(s) will be followed up to final outcome, using the pregnancy form.

10.5 Abnormal Liver-Associated Test Result Monitoring and Follow-Up Assessments

Investigators must be vigilant for abnormal liver-associated test results in subjects during the clinical trial. Transient fluctuations in serum aminotransferases occur commonly in clinical trial subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver-associated test results in clinical trial subjects who had no known liver disease and had either normal or near normal baseline liver test results (ie, alanine aminotransferase [ALT] <2× ULN, total bilirubin [Tbili] <1.5× ULN, and ALP <1.5× ULN) at the time of enrollment.

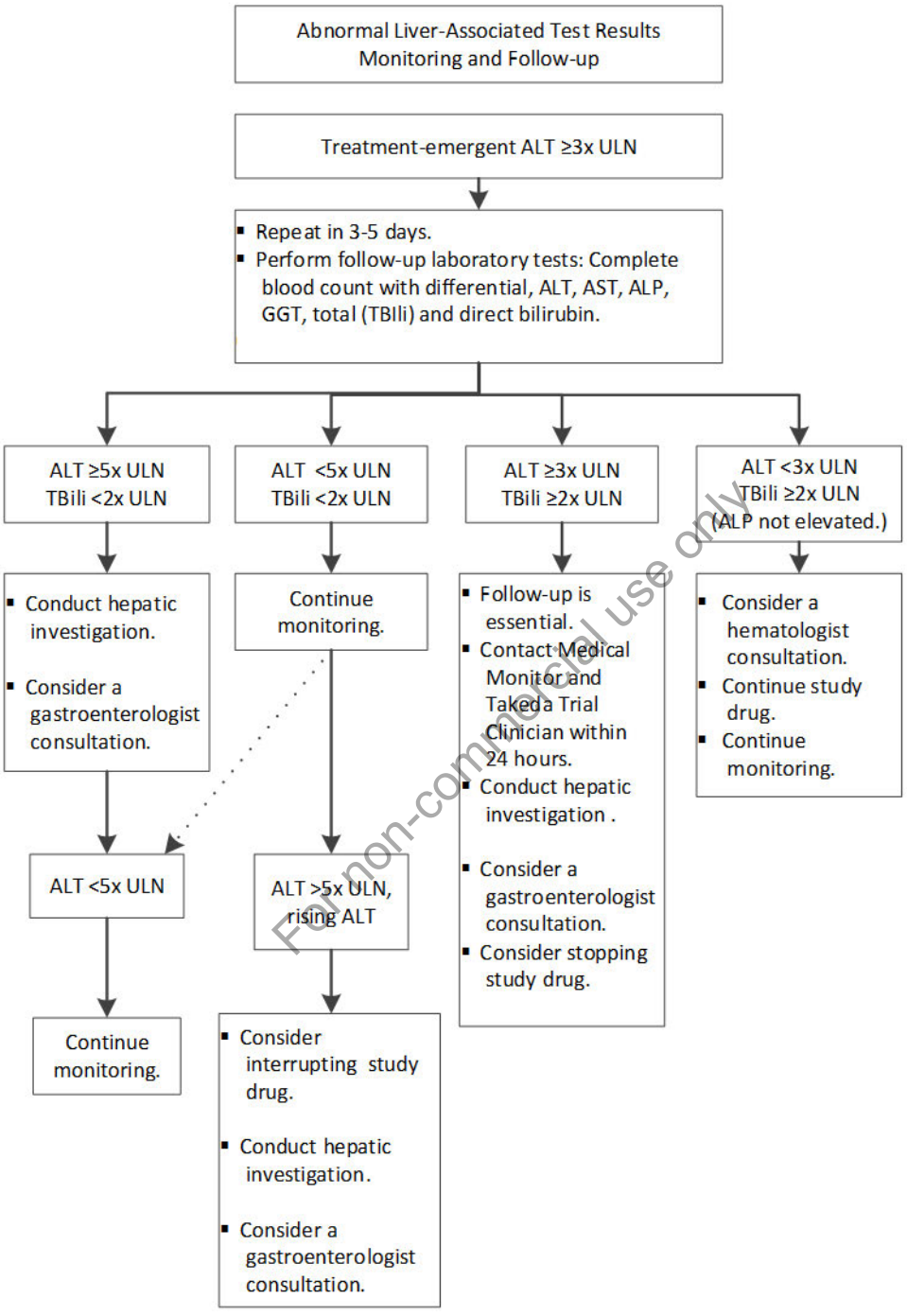
In evaluating trial subjects with abnormal liver-associated test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver-associated test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 8. Suggested hepatic investigations are listed in Table 17. Criteria for considering discontinuation of study drug are shown in Figure 9.

Subjects with Combined Elevations in Aminotransferase and Bilirubin

If a subject has elevated ALT ≥3× ULN with **concurrent** elevated Tbili >2× ULN, the investigator must contact the medical monitor and Takeda trial clinician within 24 hours. Hepatic investigations as suggested in Table 17 should be initiated. Any event of elevated ALT ≥3× ULN with concurrent elevated Tbili >2× ULN for which an alternative etiology has not been identified must be reported as an SAE.

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Figure 8. Abnormal Liver-associated Test Results: Monitoring and Follow-up



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ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl; TBili=total bilirubin; ULN=upper limit of normal.

