Clinical Study Protocol

NCT Number: NCT05513586

Title: A Phase 3, Open-label, Non-controlled, Extension Study to Evaluate the Longterm Safety of TAK-771 in Japanese Patients With Primary Immunodeficiency Disease (PID)

Study Number: TAK-771-3005

Document Version and Date: Amendment 1 / 24 MAY 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL: TAK-771-3005

Title:	A Phase 3, Open-label, Non-controlled, Extension Study to Evaluate the Long-term Safety of TAK-771 in Japanese Patients with Primary Immunodeficiency Disease (PID)
Short Title:	A Study to Evaluate the Long-term Safety of TAK-771 in Japanese PID Patients
Study Phase:	Phase 3
Drug:	TAK-771 Immune Globulin Infusion 10% (Human) [10% IGI] with Recombinant Human Hyaluronidase [rHuPH20]
IND Number:	Not Applicable
EUDRACT Number:	Not Applicable
Sponsor:	Takeda Pharmaceutical Company Limited 4-1-1, Doshomachi, Chuo-ku, Osaka, Japan 540-8645
Principal / Coordinating Investigator:	TBD
Protocol History:	**Protocol Amendment 1 (version date: 24 May 2022)** *replaces* Original Protocol (version date: 31 Jan 2022)

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature:	Date:
[redacted], M.D., Medical Director, PDT	<DD Mmm YYYY>

Investigator's Acknowledgement

I have read this protocol for Study TAK-771-3005.

Title: A Phase 3, Open-label, Non-controlled, Extension Study to Evaluate the Long-term Safety of TAK-771 in Japanese Patients with Primary Immunodeficiency Disease (PID)

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

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 subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

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.

Investigator Name and Address: (please hand print or type)	

Signature: *Date:*

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Protocol Amendment Summary and Rationale:

The following is a summary of the changes made in the amendment 1.

Protocol Amendment			
Summary of Change(s) Since the Last Version of the Approved Protocol			
Amendment Number: 1		Amendment Date: 24 May 2022	Global/Region/Country/ Site Specific: Japan
Description of Each Change and Rationale			Section(s) Affected by Change
1	Assessments of serum trough concentrations of IgG subclasses were removed.	The assessment was removed to reduce the amount of blood drawing and reduce each subject's burden.	Section 1.1 Objectives, Endpoints, Statistical analysis Section 3.1.2 Section 3.2 Table 2 Section 3.2.2 Section 8.2.2.5.7.2 Section 8.2.4.1 Section 9.7
2	Descriptions of 'Device used in clinical trial' were added.	Due to the modification of Japanese GCP, information required for the 'Device used in clinical trial' was added.	PRODUCT QUALITY COMPLAINTS Section 1.1 Mode of administration Section 6.2.3.2 Section 6.8 Section 10 Appendix 3.4
3	Infusion rate of 10%IGI was added.	It was added to present enough information in the synopsis.	Section 1.1 Mode of administration
4	Analysis set for Safety and PK were added and revised the analysis set to be used for each analysis.	For consistency between protocol and SAP	Section 1.1 Analysis populations /analysis sets, Statistical analysis Section 9.4 Section 9.5 Section 9.7
5	Additional items to be summarized descriptively were included.	For consistency with tables to be produced.	Section 1.1 Statistical analysis Section 9.5 Section 9.6
6	Analysis for treatment preference was corrected.	Error in summarization was corrected.	Section 1.1 Statistical analysis Section 9.8.1
7	Description regarding delivery of study drugs from the site to subject's home address was added.	It was added to have an alternative for dispensing investigational product.	Section 6.4
8	Version number of SAS to be used in this study was added.	For clarification	Section 9.1

Protocol Amendment			
Summary of Change(s) Since the Last Version of the Approved Protocol			
Amendment Number: 1		**Amendment Date: 24 May 2022**	**Global/Region/Country/ Site Specific: Japan**
Description of Each Change and Rationale			**Section(s) Affected by Change**
9	Description for reporting of abuse, misuse, overdose, or medication error was modified.	It was modified to reflect the actual procedure accurately.	Appendix 3.9
10	The list of abbreviations was modified.	For update	Appendix 7
11	Correction of error	Typos and errors were corrected.	Section 1.1 Statistical analysis Section 6.4 Section 9.5.5 Section 9.7

See Appendix 8 for protocol history, including all previous amendments.

CONTACTS

Contacts and Responsibilities for Study-Related Activities

Certain events and study-related activities will require the investigator and/or patient to have appropriate contact information. The sponsor or contract research organization (CRO) will provide investigators with emergency medical contact information cards to be carried by each subject, per individual country requirements.