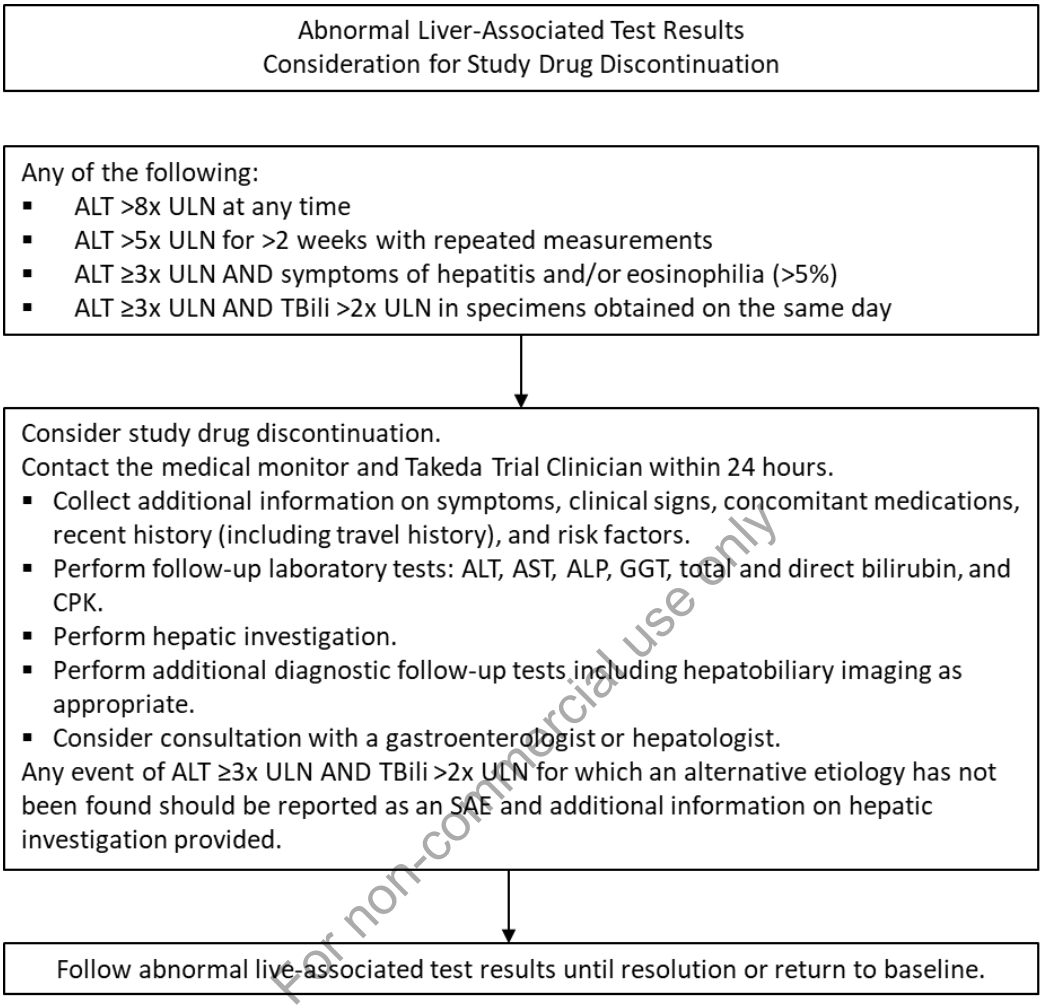
Table 17. Hepatic Investigation

Medical history	• Concomitant medications (including OTC medications, such as acetaminophen, and herbal supplements). • Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis). • Alcohol intake. • Hepatobiliary disorder. • Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia). • Travel history.
Physical examination (symptoms, signs, and laboratory results)	• General malaise, fatigue, nausea, or vomiting. • Right upper quadrant pain or tenderness, fever, jaundice, rash. • Eosinophilia >5%.
Hepatic/hepatobiliary imaging	Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging).
Viral hepatitis serology	• Hepatitis A antibody (total and IgM). • HBsAg, hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (IgM anti-HBc), hepatitis C antibodies (anti-HCV). • Hepatitis E (IgG and IgM). • Consider polymerase chain reaction for hepatitis B, C, and E. • Consider Epstein-Barr virus serology (VCA, EBNA, EA). • Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	• ANA. • ASMA. • anti-LKM.

ANA=antinuclear antibody; ASMA=antismooth muscle antibody; EA=early antigen; EBNA=Epstein-Barr nuclear antigen; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; IgG=immunoglobin G; IgM=immunoglobulin M; LKM=liver-kidney microsomal antibody; OTC: over-the-counter; VCA=viral capsid antigen.

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Figure 9. Abnormal Liver-associated Test Results: Considerations for Study Drug Discontinuation



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ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma glutamyl; SAE=serious adverse event; TBili=total bilirubin; ULN=upper limit of normal.

10.6 Country-Specific Requirements

Not applicable.

10.7 Abbreviations and Definitions

10.7.1 Abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	adverse reaction
ASBI	acute serious bacterial infection
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}\tau,ss}$	area under the curve during the dosing interval at steady-state
β-hCG	beta-human chorionic gonadotropin
BSA	body surface area
BUN	blood urea nitrogen
BW	body weight
CCGs	CRF completion guidelines
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
cIGSC	conventional subcutaneous IgG
CL/F	apparent clearance
C_{max}	maximum concentration
COA	clinical outcome assessment
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
CV	coefficient of variation
DMC	data monitoring committee
DVU	dual-vial unit
EC	ethics committee

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Abbreviation	Definition
ECG	electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ET	early termination
EU	European Union
EU CT	European Union Clinical Trial
EU CTR	European Union Clinical Trial Regulation
Eudra	European Union Drug Regulatory Authorities
EudraCT	European Union clinical trials database
FDA	Food and Drug Administration (US)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GPSE	Global Patient Safety Evaluation
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCP	healthcare professional
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRQoL	health-related quality of life
HRU	healthcare resource utilization
IB	investigator's brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IGI	immune globulin infusion
IGIV	intravenous immune globulin

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Abbreviation	Definition
IgM	immunoglobulin M
IGSC	immune globulin subcutaneous
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUIS	International Union of Immunological Societies
IV	intravenous(ly)
LDH	lactate dehydrogenase
MAR	missing at random
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NCA	non-compartmental analysis
NCI	National Cancer Institute
NS	normal saline
OTC	over-the-counter
PCR	polymerase chain reaction
PIDD	Primary Immunodeficiency Disease
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKFAS	pharmacokinetic full-analysis set
PKPPAS	pharmacokinetic per-protocol analysis set
PMDA	Pharmaceutical and Medical Devices Agency
PT	preferred term
PV	Pharmacovigilance
RBC	red blood cell
REML	restricted maximum likelihood
rHuPH20	recombinant human hyaluronidase
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	systemic allergic reaction
SAS	safety analysis set
SC	subcutaneous(ly)

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Abbreviation	Definition
SIC	subject identification code
SMQ	standard MedDRA query
SoA	schedule of activities
SOC	system organ class
SmPC	Summary of Product Characteristics
SSR	special situation reporting
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
Tbili	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TSQM-9	Treatment Satisfaction Questionnaire for Medication - 9 Items
TQ	Targeted Questionnaire
ULN	upper limit of the normal range
US	United States
V_z/F	apparent volume of distribution
WHO	World Health Organization

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10.8 Protocol Amendment History

Table 18. Protocol History

Date	Document	Global/Country/Site Specific
29 July 2024	Amendment 5	Global
05 March 2024	Amendment 4	Global
28 June 2023	Amendment 3	Global
25 April 2023	Amendment 2	Global
30 January 2023	Amendment 1	Global
29 September 2022	Original Protocol	Global

Summary of Changes Since the Last Version of the Approved Protocol	
Protocol Amendment 4	
Amendment Date: 05 March 2024	**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment The protocol was amended to incorporate feedback from European regulatory authorities and enable recruitment of a broader set of subjects with PIDD	

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Description of Each Change and Rationale		Sections Affected by Change
#	**Description Of Changes/Rationale For Changes**	**Section**
1	A binding sponsor statement that the clinical study will be conducted in compliance with Regulation [EU] No 536/2014 was added. A statement was added to clarify the location of electronic signatures in the document.	Approvals

Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
2	Subjects receiving conventional subcutaneous intravenous immunoglobin G (cIGSC) are now allowed to enroll in the study. These subjects will enter the ramp-up epoch after screening. The first study treatment will be administered 1 or 2 weeks after the last prestudy immunoglobulin G (IgG) dose depending on the prestudy IgG treatment interval. No variation in cIGSC doses is allowed during the screening period for subjects receiving weekly prestudy cIGSC. For subjects receiving weekly cIGSC, the serum trough of total IgG sample required for screening must be taken prior to the administration of the second to last prestudy IgG treatment dose (ie, 2 weeks before the first planned investigational product [IP] administration). For subjects previously treated with cIGSC the treatment interval during the study will be decided at the screening visit at the discretion of the investigator, which can be either a 3- or 4-week interval. Due to the inclusion of subjects receiving cIGSC, the possible prestudy IgG treatment intervals include 1, 2, 3, or 4 weeks. Multiple locations in the text that had previously stated only 3- or 4-week treatment intervals were updated. The "Treatment" was updated in the Estimand section.	Throughout the protocol, where applicable
3	The study schema were updated to reflect the changes in the timing of the screening visit and to clarify which subjects are required to enter the ramp-up epoch. An updated figure was created to summarize the treatment schedule for subjects who enter the ramp-up epoch. A new figure was added to summarize the dose and treatment interval options for subjects based on their prestudy treatment.	Synopsis, Section 1.2, Section 4.1.1, Section 6.1