Serious Adverse Event Reporting

If a subject experiences a serious adverse event (SAE) or a non-serious adverse event (AE) requiring expedited reporting per the protocol, the investigator must report the event to the sponsor or CRO *within 24 hours* via the Electronic Data Capture (EDC) system, if possible. If the event cannot be reported via EDC during the required period, it should be reported to

[redacted]

Protocol and Safety-Related Questions or Concerns

For protocol- or safety-related questions or concerns during normal business hours 9:00 AM through 5:00 PM Japan, the investigator must contact the CRO medical monitor:

[redacted]

For protocol- or safety-related questions or concerns outside of normal business hours, the investigator must contact the CRO local medical monitor:

[redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product/device-used-in-clinical-trial quality complaints or non-medical complaints to Takeda within 24 hours. If required, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Takeda licensed or investigational products, as well as device-used-in-clinical-trial defined in this protocol, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product/device-used-in-clinical-trial quality complaints include, but are not limited to, the following:

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

Please report the product quality complaint (including the device-used-in-clinical-trial quality issues) using "Clinical Trial Material Complaint Form" via the e-mail address:

[redacted]

For instructions on reporting AEs related to product complaints, see Appendix 3.4.

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-771-3005	**Drug:** TAK-771 Immune Globulin Infusion 10% (Human) [10% IGI] with Recombinant Human Hyaluronidase [rHuPH20]
Title of the study: A Phase 3, Open-label, Non-controlled, Extension Study to Evaluate the Long-term Safety of TAK-771 in Japanese Patients with Primary Immunodeficiency Disease (PID)	
Short title: A Study to Evaluate the Long-term Safety of TAK-771 in Japanese PID Patients	
Study phase: Phase 3	
Number of subjects (total and per treatment arm): Approximately 10 subjects will be enrolled.	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in up to 10 clinical sites in Japan.	
Study period (planned): Approximately 3 years (until the commercial TAK-771 becomes available in each study site or study termination)	**Clinical phase:** 3

Objectives:

Primary:

To evaluate the long-term safety of TAK-771 in Japanese patients with PID

Exploratory:

- To evaluate the efficacy of TAK-771 in Japanese patients with PID
- To assess serum trough immunoglobulin G (IgG) concentrations following 3- or 4-weeks intervals administration of TAK-771 in Japanese patients with PID
- To evaluate the tolerability of TAK-771 in Japanese patients with PID
- To assess treatment preference of Japanese patients with PID
- To evaluate the actual status of infusion in Japanese patients with PID

Rationale:

This study, TAK-771-3005, is an open-label extension study, offered to patients upon completion of Study TAK-771-3004 that is currently ongoing phase 3 study in Japanese patients with PID. Study TAK-771-3005 will provide data on the long-term safety of TAK-771 in Japanese patients with PID who successfully complete Study TAK-771-3004 and wish to continue TAK-771 administration.

Investigational product, dose, and mode of administration:

Investigational product: TAK-771 (10% IGI with rHuPH20)

Dosage form: injectable subcutaneous (SC) solution

Dose:
[rHuPH20] 80 U/g IgG (rHuPH20 drug product: 160 U/mL)

[10% IGI] The amount of IgG will be maintained as equivalent to that of preceding Study TAK-771-3004, which is assumed to be optimal dose for maintaining the target trough IgG level ≥5g/dL.

Mode of Administration:
SC infusion of rHuPH20 solution at a dose of 80 U/g IgG will be administered first, to be followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution. The infusion rate of rHuPH20 that was tolerated in Study TAK-771-3004 and as recommended by the investigator will be followed in this extension study, which should not exceed 300 mL/h/site. SC infusion of 10% IGI will be administered via an infusion pump (Sapphire^{TM} Multi-Therapy) at infusion rates and volumes determined by the investigator according to the weight and tolerability at 1 or 2 infusion sites (or 3 infusion sites alternatively) per infusion day. The infusion rate of 10%IGI may be increased up to 160 mL/h and 300 mL/h per infusion site for subjects <40 kg and ≥40 kg body weight, respectively.

Methodology:

This is a phase 3, prospective, multicenter, open-label, non-controlled, single-arm extension study to evaluate the long-term safety of TAK-771 in Japanese patients with PID. This study will enroll patients with PID who successfully complete Study TAK-771-3004 and wish to continue TAK-771 administration. After confirmation of eligibility, subjects can continue TAK-771 administration at the same dosage they had in the Study TAK-771-3004 until the commercial TAK-771 becomes available at each study site or study termination.
A schematic of the study design is included as Figure 1.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Subject has completed or is about to complete Study TAK-771-3004.
2. Written and/or electronic informed consent is obtained from either the subject or the subject's legally authorized representative prior to any study-related procedures and study product administration. If a subject is <18 years of age, written and/or electronic informed consent should also be obtained from the subject's legally authorized representative in addition to written informed assent by a subject if appropriate.
3. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria:

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

1. Subject has developed a new serious medical condition during Study TAK-771-3004 such that the subject's safety or medical care would be impacted by participation in the study.
2. Subject is willing to participate in other clinical trials.
3. Women of childbearing potential who meet any one of the following criteria:
   a. Subject presents with a positive pregnancy test.

b. Subject does not agree to employ adequate birth-control measures (eg, intrauterine device, condom [for male partner], or birth-control pills) throughout the course of the study.