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
4	According to ethical considerations for clinical trials on medicinal products conducted with minors (EU, 2017) to minimize blood drawing in subjects aged 2 to <16 years the following changes were made: - It was clarified that a reduced clinical chemistry panel (excluding chloride, bicarbonate, total protein, and albumin) will be performed for subjects aged 2 to <16 years. Additionally, no isoenzyme analysis will be performed if lactate dehydrogenase (LDH) is ≥ 2× upper limit of normal (ULN) in these subjects. - It was specified that for subjects aged 2 to <16 years that only if the direct Coombs test is positive, a blood sample for antibody elution will be taken. This blood sample will be collected in an unscheduled visit within 72 hours after the positive result. - It was clarified that only serum and not plasma retention samples will be taken for subjects 2 to < 16 years. - It was specified that specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and hepatitis B) will only be determined for subjects ≥16 years. - For subjects aged 2 to <16 years, blood sampling for the reduced clinical chemistry panel, IgG subclasses trough level, and anti-recombinant human hyaluronidase (rHuPH20) antibodies will not be performed at the End-of-Study/Early Termination (EOS/ET) Visit but instead at Week 21 (4-week treatment interval) or Week 22 (3-week treatment interval). - For subjects aged 2 to <16 years, there will be limited collection of back-up samples.	Synopsis, Section 1.3, Section 3, Section 3.2.2.3, Section 8.3.3.2, Section 8.3.3.4, Section 8.3.3.6, Section 8.3.3.7, Section 8.4.2, Section 9.3.2.1, Section 10.2
5	The study visit window was increased to ±3 days for visits that are not included in the ramp-up epoch and are not associated with serial/sparse PK sampling. The Pharmacokinetic Per-Protocol Analysis Set was also updated accordingly. It was clarified that deviations of >1 days but <3 days for IP ramp-up visits and IP visits coinciding with serial/sparse PK sampling will not lead to study discontinuations.	Synopsis, Section 1.3, Section 4.1, Section 9.2.3
6	The timing of randomization prior to the first planned study infusion was increased from 3 to 4 days to allow more time to organize the preparation of the first IP dose to be administered.	Synopsis, Section 1.3, Section 4.1.2.1, Section 4.1.2.2
7	It was clarified that serum trough levels of total IgG will be assessed prior to each infusion and it was specified that the blood drawing for all IgG trough level determinations should take place before the IgG infusion is administered on the same day.	Synopsis, Section 1.3, Section 4.1.2.2, Section 8.4.2
8	It was added that sites must consent subjects for the long-term follow-up study (Study TAK-881-3002) at the time of consenting to Study TAK-881-3001 participation, if permitted by Institutional Review Board/Institutional Ethics Committee (IRB/IEC).	Synopsis, Section 1.3, Section 5, Section 6.6

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
9	The acceptable variations in treatment interval at and during screening was changed.	Synopsis, Section 1.3, Section 5.1, Section 8.4.1
10	It was clarified that TAK-881/HYQVIA doses must not be administered over multiple days and that the maximum daily absolute dose of TAK-881/HYQVIA is 120 g.	Synopsis, Section 1.3, Section 6.1, Section 6.2.6.2
11	It was clarified that when dose modification due to body weight (BW) changes are required, the Interactive Response Technology system will make these calculations.	Synopsis, Section 1.3, Section 6.5
12	The reason for the healthcare resource utilization (HRU) endpoint "days not able to go to school, work, daycare, or to perform normal daily activities..." was updated for clarity. The description of the analysis of HRU endpoints was updated accordingly.	Synopsis, Section 3, Section 3.2.2.2, Section 8.3.6.4, Section 9.5.3
13	The anticipated number of subjects to be screened was increased. Due to updates to the exclusion criteria, a higher screen failure rate is expected.	Synopsis, Section 4.1
14	For subjects in AB/BA crossover treatment epochs it was clarified that 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.	Synopsis, Section 4.1.2.1
15	Randomization for the crossover epochs will be stratified by IgG treatment interval during the study, as opposed to the prestudy treatment interval that changed following the modification to inclusion criterion (IC)#3.	Synopsis, Section 4.1.2.1, Section 6.3.1
16	The following changes to IC were made: IC#3: It was added that subjects should be on the same product of IGIV or cIGSC during the 12-week period prior to screening. Additionally, the definition of what constitutes a stable dose was added and the maximum allowed dose for this period was also specified. IC#4: It was added that a serum trough level of IgG >5 g/L within the 12 weeks prior to screening is required. IC#6: It was added that complying with the pharmacokinetic (PK) blood sampling schedule is required.	Synopsis, Section 5.1

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
17	The following exclusion criteria (EC) were added or modified: EC#1 was modified to clarify that cured subjects with a history of hepatitis C infection who have a negative polymerase chain reaction (PCR) test at screening are eligible. EC#6: Subjects with a known systemic hypersensitivity to any of the excipients of TAK-881/HYQVIA in accordance with the investigator's brochure (IB)/package insert/Summary of Product Characteristics (SmPC). EC#9: was modified to replace "allergy to hyaluronidase" to "systemic hypersensitivity to hyaluronidase or rHuPH20". EC#12: Treatment with immunosuppressants including chemotherapeutic agents, immunomodulators, and long-term systemic corticosteroid (defined as a daily dose of >1 mg of prednisone equivalent/kg/day for >30 days) within 12 weeks prior to screening. Short or intermittent courses (≤10 days) of corticosteroids are allowed. EC#13: Live-attenuated viral vaccination within 12 weeks prior to screening. EC#16: Subject has a medical condition, laboratory finding, or physical examination finding that precludes participation, or with clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may interfere with successful completion of the study or place the subject at undue medical risk.	Synopsis, Section 5.2
18	The infusion rates for HYQVIA were clarified to provide options for subjects who did or did not previously receive HYQVIA. The maximum number of infusion sites and recommended infusion locations were updated. Recommendations for the selection of the number of infusion sites for subjects based on their prestudy IgG treatment were provided.	Synopsis, Section 6.2.6.2
19	It was clarified that the weekly IgG dose after the first full dose of the study treatment can be changed only if clinically indicated. Previously, it was stated the dose can be "increased"; however, the dose may also be decreased for a clinical reason. Additionally, it was clarified that if the IP 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.	Synopsis, Section 6.5
20	It was clarified that no administrative analysis will be performed 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 statement stating that the administrative interim analysis would be submitted to the regulatory authorities was removed.	Synopsis, Section 9.6

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
21	The timing of collection of samples for antigen-specific IgG antibodies trough levels and anti-rHuPH20 antibodies (binding/ neutralizing, if applicable) was changed for subjects aged ≥16 years on the 4-week dosing interval due to an administrative error.	Section 1.3
22	It was clarified that vital signs will be measured at least 60 minutes (as opposed to 30 minutes) after the completion of each infusion.	Section 1.3, Section 8.3.2
23	It was specified that the presence of menstruation must be recorded for female subjects, if applicable, at the time of the urine sample collection as blood contamination may confound the results.	Section 1.3, Section 8.3.3.3
24	Text was added to clarify that informed consent must be obtained for adolescents who reach majority during the course of the crossover treatment epochs only when required by the local IEC/IRB.	Section 1.3, Section 10.1.3.1
25	Relevant data on HYQVIA was updated in line with the most recent IB version. Information regarding the incidence of treatment-emergent rHuPH20-reactive binding antibodies and non-neutralizing antibodies in PIDD clinical trials was updated.	Section 2.2.1, Section 2.4.2
26	Information on the phase 1 study with TAK-881 was updated. Additional justification for administering TAK-881 without in-line warming was added.	Section 2.3
27	The justification for the timing of area under the curve (AUC) assessment in the crossover epochs was modified. Text that was already included in the protocol regarding the Data Monitoring Committee (DMC) decision to include subjects aged 2 to <16 years was added to justify the inclusion of minors in the study. Justification for frequent blood sampling was added.	Section 4.3
28	Further details on the process to confirm a subject's eligibility were added.	Section 5.4
29	Details describing the process for generating the subject identification codes and the pseudonymization was added. Text about collection and use of subjects' initials were removed as this is not applicable.	Section 5.4, Section 10.1.4, Section 10.1.10
30	Possible reasons for rescreening a subject were updated to reflect changes in inclusion/exclusion criteria. Additionally, the possible reasons for screening were expanded to include subjects that failed screening for issues related to laboratory sample collection or due to unforeseen circumstances. It was additionally specified that a new electronic case report form is required for re-screened subjects, and that screening laboratory and other assessments will be repeated at rescreening.	Section 5.4.2
31	The dose strengths of TAK-881 and HYQVIA were corrected.	Section 6.1