Maximum duration of subject participation in the study:

The subject's maximum duration of participation is expected to be approximately 3 years. The study will be continued until the commercial TAK-771 becomes available in each study site.

Analysis Populations /Analysis Sets:

- Enrolled Set: All enrolled subjects who have signed informed (e)Consent in Study TAK-771-3004 and are assigned a subject identifier.
- Safety Analysis Set (SAS): All enrolled subjects who received investigational drug in Study TAK-771-3004 at least once. Analysis of safety, tolerability, and product administration will be based on the SAS.
- Safety Analysis Set for Extension Study (EXSAS): All enrolled subjects who received investigational drug in Study TAK-771-3005 at least once. Some of the analyses for SAS will be based on the EXSAS as well. The data after the start of Study TAK-771-3005 will be included in these analyses.
- Full Analysis Set (FAS): All enrolled subjects who received investigational drug in Study TAK-771-3004 at least once. Analysis of efficacy will be based on the FAS.
- Pharmacokinetic Analysis Set (PKAS): All enrolled subjects who received investigational drug at least once in Study TAK-771-3004, have had at least 1 evaluable serum IgG concentration, and no major protocol deviations or events that would affect the serum IgG concentration analysis results. Analysis of serum IgG trough concentrations will be based on the PKAS.

Endpoints:

Primary Endpoints

Safety endpoints

- Occurrence of treatment-emergent adverse events (TEAEs)
- Development of positive titer (≥1:160) binding antibodies to rHuPH20 and development of positive neutralizing antibodies to rHuPH20

Exploratory Endpoints

Efficacy endpoints

- Annual rate of validated acute serious bacterial infections per subject
- Annual rate of all infections per subject
- Healthcare Resource Utilization:
  - Days not able to attend school/work or to perform normal daily activities due to illness/infection
  - Days on antibiotics
  - Number of hospitalizations due to illness/infection and length of stay (in days)
  - Number of acute (urgent or unscheduled) physician visits due to illness/infection

Pharmacokinetic endpoint

- Serum trough levels of total IgG measured in the treatment period

Safety endpoints

- Changes in clinical laboratory parameters
- Changes in vital signs and body weight
- Relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs Assessed only if at least 5 subjects have elevated titers cumulatively from the preceding Study TAK-771-3004.

Tolerability endpoints

- Occurrence of tolerability events related to the infusion of TAK-771 in the treatment period
- Ability to maintain a regular treatment interval of 3 or 4 weeks

Other endpoints

- Treatment preference assessed by a Patient Preference Questionnaire at End-of-Study/Early termination
- Mode of administration, including but not limited to: number of infusions per month, number of infusion sites per infusion, number of infusion sites per month, duration of individual infusions, maximum infusion rate/site, and infusion volume/site

Statistical analysis:

This study is not designed for hypothesis testing. Continuous endpoints/outcome measures (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation, minimum value, maximum value. In addition, 1st quartile (Q1) and 3rd quartile (Q3) will be summarized for safety and efficacy tables. Categorical endpoints/outcome measures will be summarized in terms of number and percent of subjects and number of occurrences of events in each category.

Safety and tolerability endpoints will be summarized descriptively using the SAS (for pooled analysis) and EXSAS (for the data after the start of Study TAK-771-3005). The number and percentage of subjects with TEAEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA version 24.0 or higher) system organ class and preferred term overall. The number and percentage of subjects with any TEAEs, local/systemic TEAEs, related/non-related TEAEs, severe TEAEs, severe related TEAEs, serious/non-serious TEAEs, serious related TEAEs, infusion-associated TEAEs, TEAEs leading to premature discontinuation from study, and TEAEs leading to death will be presented. For change from baseline in clinical laboratory tests, and vital signs, descriptive statistics will be presented. Number and percentage of subjects who develop anti-rHuPH20 binding antibodies (titers ≥1:160)/neutralizing antibodies will be presented. The detailed definitions of tolerability events and maintenance of treatment intervals will be described in Statistical Analysis Plan.

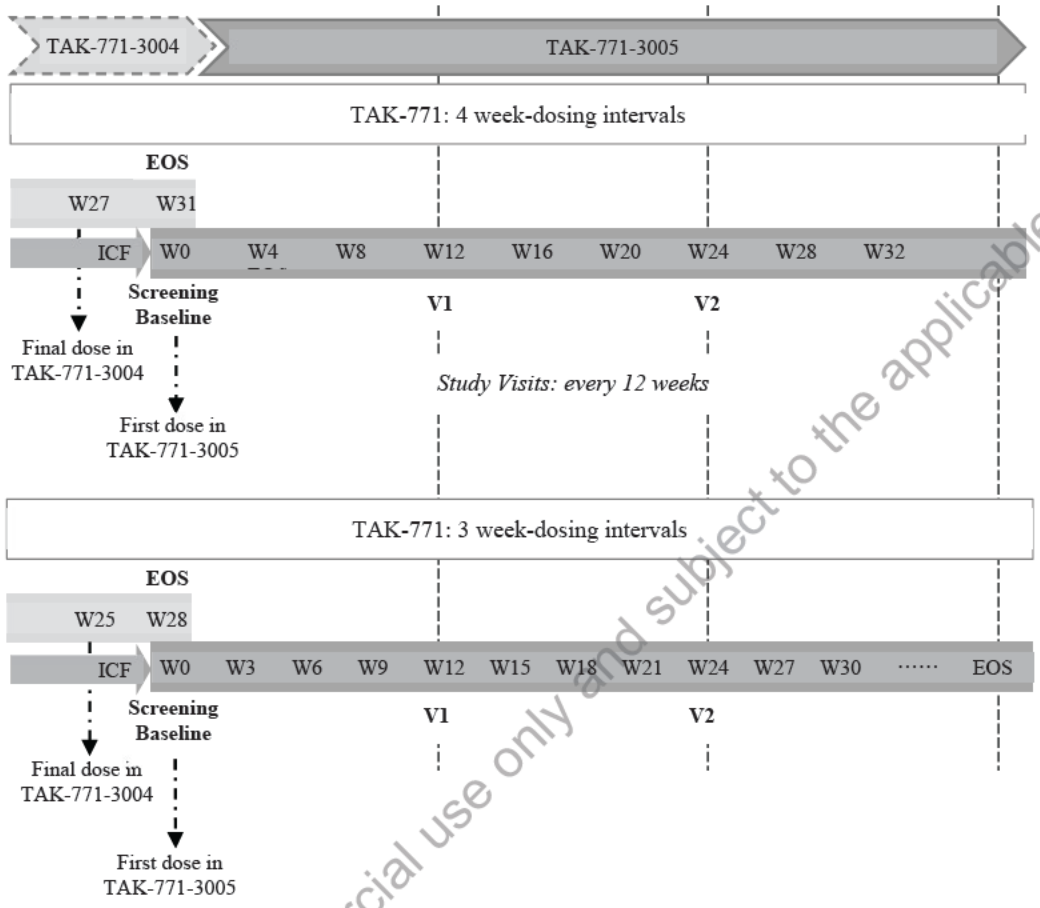
Efficacy endpoint and mode of administration will be summarized descriptively using the FAS. Treatment preference will be summarized in terms of number and percent of subjects in each category using the FAS.

Pharmacokinetic endpoint will be summarized descriptively using the PKAS. For trough serum concentrations of IgG, descriptive statistics including geometric mean and the corresponding 2-sided 95% confidence interval will be presented. Confidence intervals are for descriptive purposes.

Caution should be exhibited in their interpretation as this study is not designed for hypothesis testing.

1.2 Schema

Figure 1. Study Schematic Diagram



Abbreviations: EOS=end-of-study; ICF=informed consent form; V=visit; W=week

1.3 Schedule of Activities

Table 1. Schedule of Activities

Procedure/Assessment		Screening /Baseline Visit [a]	Treatment Period [b] (Visit schedule: a set of 12 weeks to be repeated)											EOS/ET Visit [c]
Week			**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	
Study Visits (n=1,2…)		–	–	–	–	–	–	–	–	–	–	–	–	**Vn**	
Allowance (days)		–	–	–	**±3**	**±3**	–	**±3**	–	**±3**	**±3**	–	–	**±3**	**±3**
Informed Consent [d]		X													
Eligibility Criteria		X													
Demographic/Other Baseline Characteristics[e]		X													
Body Height [f]		X												(X)	
Physical Examination		X												X	X
Clinical Laboratory and PK Assessments [g]		X												X	X
Concomitant Medication, Non-drug Therapies		←	←	←	←	←	←	X	→	→	→	→	→	→	→
Pregnancy Test [h]		X												(X)	X
3-week dosing interval	Study Drug Dispensing/Administration [i]	X [j]			X			X			X			X	
	Vital Signs [k,l]	X			X			X			X			X	X
	Body Weight [l]	X			X			X			X			X	X
4-week dosing interval	Study Drug Dispensing/Administration [i]	X [j]				X				X				X	
	Vital Signs [k,l]	X				X				X				X	X
	Body Weight [l]	X				X				X				X	X
Adverse Events		←	←	←	←	←	←	X	→	→	→	→	→	→	→
Collection/Review Diaries														X	X
Treatment Preference															X
Healthcare Resource Utilization			←	←	←	←	←	←	X	→	→	→	→	→	→
Self-administration Proficiency [i]		X			(X)	(X)		(X)		(X)	(X)			(X)	

Table 1. Schedule of Activities

Abbreviations: EOS=end-of-study; ET=early termination; PK=pharmacokinetic(s)

[a] The assessments at the Screening/Baseline visit can be combined with the EOS visit assessments in Study TAK-771-3004. In such a case, the EOS visit in Study TAK-771-3004 and the Screening/Baseline visit in this study should be on the same day. If those visits happen on separate dates for a compelling reason, the Screening/Baseline visit in this study must be within 6 days at a maximum (it should be aligned with the timepoint of SC infusion) from the EOS visit in Study TAK-771-3004 and the assessments at both visits can still be combined.