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
32	The reference information for HYQVIA was clarified from the IB to the package insert and SmPC.	Section 6.1, Section 10.3.4.7, Section 10.3.4.8
33	Detailed instructions for the documentation of drug accountability, including destruction or return of study interventions, were removed and replaced with a high-level description. In-depth details are provided in the Pharmacy Manual.	Section 6.2.1, Section 6.2.3, Section 6.2.6.1, Section 6.2.7, Section 10.1.11.2, Section 10.1.11.2.1
34	More detailed instructions for flushing the infusion line were added.	Section 6.2.5
35	Infusions will not be permitted at alternate locations (ie, not the study site). All references to the possibility of performing infusions at an alternate location and related considerations (dispensing, study assessments etc) were removed.	Section 6.2.6, Section 6.2.6.1, Section 6.2.6.2, Section 8.3.2.1
36	It was added that if a catheter leakage occurs at the infusion site, the investigator should consult the Site Infusion Manual for guidance. Background details on the starting infusion rates were added for both TAK-881 and HYQVIA.	Section 6.2.6.2
37	It was clarified that the master randomization list will be stored in a secure system accessible only to authorized staff.	Section 6.3.2
38	The list of prohibited medications and therapies and the circumstances under which the drug is prohibited/allowed were updated: - Removal of immunosuppressive drugs after solid organ or bone marrow transplantation - Addition of live-attenuated viral vaccination, immunosuppressants including chemotherapeutic agents, immunomodulators, and long-term systemic corticosteroids - Update to use of antipyretics, and antihistamines Justification for prohibited medications was added.	Section 6.8.2, Section 6.8.2.1
39	Further details on the collection of race and ethnicity data and the justification for their use was added.	Section 8.1.1
40	More detail was provided regarding the collection of a subject's medical history.	Section 8.1.2
41	The hemolytic panel was updated to change "reticulocyte count" to "the number and percentage of reticulocytes". The criteria for repeating the hemolytic panel were changed.	Section 8.3.3.4, Section 10.2
42	It was clarified that subjects can still participate in the study even if they do not agree with the use of their samples for future research. Details about Takeda Future Research, including the storage and destruction of samples, were added.	Section 8.3.3.6, Section 10.2.2
43	Text was amended to clarify that Targeted Questionnaires will only be sent for serious AESIs.	Section 8.3.10.8, Section 10.3.3.2

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
44	For the analysis of tolerability events, it was specified that if more than 1 intervention is made to a particular infusion, the final intervention will be considered for the endpoint.	Section 9.4
45	In relation to the ICF, the following statements were changed: - "Explanation of required actions (such as discontinuation of treatment or from the study) if a subject or their partner becomes pregnant during study" - removal of "or their partner", as information on pregnant partners does not need to be obtained. - "Statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so" - statement deleted as this is not applicable for the current study. - "If the subject is not capable of rendering adequate written informed consent, then the subject's legally authorized representative may provide such consent for the subject in accordance with applicable laws and regulations" -statement deleted as this is not applicable for the current study.	Section 10.1.3.2, Section 10.1.3.5
46	Additional details on the sponsor and contract research organization (CRO) processes to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed.	Section 10.1.4
47	A reference to Article 10(e) of the Directive 2001/20/EC was removed as it is no longer applicable.	Section 10.1.9.2
48	The methods for calculating eGFR were added.	Section 10.2
49	The list of options to note the action taken with study drug after an (S)AE was updated to remove "dose delayed", "all drugs withdrawn", and "unknown" and to add "infusion rate reduced".	Section 10.3.4.4
50	The requirements for SUSAR reporting were updated.	Section 10.3.5.3
51	Text was rephrased to clarify that the investigator must assess the relationship to both IPs and each occurrence of each AE/SAE	Section 10.3.4.3
52	The time period for reporting pregnancies was changed.	Section 10.4.3
53	The term "legally authorized representative" or "caregiver" was changed to "parent(s)/legal guardian(s)".	Throughout the document
54	The term "acceptable contraception" was replaced by "highly effective contraception" as highly effective contraception methods are required for subject participation.	Throughout the document
55	Minor grammatical, editorial, and/or administrative changes have been made to improve the readability and/or clarity of the protocol and reduce redundancy.	Throughout the document

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Summary of Changes Protocol Amendment 3	
Protocol Amendment 3	
Amendment Date: 28 June 2023	**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment Updates to incorporate feedback from the Food and Drug Administration (FDA) (received 11 May 2023 and 26 June 2023)	

Description of Each Change and Rationale		Sections Affected by Change
#	**Description Of Changes/Rationale For Changes**	**Section**
1	The planned study periods were updated.	Synopsis
2	Text was added to describe that subjects rolling over to the long-term follow-up Study TAK-881-3002 will keep the paper diary for Study TAK-881-3001 until the Study Visit 1/Week 1 of Study TAK-881-3002 and the site will continue reporting concomitant medications, AEs, occurrence of fever and HRU outcomes up to the TAK-881-3002 Study Visit 1/Week 1 in TAK-881-3001 eCRFs.	Synopsis, Section 1.3, Section< 8.3.8, Section 8.3.10.1
3	The secondary objective to assess infections was rephrased. Additional endpoints were added for this objective.	Synopsis, Section 3, Section 3.1.2, Section 3.2.2.1, Section 9.3.2.2
4	The exploratory objective to assess healthcare resource utilization (HRU) was changed to a secondary objective. Additional endpoints were added for this objective.	Synopsis, Section 3, Section 3.1.2, Section 3.2.2.2, Section 8.3.8, Section 9.5.3
5	The unit of measurement for endpoints the duration of infusions and monthly infusion time was changed from hours to minutes.	Synopsis, Section 3, Section 3.2.2.5, Section 9.5.1
6	It was clarified that 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). It was clarified that the DMC evaluation will not stop further enrollment of subjects ≥16 years, unless a criterion for premature termination/suspension of the study is met.	Synopsis, Section 4.1.2.2, Section 9.6, Section 10.1.5.2
7	The maximum subject participation period was changed.	Synopsis, Section 4.5
8	It was clarified that the administrative interim analysis (if performed) will be submitted to regulatory authorities.	Synopsis, Section 9.6
9	Total IgG trough levels will be assessed at the Ramp-up Visit 2 (if ramp-up is applicable).	Section 1.3
10	Pain assessment by a numeric rating scale (NRS) was removed. Infusion-related pain is already being collected as part of adverse events (CTCAE grades). Including both the pain NRS scale and the CTCAE grading scale may have led to inconsistent outcomes and difficulty in interpretation.	Section 1.3, Section 8.3.6, Section 9.5.2
11	The section was updated with the most recent clinical information.	Section 2.2.1
12	Age thresholds were specified for the exploratory objectives.	Section 3, Section 3.1.3
13	Study suspension was added as a possible reason for screen failure.	Section 5.4.1

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
14	It was added that subjects who failed screening because the study stopping rules were met and the treatment of new subjects was paused are allowed to be rescreened.	Section 5.4.2
15	Text relating to the sharing of bulk IP used in this study with other studies within the program was removed as it is no longer applicable.	Section 6.1
16	It was clarified that the study intervention may only be shipped to the subject's home address in exceptional circumstances following discussion and approval of the sponsor.	Section 6.2.6.1
17	Text was modified to state that for subjects who have been on HYQVIA within 12 weeks prior to screening, HYQVIA is permitted to be infused at previously tolerated maximum infusion rates, both the recommended time intervals and number of rate changes of the infusion rate escalation can be adjusted for HYQVIA infusions at the discretion of the investigator and subject.	Section 6.2.6.2
18	Further details on the long-term follow-up study and the consent process for Study TAK-881-3002 were added.	Section 6.6
19	It was clarified that subjects meeting discontinuation of study intervention criterion will not receive subsequent IP treatment. Criteria to stop an infusion as well as to discontinue the study intervention were amended upon FDA request.	Section 7.1
20	Text has been added to state that the severity of systemic allergic reactions will be graded by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System.	Section 7.1, Section 9.4, Section 10.1.12.2, Section 10.3.4.2
21	The collection of vital signs at the end of study (EOS) visit was clarified.	Section 8.3.2
22	The definition of a fever and the calculation of the duration of a fever episode was added.	Section 8.3.8
23	It was clarified that measurements of serum IgG trough levels will be performed at the specialty laboratory.	Section 8.4.2
24	It was clarified that study suspension means the temporary cessation of some or all research activities. Additional criteria for premature termination or suspension of the study were added upon FDA request.	Section 10.1.12.2
25	Infusion site pruritus was added to the list of infusion-site related AEs.	Section 10.3.4.2
26	The World Allergy Organization Systemic Allergic Reaction Grading System and Clinical Criteria for Diagnosing Anaphylaxis were added.	Appendix 2 and Appendix 3
27	Minor grammatical, editorial, and/or administrative changes have been made to improve the readability and/or clarity of the protocol.	Throughout the document