[b] Study visits are scheduled to repeat a set of 12 weeks until the commercial TAK-771 becomes available in each study site or study termination. The dose of TAK-771 administration can be modified every 3 months if it is necessary in the discretion of the investigator but cannot be changed in the middle of the planned 12 weeks.

[c] All study subjects completing or exiting the study should complete the EOS/ET procedures. The visit will be 21 days after the last dose for 3-week dosing intervals and 28 days after the last dose for 4-week dosing intervals.

[d] Written and/or electronic informed consent must be obtained prior to any study procedures including screening. Data obtained in Study TAK-771-3004 may be utilized for eligibility assessments in some cases. Informed consent is expected to be obtained prior to or at the last visit of Study TAK-771-3004.

[e] Subject demographic information collected in the preceding Study TAK-771-3004 will be used in this study. Subject's dosing intervals in Study TAK-771-3004 derived from the data collected in Study TAK-771-3004 will be used in this study as other baseline characteristics.

[f] Body height will be measured at Screening/Baseline visit, Week 48 and every 48 weeks thereafter, or for subjects <18 years of age it will be measured at Screening/Baseline visit, Week 24 and every 24 weeks thereafter.

[g] For clinical laboratory and PK assessments specific to the visits, see Appendix 2.

[h] A urine pregnancy test will be performed on all females of childbearing potential. It will be performed at Screening/Baseline visit, Week 24, and every 24 weeks thereafter.

[i] After confirming the eligibility, subject's (and/or caregiver's) proficiency in self-infusion procedures will be verified by the investigator/designee using a proficiency checklist. If a subject (and/or a caregiver) had already been verified to be proficient to have self-infusion in the preceding Study TAK-771-3004, the initial administration of TAK-771 in this study can be self-infusion at home. For a subject (and/or a caregiver) who is not proficient enough, SC infusions will be administered at the study site and training will be provided on self-infusion procedures. After the training, evaluation and verification of subject's (and/or caregiver's) proficiency in self-infusion procedures using proficiency checklist are completed, self-administration at home will be allowed at the discretion of investigator. Subject who has not been confirmed to be proficient enough needs to visit study site every 3 or 4 weeks for the study drug administration until his or her (and/or caregiver's) proficiency is verified.

[j] Study drug will be dispensed only after the subject's eligibility is confirmed.

[k] Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute. Vital signs will be recorded multiple times if an AE occurs.

[l] Vital signs and body weight will be measured once per administration. Both will be measured at study site when subject has visits regardless if it is for mandatory visit or for study drug administration. When subjects have self-infusion at home, subjects (and/or caregiver) should measure vital signs and body weight by themselves and record the values on subject diary.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Primary immunodeficiency diseases (PIDs) are disorders that result in increased susceptibility to recurrent infections, secondary to the underlying defects in adaptive (humoral and/or cell-mediated immunity) and/or innate immune system (Hernandez-Trujillo 2014; Picard et al. 2018; Rosen et al. 1995). The number of known PID defects has increased in the last 20 years and the World Health Organization (WHO) currently recognizes more than 354 distinct disorders (with 344 gene defects) (Picard et al. 2018). The most recent classification of molecularly defined PIDs issued by the Expert Committee of the International Union of Immunological Societies (IUIS) (Tangye et al. 2020) distinguishes 10 PID categories according to common disease phenotypes.

Considered rare diseases until recently, PIDs may affect up to 1/1200 people worldwide according to current estimates (Bousfiha et al. 2013). In Japan, the prevalence of PIDs and number of patients are estimated as 2.3 per 100,000 people and 2,900 patients, respectively, though the accurate prevalence is not well known (Ishimura et al. 2011). In addition, it is well known that patients with PID are at high risk of developing malignancy, and, it is reported that 3.2% of patients with PID have developed malignant diseases (de la Morena and Nelson 2014). Primary immunodeficiency diseases are specified as a designated intractable disease by Ministry of Health, Labor and Welfare in Japan.

Therapeutic options for the treatment of infections in PID with antibody production defects include standard antibiotic treatment and administration of immunoglobulin G (IgG) as a replacement therapy. Antibody replacement can be administered either intravenously or subcutaneously (Melamed et al. 2012). Therapeutic options for treatment of PID itself to correct the defect are transplantation of bone marrow-derived stem cells, and recently, gene therapy (de la Morena and Nelson 2014; Hernandez-Trujillo 2014; Kuo 2018; Picard et al. 2018; Sauer et al. 2014).

Currently, the majority of IgG products are licensed for intravenous (IV) administration, though in the past several years, subcutaneous (SC) administration has gained popularity. When given weekly or every other week, subcutaneous immunoglobulin (SCIG) leads to higher trough serum IgG concentrations than monthly IV infusions (Berger 2011; Gardulf et al. 1995; Gardulf et al. 1991). Immunoglobulin (IG) replacement therapy administered by the SC route is considered to be effective, safe and is also well accepted by patients with PID (Gardulf and Hammarström 1996). This route of administration may be of particular interest in patients with poor venous access such as pediatric patients (Melamed et al. 2012; Wasserman 2012) and those patients interested in home-based therapy since it can be self-administered (Abolhassani et al. 2012; Wasserman 2012; Zuizewind et al. 2018).

Another major potential benefit of SCIG is the lower incidence of systemic adverse events (AEs) compared to intravenous immunoglobulin (IVIG) (Berger 2013; Suez et al. 2016). The IG preparations currently approved for SC use in the United States (US), Canada and the European Union (EU) are formulated at 10% to 20%. The higher concentration products allow for a relatively smaller infusion volume, which may reduce the number of infusion sites and/or duration of infusion, thereby improving patient quality of life (Wasserman 2012).

Currently in Japan, only one product of IgG formulation for SC use (20% SCIG formulation Hizentra®) is available. The availability of additional alternative IgG formulation for SC use is highly needed for patients who do not tolerate their current SCIG. In addition, to be prepared in the event of product shortages, due to manufacturing constraints or natural disasters, stable supply of SCIG products should be secured by several companies.

2.2 Product Background and Clinical Information

The pharmacokinetics (PK) of SC administration are different from that of IV infusions, and bioavailability of IG administered subcutaneously may be lower than after IV infusions. This reduced bioavailability after SC administration may be due to the mode of absorption of large protein molecules, which cannot readily diffuse through the capillary walls and must be absorbed via the lymphatics (Supersaxo et al. 1990).

A major disadvantage of conventional SC administration is that only small volumes can be infused at each injection site, necessitating the use of multiple sites on a weekly or bi-weekly (every other week) basis. Generally, using a 16% solution, approximately 20 mL can be infused per site; an adult patient receiving 400 mg/kg body weight every 4 weeks thus would require at least 3 sites per week or 12 sites per month. Even though weekly or bi-weekly administration has the added advantage of maintaining better trough levels than monthly IV infusions, since SCIG which is currently available in Japan requires weekly injections, the requirement of multiple needle insertions in a lifelong treatment has been discouraging many patients with PID from using SCIG.

TAK-771 (10% immune globulin infusion [IGI] with rHuPH20) has been developed to address the major limitation of conventional SCIG (cSCIG) therapy and it significantly enhances SC administration in PID by offering improved bioavailability (as compared to cSCIG therapy) without requiring greater doses than those administered intravenously (Schiff et al. 2008). In addition, TAK-771 allows the SC administration of standard PID monthly dosing volumes, and the utilization of infusion rates equal to IV administration while preserving the advantages of SC administration (Schiff et al. 2008).

2.3 Study Rationale

Study TAK-771-3004 is currently ongoing, which is designed to evaluate serum trough IgG levels, safety and tolerability, and efficacy of TAK-771 administered subcutaneously at 3- or 4-week intervals and assess disease activity and health-related quality of life in subjects with PID in Japan. It aims to demonstrate maintenance of total IgG trough levels in PID patients after being on stable doses of TAK-771. This study, TAK-771-3005, is an open-label extension study, offered to patients upon completion of Study TAK-771-3004. Study TAK-771-3005 will provide data on the long-term safety of TAK-771 in Japanese patients with PID who successfully complete Study TAK-771-3004 and wish to continue TAK-771 administration.

2.4 Benefit/Risk Assessment

The clinical program for TAK-771 includes 7 completed interventional clinical studies (160601, 160602, 160603, 160902, 161101, 170901, and 161001) in subjects with PID and healthy volunteers, and 1 completed non-interventional registry study (161301) in women exposed to treatment before or during pregnancy (pregnancy registry). These studies provide evidence demonstrating the efficacy, PK, safety and tolerability of TAK-771 in subjects with PID, healthy volunteers and pregnant women. rHuPH20 increased the bioavailability of 10% IGI administered SC normalized by area under the curve (AUC)/dose/kg body weight by approximately 20%, thus reducing the clinically effective dose. When administered at 108% of the IV dose, TAK-771 was pharmacokinetically equivalent to 10% IGI administered IV with respect to area under the curve from time 0 to time τ ($AUC_{0-\tau}$) and resulted in comparable trough IgG levels. The IgG trough levels were well above 5.0 g/L, the accepted minimum level for effective prophylaxis against infections in patients with PID (Orange et al. 2006).

TAK-771 administered over 3 years at a similar frequency to IVIG was safe with a comparable AE profile to SCIG at infusion volumes and rates equivalent to IVIG, and effectively maintained low rates of infection in patients with PID (Wasserman et al. 2015). Large infusion volumes up to 600 mL/site were well-tolerated, enabling treatment of pediatric and adult patients with PID at the same interval used for 10% IGI administered IV. When administered at 108% of the IV dose, TAK-771 resulted in a somewhat lower rate of infections per subject-year (SY) than 10% IGI administered IV or SC. Trough IgG levels were comparable for TAK-771 and 10% IGI administered IV. Protective trough levels were maintained during long-term treatment with TAK-771. TAK-771 reduced the clinically effective SC dose of 10% IGI compared to SC administration alone and resulted in decreased frequency, severity and duration of local induration. A decline in the rate of related local AEs per subject per year was observed during long-term replacement therapy with TAK-771 in subjects with PID.