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Summary of Changes Protocol Amendment 2	
Protocol Amendment 2	
Amendment Date: 25 April 2023	**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment Updates to incorporate feedback from the Food and Drug Administration (FDA) (received 03 March 2023)	

Description of Each Change and Rationale		Sections Affected by Change
#	**Description Of Changes/Rationale For Changes**	**Section**
1	The EU CT number was shortened to remove the last 2 digits, in accordance with CTIS recommendations.	Title Page, Synopsis
2	The study will not be conducted in any sites in Japan. All references to Japan-specific requirements were removed.	Title Page, Synopsis, Section 1.3, Section 4.1.1, Section 4.2, Section 5.1, Section 5.2, Section 5.4, Section 5.4.2, Section 8.3.7, Section 8.3.10.4, Section 10.1.1, Section 10.1.5.1, Section 10.1.7.1, Section 10.1.7.2, Section 10.1.7.3, Section 10.1.8.4, Section 10.1.11.2
3	The contact phone number was removed, as complaints should only be submitted via e-mail.	Product Quality Complaints
4	Details were added in parentheses after "randomization" to specify that for the AB/BA Crossover Treatment Epochs subjects will be randomized to a treatment schedule whereas subjects in the single-arm treatment epoch will be randomized to a sparse PK sampling schedule.	Synopsis
5	A statement was added to clarify how the ramp-up doses are calculated.	Synopsis
6	An objective and corresponding endpoints and assessments were added to characterize the PK of TAK-881 between subjects aged ≥16 years and subjects aged 2 to <16 years with PIDD.	Synopsis, Section 1.3, Section 3, Section 3.1.2, Section 4.1.2.2, Section 6.3.1, Section 8.4.1, Section 8.4.2
7	To ensure complete washout of the previous IgG treatment and the achievement of a steady-state with the new treatment, the protocol was revised to conduct PK sampling after the eighth dose for subjects on the 3-week dosing regimen and after the sixth dose for subjects on the 4-week dosing regimen in the AB/BA crossover treatment epoch.	Synopsis, Section 1.3, Section 4.1.2.1, Section 4.1.2.2, Section 4.3, Section 8.4.1
8	Text was changed to reflect that infusions at home are no longer permitted (except in exceptional circumstances).	Synopsis, Section 1.3, Section 6.2.6.2, Section 8.3.7
9	The ramp-up epoch was revised to include two doses, ie, a 1-week dose, followed by a 2-week dose.	Synopsis, Section 1.3, Section 4.1.1. Section 4.1.2.1, Section 4.1.2.2, Section 4.4, Section 6.1

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
10	An objective and corresponding endpoints and assessments were added to assess the rate of all infections and the rate of acute serious bacterial infections (ASBIs).	Synopsis, Section 3, Section 3.1.2, Section 3.2.2, Section 8.2, Section 9.3, Section 9.3.2.2
11	The sample size for the AB/BA crossover treatment epoch was increased.	Synopsis, Section 4.1, Section 4.1.2.1, Section 9.7
12	Language relating to the start of enrollment of subjects in the single-arm treatment epoch (2 to <16 years) was changed.	Synopsis, Section 4.1.2.2, Section 9.6, Section 10.1.5.2
13	The planned enrollment and completion periods and overall duration of the study for subjects were updated.	Synopsis, Section 4.5
14	It was clarified that any subject for whom a dose modification of >10% is required should not undergo serial PK or sparse PK sampling.	Synopsis, Section 6.5
15	It was specified that details of the PK analysis/population PK modeling will be described in a separate pharmacology analysis plan (CPAP).	Section 8.4, Section 9
16	Information in parentheses “ie, non-adjusted for endogenous levels” was removed as it is considered redundant.	Synopsis, Section 8.4.1
17	Further details were added to specify that photographs of the injection site would only be taken for subjects ≥16 years and that a specific informed consent form (ICF) must be signed.	Synopsis, Section 8.9
18	There are age restrictions for the completion of the pain intensity numeric rating scale (NRS) and the EuroQol 5 Dimension 5 Level Questionnaire (EQ-5D-5L). It was clarified that the age of the subject at the time of signing the ICF determines if the subject can complete these assessments.	Section 1.3, Section 8.3.6.1, Section 8.3.6.2
19	An exploratory objective and corresponding endpoints and assessments were added to assess healthcare resource utilization (HRU).	Section 1.3, Section 3, Section 3.1.3, Section 3.2.3, Section 8.4.7, Section 8.3.8, Section 9.5.3
20	Minor edits were made to the text to align with the most recent language in the Investigator’s Brochure.	Section 2.2, Section 2.2.1, Section 2.2.2
21	Language was updated to specify when the subject should sign the ICF in relation to their last prestudy IgG infusion.	Section 5.4
22	The allowed variation in the prestudy treatment interval was increased.	Section 5.4.2
23	The definition of enrollment was updated to reflect that all subjects will now be randomized.	Section 5.6
24	Instructions for administration of TAK-881 were updated.	Section 6.2.5
25	Text was added to describe the infusion rate approach to be implemented for subjects randomized to Sequence 1 of the AB/BA crossover treatment epoch, who had not previously been treated with HYQVIA.	Section 6.2.6

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
26	To ensure subject safety, criteria to determine if an infusion should be slowed were added based on adverse event (AE) severity (as rated by the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0).	Section 6.2.6.2
27	The rate of infusion of the rHuPH20 component was modified.	Section 6.2.6.2
28	The objectives of the long-term follow-up study were modified.	Section 6.6
29	An additional circumstance which requires special situation reporting (SSR) was added. The timelines for SSR reporting were added.	Section 6.7
30	The exceptional circumstances in which otherwise prohibited premedications can be used on the day of investigational product administration were clarified.	Section 6.8.2
31	To ensure subject safety, criteria to stop an infusion as well as to discontinue the study intervention were added.	Section 7.1
32	Language relating to the collection of back-up and retention samples was edited.	Section 8.3.3.6, Section 8.3.3.7
33	An additional time point for evaluation was added.	Section 8.3.7
34	Language was added on how to optimize study visits to best accommodate PK sampling.	Section 8.4.1
35	Language detailing the methods used to calculate the $AUC_{0-\tau,ss}$ was removed.	Section 8.4.1
36	Text was modified to clarify that the adverse event of special interest (AESI)/SAE form to be completed is a form on the eCRF (as opposed to a paper form, which should only be used as a back-up).	Section 8.3.10.8
37	It was clarified that infusion time includes the time required to flush the line.	Section 9.5.1
38	A criterion for premature termination or suspension of the study was modified. More detail was provided to describe the events after study stopping criteria are met.	Section 10.1.12.2
39	FDA guidelines for diagnosing serious bacterial infections were added.	Appendices
40	All figures were changed to reflect the updated study design.	Figures
41	The treatment epochs were renamed.	Throughout the protocol where applicable
42	To reinforce the importance of instructions, a number of instances where “should” was used were changed to “must”.	Throughout the protocol where applicable
43	The nomenclature of $AUC_{0-\tau;ss}$ was changed to $AUC_{0-\tau,ss.}$	Throughout the protocol where applicable
44	Minor grammatical, editorial, and/or administrative changes have been made to improve the readability and/or clarity of the protocol	Throughout the document

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Summary of Changes Protocol Amendment 1	
Amendment Date: 30 January 2023	**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment Updates to improve accuracy and quality of the protocol	