TAK-771 was shown to be effective in preventing infections in patients with PID.

The primary endpoint of the pivotal study 160603 was met with respect to the frequency of validated acute serious bacterial infections (ASBIs) during TAK-771 treatment. Studies 160902 and 161101 confirmed the efficacy outcomes in terms of validated ASBIs and overall infection rate. In these studies, the rate of validated ASBIs/subject/year were well below 1.0 validated ASBI/subject/year, the threshold specified as providing substantial evidence of efficacy by the Food and Drug Administration (FDA) Guidance (Food and Drug Administration 2008) and also complies with the European Medicines Agency (EMA) Guidance (Committee for Proprietary Medicinal Products 2002). Protection against infection was maintained during long-term TAK-771 in pivotal study 160603 and extension study 160902. The overall annual rate of infections per SY while on TAK-771 treatment in the 2 studies was 2.99 (95% confidence interval: 2.60 to 3.42). It compares favorably to published data; 4.1 infections per SY reported from SC treatment with another 10% IgG preparation (Wasserman et al. 2010), 3.4 to 5.6 infections per SY reported in 3 studies with SC administration of 16% IgG preparation (Berger et al. 2010; Borte et al. 2011; Ochs et al. 2006), and 2.4, 2.76 and 3.3 infections per SY were reported from long-term SC treatment with a 20% IgG preparation (Borte et al. 2012; Borte et al. 2013; Hagan et al. 2010).

Overall, the clinical program for TAK-771 demonstrated the positive safety profile.

In Study 160603, subjects received TAK-771 treatment for at least 1 year, and majority of subjects who received TAK-771 were treated at the same interval used previously for IV treatment (3 or 4 weeks). TAK-771 was well-tolerated at large volumes (up to 600 mL/site) and utilizing maximum flow rates significantly higher than those used for IV infusions ($p<0.0001$) as compared by Wilcoxon test stratified by subject (van Elteren's test). In extension study 160902, subjects continued on TAK-771 treatment for a median of 669 days (mean 565.9 days). A decline in the rate of related AEs, both local and systemic was observed during long-term treatment with TAK-771.

The rate of adverse drug reactions (ADRs) per infusion obtained for TAK-771 compares favorably with published data on SCIG (Ochs et al. 2006). A lower rate of systemic ADRs was reported for TAK-771 than IVIG treatment; this is in line with numerous studies comparing SCIG with IVIG (Berger 2004; Gardulf and Hammarström 1996; Moore and Quinn 2008). While in Study 160603 local ADRs during TAK-771 treatment, which were mostly mild and moderate in severity, were reported at a rate of 0.203 AEs per infusion, the frequency of local ADRs per infusion was as low as 0.103 during long-term treatment with TAK-771 in extension Study 160902.

The nature of ADRs was similar for 10% IGI administered SC in Studies 160601 and 160603, and for TAK-771 treatment in Studies 160603, 160902, and 161101; the most commonly reported reactions were infusion site reactions. Infusion site reactions are expected in most patients during SCIG therapy, but they are not reported to be troublesome in the majority of patients (Gardulf et al. 1995; Misbah et al. 2009; Moore and Quinn 2008).

Across 7 completed clinical studies, 2 serious adverse events (SAEs) were reported that were considered to be related to TAK-771. These events were cases of hemolytic anemia in healthy volunteers. They were conservatively assessed by the investigator as possibly being related to TAK-771, with an alternative etiology of viral infection (H1N1 Influenza A California) which affected 10 of the 12 subjects who participated in this study and was documented by seroconversion.

There have been no serious hypersensitivity reactions, including anaphylactic reactions, attributed to rHuPH20 in the studies with TAK-771. The current clinical and safety data for TAK-771 demonstrate that exposure is safe and well-tolerated, and there has been no evidence of a lack of treatment effect when rHuPH20-reactive binding antibodies have been detected. Based upon data available to date, the incidence of the formation of anti-rHuPH20 antibodies is low, no neutralizing antibodies have been observed, no clinical signs or symptoms have been associated with positive anti-rHuPH20 antibody titers.

Based on all the above, it was considered that the benefits of TAK-771 for treatment of patients with PID outweigh the risks.

Always refer to the latest version of the TAK-771 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of TAK-771.