Description of Each Change and Rationale		Sections Affected by Change
#	**Description Of Changes/Rationale For Changes**	**Section**
1	The EU CT number was added	Title Page, Synopsis
2	An additional section entitled “Benefits and Risk” was added to comply with the EU CTR	Synopsis
3	The planned enrollment and completion periods were extended to account for the later onboarding of EU sites and for the delayed enrollment of subjects <16 years based on the DMC decision	Synopsis
4	The duration of the screening epoch was clarified	Synopsis, Tables 1 to 4 and 7 to 10, Section 4.1.1
5	The option to self-administer the infusion was removed as the pump used to administer the infusions is not considered patient-user friendly	Synopsis, Tables 1 to 4, Section 6.2.6.2, Section 6.4
6	Secondary endpoints relating to infusion parameters at full dose were modified	Synopsis, Section 3, Section 3.2.2.3, Section 9.5.1
7	The schematic depicting the treatment schedule for subjects entering a ramp-up epoch was corrected to remove “if applicable”	Synopsis, Figure 6
8	Inclusion criterion #2 was modified to state that age at the time of signing the ICF determines the age cohort assignment. This was changed to provide a more precise date than the previously stated “at screening”	Synopsis, Section 4.1, Section 5.1
9	Inclusion criterion #3 was modified to increase the allowable time window for treatment interval variation and to remove the allowable dose variation of ±20% Table footnotes were updated to include the allowable time window for treatment interval variation.	Synopsis, Tables 1, 3, 7 and 9, Section 5.1
10	Inclusion criterion #4 was modified to specify that only one IgG trough level sample >5 g/L is required. It was determined that one sample was adequate for screening purposes	Synopsis, Section 5.1, Section 5.4, Section 5.4.2
11	The planned number of sites was increased	Synopsis, Section 4.2
12	The timing of the DMC/enrollment of pediatric subjects was clarified	Synopsis, Section 4.1.2.2, Section 9.6, Section 10.1.5.2
13	Exclusion criterion #4 was modified to add “at the discretion of the investigator”	Synopsis, Section 5.2

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
14	Text was changed to specify that dose modifications can only occur after the first full dose of the study treatment The "X" specifying that height, weight and BMI measurements were required during the ramp-up epoch were removed	Synopsis, Tables 1, 3, 7 and 9, Section 6.5
15	Justification was added for the sample size calculations for subjects aged 2 to <16 years	Synopsis, Section 9.7
16	Figures were corrected to remove "Treatment with prestudy IgG* if the schedule falls in the screening period"	Figures 2 to 5
17	An additional time point (ie, 72±8 hours) for photographic assessment of the infusion sites was added It was specified that photographs of infusion sites would only be collected at selected US study sites Time windows were added to the time points for the photographs	Tables 1 and 3, Section 8.9
18	The timing of study visits was clarified to state that visits should be calculated using the previous prestudy IgG infusion date as the reference	Tables 1 to 4 and 8 to 10, Section 4.1
19	The timing of Study 1/Week 1 in relation to the last prestudy IgG dose was clarified	Tables 2, 4, 8 and 10
20	Timing of PK assessments was clarified	Tables 5 and 6, Section 8.4.1
21	Text relating to the EQ-5D-5L was changed to clarify the age range of subjects and to remove the need for proxy-reported versions of the questionnaire	Tables 7 to 10, Section 8.3.6.2
22	"EU" changed to "European"	Section 2.2, Section 2.2.1, Section 8.3.7
23	Details were added to describe study visit window of ±1 day and that a deviation of ≥3 days for visits with IP administration will be considered as a missed dose and the subject will be discontinued from the study	Section 4.1, Section 7.1
24	A justification for the inclusion of subjects who are incapable of providing informed consent was added	Section 4.3, Section 10.1.3.1
25	Additional detail for the dose justification from a Phase 1 study was added	Section 4.4
26	Recommendations on the use of contraceptives was updated to correspond with the safety follow-up period	Section 5.3.4.1
27	Specific details for subjects rolling over from Japan studies was added	Section 5.4
28	The definition of enrolled subjects, screen failures, and prematurely discontinued subjects were clarified	Section 5.4.1, Section 5.6, Section 7.1
29	It was clarified that no other products other than TAK-881 and HYQVIA are required for the study	Section 6.1
30	Text relating to the various lengths of needle sets was added	Section 6.2.6.2

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Description of Each Change and Rationale		Sections Affected by Change
#	Description Of Changes/Rationale For Changes	Section
31	The infusion rates for rHuPH20 were modified	Section 6.2.6.2, Tables 14 to 17
32	Minor modifications were made to the text describing the duration it takes for TAK-881 and HYQVIA to reach room temperature after refrigeration	Section 6.2.31, Section 6.2.5
33	It was clarified that events of overdose, abuse, misuse, or medication error must be reported via a paper form	Section 6.7
34	Permitted and prohibited concomitant medications and therapies were further described	Table 18, Section 6.8.3
35	It was clarified that only "selected" protocol deviations would result in discontinuation. It was added that the evaluation of the risk to the subject's health for continued participation after not adhering to protocol requirements is per the investigator's discretion	Section 7.1
36	The definition of prior medications/treatments was updated to specify that this also includes prestudy IgG treatment	Section 8.1.3
37	The body parts and systems to be examined were updated	Section 8.3.1
38	Text/table was updated to allow the possibility for a reduced clinical chemistry panel for subjects aged between 2 and 6 years when there is insufficient blood volume	Section 8.3.3.2, Table 19
39	The threshold for reduction of hemoglobin levels which require re-testing was changed	Section 8.3.3.4
40	The collection and use of back-up and retention samples was clarified	Section 8.3.3.6, Section 8.3.3.7
41	Text relating to the TSQM-9 was changed to specify the age range of subjects and to describe that appropriate translated versions of the questionnaire will be administered	Section 8.3.6.4
42	The reference location for documenting the duration of infusion preparation was changed An additional time point for documenting the duration of infusion preparation was added	Section 8.3.7
43	Further justification for the follow-up calls was added	Section 8.3.10.2
44	The time period for reporting pregnancy outcomes was updated	Section 8.3.10.5
45	An option for PK sampling to be performed at home was added	Section 8.4.1
46	The specification of the type of interpolation/extrapolation used to calculate the AUC for the exact duration of the infusion interval was changed to remove the term "linear" as other types may be used	Section 8.4.1
47	A new section defining the timing of the EOS/ET Visits was added	Section 8.10
48	The calculation of the infusion duration if multiple infusion sites are used was clarified	Section 9.5.1

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Description of Each Change and Rationale		Sections Affected by Change
#	**Description Of Changes/Rationale For Changes**	**Section**
49	Minor modification of the statistical analysis of the clinical outcome assessments	Section 9.5.2
50	Text was updated to included Japan-specific regulatory guidelines	Section 10.1.1
51	A description of measures to be implemented in case of data security breach was added to comply with EU CTR	Section 10.1.4
52	Text was updated to included Japan-specific record retention requirements	Section 10.1.8.4
53	The protocol-required laboratory tests were modified	Table 19
54	All language relating to auxiliary medicinal products was removed from the protocol, as no auxiliary medicinal products will be used in this study	Table 20, Section 10.3.5, Section 10.3.5.2, Section 10.3.6, Section 10.7.1
55	A new section related to “SAEs that do not require immediate reporting” was added to comply with EU CTR	Section 10.3.5.1
56	The dose of TAK-881/HYQVIA was changed from “mg/kg” to “g/kg”	Throughout the document
57	Minor grammatical, editorial, and/or administrative changes have been made to improve the readability and/or clarity of the protocol	Throughout the document

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11. REFERENCES

Baxalta US Inc. 2020. *HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] - Prescribing Information.* [Online]. Available: https://www.shirecontent.com/PI/PDFs/HYQVIA_USA_ENG.pdf.

Berger, M. 2004. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol,* 112, 1-7.

Berger, M., Murphy, E., Riley, P. & Bergman, G. E. 2010. Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. *South Med J,* 103, 856-863.

Bharmal, M., Payne, K., Atkinson, M. J., Desrosiers, M. P., Morisky, D. E. & Gemmen, E. 2009. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes,* 7, 36.

Bonilla, F. A. 2008. Intravenous immunoglobulin: Adverse reactions and management. *J. Allergy Clin. Immunol,* 122, 1238-1239.

Bousfiha, A., Jeddane, L., Picard, C., Al-Herz, W., Ailal, F., Chatila, T., Cunningham-Rundles, C., Etzioni, A., Franco, J. L., Holland, S. M., Klein, C., Morio, T., Ochs, H. D., Oksenhendler, E., Puck, J., Torgerson, T. R., Casanova, J.-L., Sullivan, K. E. & Tangye, S. G. 2020. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. *Journal of Clinical Immunology,* 40, 66-81.

Cox, L. S., Sanchez-Borges, M. & Lockey, R. F. 2017. World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? *Journal of Allergy and Clinical Immunology: In Practice,* 5, 58-62.e5.

EMA. 2015. *Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)- Revision 1* [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-subcutaneous/intramuscular-administration-scig/imig-revision-1_en.pdf.

EU 2017. Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Revision 1. [Online]. Available: https://health.ec.europa.eu/system/files/2018-02/2017_09_18_ethical_consid_ct_with_minors_0.pdf

For non-commercial use only

Fasth, A. & Nyström, J. 2008. Quality of life and health-care resource utilization among children with primary immunodeficiency receiving home treatment with subcutaneous human immunoglobulin. *J. Clin. Immunol,* 28, 370-378.

FDA. 1998a. *Guidance for Industry "Acute Bacterial Meningitis – Developing Antimicrobial Drugs for Treatment," Draft Guidance, July 1998. This draft guidance, when finalized,will represent FDA's current thinking on this topic.* [Online]. Available: http://www.fda.gov/cder/guidance/2573dft.pdf.

FDA. 1998b. *Guidance for Industry "Community Acquired Pneumonia – DevelopingAntimicrobial Drugs for Treatment," Draft Guidance, July 1998. This draft guidance,when finalized, will represent FDA's current thinking on this topic.* [Online]. Available: http://www.fda.gov/cder/guidance/2570dft.pdf.

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/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human [Accessed].

Gardulf, A. 2007. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. *BioDrugs,* 21, 105-116.

Gardulf, A., Björvell, H., Gustafson, R., Hammarström, L. & Smith, C. I. 1993. Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. *Immunodeficiency,* 4, 81-84.

Gardulf, A. & Hammarström, L. 1996. Subcutaneous administration of immunoglobulins. What are the advantages? *Clin Immunother* [Online], 6 (2) 108-116. Available: https://link.springer.com/content/pdf/10.1007/BF03259507.pdf [Accessed 1996].

Gardulf, A., Hammarström, L. & Smith, C. I. 1991. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. *Lancet,* 338, 162-166.

Gardulf, A., Möller, G. & Jonsson, E. 1995. A comparison of the patient-borne costs of therapy with gamma globulin given at the hospital or at home. *Int J Technol Assess Health Care,* 11, 345-353.

Gardulf, A., Nicolay, U., Asensio, O., Bernatowska, E., Böck, A., Costa-Carvalho, B. T., Granert, C., Haag, S., Hernández, D., Kiessling, P., Kus, J., Matamoros, N., Niehues, T., Schmidt, S., Schulze, I. & Borte, M. 2004. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. *J Allergy Clin Immunol,* 114, 936-942.

For non-commercial use only

Gardulf, A., Nicolay, U., Asensio, O., Bernatowska, E., Böck, A., Costa Carvalho, B., Granert, C., Haag, S., Hernández, D., Kiessling, P., Kus, J., Pons, J., Niehues, T., Schmidt, S., Schulze, I. & Borte, M. 2006. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies - A prospective multi-national study. *J Clin Immunol,* 26, 177-185.

Goldstein, B., Giroir, B. & Randolph, A. 2005. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med,* 6, 2-8.

Hustad, N. B., Degerud, H. M., Hjelmerud, I., Fraz, M. S. A., Nordøy, I., Trøseid, M., Fevang, B., Aukrust, P. & Jørgensen, S. F. 2021. Real-World Experiences With Facilitated Subcutaneous Immunoglobulin Substitution in Patients With Hypogammaglobulinemia, Using a Three-Step Ramp-Up Schedule. *Frontiers in Immunology,* 12, 670547.

Inker, L. A., Eneanya, N. D., Coresh, J., Tighiouart, H., Wang, D., Sang, Y., Crews, D. C., Doria, A., Estrella, M. M., Froissart, M., Grams, M. E., Greene, T., Grubb, A., Gudnason, V., Gutiérrez, O. M., Kalil, R., Karger, A. B., Mauer, M., Navis, G., Nelson, R. G., Poggio, E. D., Rodby, R., Rossing, P., Rule, A. D., Selvin, E., Seegmiller, J. C., Shlipak, M. G., Torres, V. E., Yang, W., Ballew, S. H., Couture, S. J., Powe, N. R. & Levey, A. S. 2021. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *New England Journal of Medicine,* 385, 1737-1749.

Levy, M. M., Fink, M. P., Marshall, J. C., Abraham, E., Angus, D., Cook, D., Cohen, J., Opal, S. M., Vincent, J. L. & Ramsay, G. 2003. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med,* 31, 1250-1256.

Meth, M. J., Rosenthal, D. W. & Bonagura, V. R. 2010. Subcutaneous immunoglobulin infusion to treat infants and toddlers with antibody deficiencies. *Ann Allergy Asthma Immunol,* 105, 187-188.

Misbah, S., Sturzenegger, M. H., Borte, M., Shapiro, R. S., Wasserman, R. L., Berger, M. & Ochs, H. D. 2009. Subcutaneous immunoglobulin: Opportunities and outlook. *Clin Exp Immunol,* 158 Suppl 1, 51-59.

Moore, M. L. & Quinn, J. M. 2008. Subcutaneous immunoglobulin replacement therapy for primary antibody deficiency: advancements into the 21st century. *Ann Allergy Asthma Immunol,* 101, 114-121.

Nagy, A., Duff, K., Bauer, A., Okonneh, F., Rondon, J. C., Yel, L. & Li, Z. 2023. A phase 1 open-label study to assess the tolerability, safety, and immunogenicity of hyaluronidase-facilitated subcutaneous immunoglobulin 20% in healthy adults. *J Clin Immunol,* 44, 28.

For non-commercial use only

Nicolay, U., Kiessling, P., Berger, M., Gupta, S., Yel, L., Roifman, C. M., Gardulf, A., Eichmann, F., Haag, S., Massion, C. & Ochs, H. D. 2006. Health-related quality of life and treatment satisfaction in North American patients with primary immunedeficiency diseases receiving subcutaneous IgG self-infusions at home. *J Clin Immunol,* 26, 65-72.

Notarangelo, L. D. 2010. Primary immunodeficiencies. *J. Allergy Clin. Immunol,* 125, S182-S194.

Ochs, H. D., Gupta, S., Kiessling, P., Nicolay, U., Berger, M. & Group, S. I. S. 2006. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol,* 26, 265-273.

Perez, E. E., Orange, J. S., Bonilla, F., Chinen, J., Chinn, I. K., Dorsey, M., El-Gamal, Y., Harville, T. O., Hossny, E., Mazer, B., Nelson, R., Secord, E., Jordan, S. C., Stiehm, E. R., Vo, A. A. & Ballow, M. 2017. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol,* 139, S1-S46.

Printz, M. A., Sugarman, B. J., Paladini, R. D., Jorge, M. C., Wang, Y., Kang, D. W., Maneval, D. C. & LaBarre, M. J. 2022. Risk Factors, Hyaluronidase Expression, and Clinical Immunogenicity of Recombinant Human Hyaluronidase PH20, an Enzyme Enabling Subcutaneous Drug Administration. *AAPS Journal, The,* 24.

Rabin, R. & de Charro, F. 2001. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med,* 33, 337-43.

Sampson, H. A., Munoz-Furlong, A., Campbell, R. L., Adkinson, N. F., Jr., Bock, S. A., Branum, A., Brown, S. G., Camargo, C. A., Jr., Cydulka, R., Galli, S. J., Gidudu, J., Gruchalla, R. S., Harlor, A. D., Jr., Hepner, D. L., Lewis, L. M., Lieberman, P. L., Metcalfe, D. D., O'Connor, R., Muraro, A., Rudman, A., Schmitt, C., Scherrer, D., Simons, F. E., Thomas, S., Wood, J. P. & Decker, W. W. 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *The Journal of allergy and clinical immunology,* 117, 391-7.

Schwartz, G. J., Munoz, A., Schneider, M. F., Mak, R. H., Kaskel, F., Warady, B. A. & Furth, S. L. 2009. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol,* 20, 629-37.

Skoda-Smith, S., Torgerson, T. R. & Ochs, H. D. 2010. Subcutaneous immunoglobulin replacement therapy in the treatment of patients with primary immunodeficiency disease. *Ther Clin Risk Manag,* 6, 1-10.

For non-commercial use only

Tangye, S. G., Al-Herz, W., Bousfiha, A., Cunningham-Rundles, C., Franco, J. L., Holland, S. M., Klein, C., Morio, T., Oksenhendler, E., Picard, C., Puel, A., Puck, J., Seppänen, M. R. J., Somech, R., Su, H. C., Sullivan, K. E., Torgerson, T. R. & Meyts, I. 2021. The Ever-Increasing Array of Novel Inborn Errors of Immunity: an Interim Update by the IUIS Committee. *Journal of Clinical Immunology,* 41, 666-679.

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. [Accessed].

Wasserman, R. L. 2020. Clinical Practice Experience with HyQvia in Adults Using Alternative Dosing Regimens and Pediatric Patients: A Retrospective Study. *Advances in Therapy,* 37, 1536-1549.

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12. APPENDICES

Appendix 1. Diagnostic Criteria for Serious Infection Types

Infection: Bacteremia/Sepsis[a]

- *Symptoms:* chills, rigors
- *Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mm Hg or a reduction of >40 mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction
- *Laboratory tests:* **positive blood culture[b]**, leukocytosis (white blood cell [WBC] count >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis

Infection: Bacterial Meningitis

- *Symptoms:* headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures
- *Physical findings:* Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38°C oral or >39°C rectal
- *Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay**, positive blood culture[c], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose

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Infection: Osteomyelitis/Septic Arthritis

- *Symptoms:* pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults.)
- *Physical findings*: evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38°C oral or >39°C rectal
- *Laboratory tests:* positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture

Imaging studies: **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging (MRI) scan, or computed tomography (CT) scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra**

Infection: Bacterial Pneumonia[d]

- *Symptoms:* productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias
- *Physical findings:* rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or >39°C rectal, or <36°C, hypothermia (temperature <36°C oral or <37°C rectal)
- *Laboratory tests:* leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO_2 <60 mm Hg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum[e], positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage (BAL) or protected brush sampling
- *Imaging studies:* **Pulmonary infiltrate with consolidation on chest X-Ray (CXR)** (new in comparison with baseline CXR)

Infection: Visceral Abscess

- *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present)
- *Physical findings*: intermittent fevers (temperature >38°C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice
- *Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen**, positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess
- *Imaging studies:* **typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan**

Note: Items in bold are considered essential diagnostic features.

[a] Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38°C oral/ >39°C rectal or <36°C oral or <37°C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or $PaCO_2$ <32 mm Hg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms (Levy et al., 2003). For pediatric subjects, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (2005).

[b] Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IGIV replacement therapy. For subjects without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. (Multiple blood cultures are typically obtained in cases of suspected bacteremia/sepsis, as per standard medical practice, and the finding of a single positive culture should prompt additional confirmatory cultures). Subjects meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia.

[c] A blood culture positive for growth of Streptococcus pneumoniae, Neisseria meningitides, or Haemophilus influenzae, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis (FDA, 1998a).

[d] For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious infection episodes in a clinical trial of IGIV, the finding of a new pulmonary infiltrate with consolidation on CXR is considered sufficient. To establish the diagnosis of bacterial pneumonia for pediatric patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants aged 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature >38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature >38°C (100.4°F). In pediatric patients, elevations of WBC counts >15,000/mm^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm^3 may be observed, usually associated with severe infection (FDA, 1998b).

[e] The FDA recommend a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture (FDA, 1998b).

Source: FDA, 2008

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Appendix 2. World Allergy Organization Systemic Allergic Reaction Grading System

Grading System for Systemic Allergic Reactions				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
			Anaphylaxis	
Symptom(s)/sign(s) from 1 organ system present Cutaneous • Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site And/or • Tingling, or itching of the lips* Or • Angioedema (not laryngeal)* Or Upper respiratory • Nasal symptoms (eg, sneezing, rhinorrhea, nasal pruritis, and/or nasal congestion) And/or • Throat-clearing (itchy throat)* And/or • Cough not related to bronchospasm	Symptom(s)/sign(s) from ≥2 organ systems listed in Grade 1	Lower airway • Mild bronchospasm eg, cough, wheezing, shortness of breath which responds to treatment and/or Gastrointestinal • Abdominal cramps* Other • Uterine cramps • Any symptom(s)/sign(s) from Grade 1 would be included	Lower airway • Severe bronchospasm, eg, not responding or worsening in spite of treatment And/or Upper airway • Laryngeal edema with stridor • Any symptom(s)/sign(s) from grades 1 or 3 would be included	Lower or upper airway • Respiratory failure and/or Cardiovascular • Collapse/hypotension† And/or • Loss of consciousness (vasovagal excluded) • Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included

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Grading System for Systemic Allergic Reactions				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
			Anaphylaxis	
Or Conjunctival • Erythema, pruritus, or tearing Or Other • Nausea • Metallic taste				

AIT=allergen immunotherapy, OIT=oral immunotherapy, SAR=systemic allergic reaction, SLIT=sublingual immunotherapy, WAO=World Allergy Organization.

The final grade of the reaction is not determined until the event is over, regardless of the medication administered to treat the reaction. The final report should include the first symptom(s)/sign(s) and the time of onset after the causative agent exposure and a suffix reflecting if and when epinephrine was or was not administered: a, ≤5 min; b, >5 min to 10 min; c, >10 to 20 min; d, >20 min; z, epinephrine not administered.

Final report: Grade 1-5; a-d, or z; First symptom(s)/sign(s); Time of onset of first symptom(s)/signs(s).

Case example. Within 10 min of receiving an AIT injection, a patient develops generalized urticaria followed by a tickling sensation in the posterior pharynx. Intramuscular epinephrine is administered within 5 min of symptoms(s)/sign(s) resulting in complete resolution of the reaction. The final report would be: Grade 2; a; Urticaria; 10 min.

*Application-site reactions would be considered local reactions. Oral mucosa symptoms, such as pruritus, after SLIT administration, or warmth and/or pruritus at a subcutaneous immunotherapy injection site would be considered a local reaction. However, tingling or itching of the lips or mouth could be interpreted as a SAR if the known allergen, eg, peanut, is inadvertently placed into the mouth or ingested in a subject with a history of a peanut-induced SAR. Gastrointestinal tract reactions after SLIT or oral immunotherapy (OIT) would also be considered local reactions, unless they occur with other systemic manifestations. SLIT or OIT reactions associated with gastrointestinal tract and other systemic manifestations would be classified as SARs. SLIT local reactions would be classified according to the WAO grading system for SLIT local reactions. A fatal reaction would not be classified in this grading system but rather reported as a serious adverse event.

†Hypotension is defined per the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Expert Panel criteria: Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours).

Source: Cox et al., 2017

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Appendix 3. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF=peak expiratory flow; BP=blood pressure.

*Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson et al., 2006

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Signature Page for TAK-881-3001-protocol-amend-5-29jul2024
Title: TAK-881-3001 protocol Amendment 5 29Julr2024

Approval	PPD Statistics 29-Jul-2024 13:08:00 GMT+0000

Approval	PPD Clinical 29-Jul-2024 13:12:52 GMT+0000

Approval	PPD Clinical 29-Jul-2024 17:27:41 GMT+0000

Document Number: TDN-000420459 v1.0

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