2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; ICH E6 R2, 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), as well as Ministerial Ordinance on Good Clinical Practice for Drugs Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997 (J-GCP), (as last amended by the Ordinance of Ministry of Health, Labor and Welfare No. 21 of January 29, 2021) and other relevant regulations in Japan. Generally, the priority will be given to J-GCP for the definition of terminology and other minor difference among applicable regulations.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

To evaluate the long-term safety of TAK-771 in Japanese patients with PID

3.1.2 Exploratory Objectives

- To evaluate the efficacy of TAK-771 in Japanese patients with PID
- To assess serum trough IgG concentrations following 3- or 4-week intervals administration of TAK-771 in Japanese patients with PID
- To evaluate the tolerability of TAK-771 in Japanese patients with PID
- To assess treatment preference of Japanese patients with PID
- To evaluate the actual status of infusion in Japanese patients with PID

3.2 Study Endpoints

3.2.1 Primary Endpoint(s)

Safety endpoints

- Occurrence of treatment-emergent adverse events (TEAEs)
- Development of positive titer (≥1:160) binding antibodies to rHuPH20 and development of positive neutralizing antibodies to rHuPH20

3.2.2 Exploratory Endpoint(s)

Efficacy endpoints

- Annual rate of validated ASBIs per subject
- Annual rate of all infections per subject
- Healthcare Resource Utilization
  - Days not able to attend school/work or to perform normal daily activities due to illness/infection
  - Days on antibiotics
  - Number of hospitalizations due to illness/infection and length of stay (in days)
  - Number of acute (urgent or unscheduled) physician visits due to illness/infection

Pharmacokinetic endpoint

- Serum trough levels of total IgG measured in the treatment period

Safety endpoints

- Changes in clinical laboratory parameters
- Changes in vital signs and body weight
- Relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs
  It will be assessed if at least 5 subjects have elevated titers cumulatively from the preceding Study TAK-771-3004. Subjects who have two consecutive anti-rHuPH20 binding antibody titers of ≥1:160 which are elevated from the subject's titers at baseline in the preceding Study TAK-771-3004 are defined as having elevated titers.

Tolerability endpoints

- Occurrence of tolerability events related to the infusion of TAK-771 in the treatment period
- Ability to maintain a regular treatment interval of 3 or 4 weeks

Other endpoints

- Treatment preference assessed by a Patient Preference Questionnaire at End-of-Study (EOS)/Early termination (ET)
- Mode of administrations, including but not limited to: number of infusions per month, number of infusion sites per infusion, number of infusion sites per month, duration of individual infusions, maximum infusion rate/site, and infusion volume/site

Table 2. Objectives and Endpoints

Objective	Endpoint(s)
Primary	
To evaluate the long-term safety of TAK-771 in Japanese patients with PID	• Occurrence of TEAEs • Development of positive titer (≥1:160) binding antibodies to rHuPH20 and development of positive neutralizing antibodies to rHuPH20 (Exploratory) • Changes in clinical laboratory parameters • Changes in vital signs and body weight • Relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs (assessed only when at least 5 subjects have elevated titers cumulatively from the preceding Study TAK-771-3004)
Exploratory	
To evaluate the efficacy of TAK-771 in Japanese patients with PID	• Annual rate of validated ASBIs per subject • Annual rate of all infections per subject • Healthcare Resource Utilization - Days not able to attend school/work or to perform normal daily activities due to illness/infection - Days on antibiotics - Number of hospitalizations due to illness/infection and length of stay (in days) - Number of acute (urgent or unscheduled) physician visits due to illness/infection
To assess serum trough IgG concentrations following 3- or 4-week intervals administration of TAK-771 in Japanese patients with PID	• Serum trough levels of total IgG measured in the treatment period
To evaluate the tolerability of TAK-771 in Japanese patients with PID	• Occurrence of tolerability events related to the infusion of TAK-771 in the treatment period • Ability to maintain a regular treatment interval of 3 or 4 weeks
To assess treatment preference of Japanese patients with PID	• Treatment preference assessed by a Patient Preference Questionnaire at EOS/ET
To evaluate the actual status of infusion in Japanese patients with PID	• Mode of administrations, including but not limited to: number of infusions per month, number of infusion sites per infusion, number of infusion sites per month, duration of individual infusions, maximum infusion rate/site, and infusion volume/site

4. STUDY DESIGN

4.1 Overall Design

This is a phase 3, prospective, multicenter, open-label, non-controlled, single-arm extension study to evaluate the long-term safety of TAK-771 in Japanese patients with PID. This study will enroll patients with PID who successfully complete Study TAK-771-3004 and wish to continue TAK-771 administration. Of the 15 subjects to be enrolled in the Study TAK-771-3004, 12 subjects are expected to complete the study and approximately 10 subjects are expected to be enrolled in this Study TAK-771-3005. Up to 10 clinical sites located in Japan are planned.

The study consists of signing informed (e)Consent, Screening/Baseline visit, treatment period, and EOS/ET visit.

Informed consent for this Study TAK-771-3005 is expected to be obtained prior to or at the last visit of the preceding Study TAK-771-3004.

Screening/Baseline Visit

After informed consent has been obtained, the subjects will undergo procedures for the determination of eligibility before the first administration of TAK-771 in this extension study. Baseline can correspond to the EOS visit of Study TAK-771-3004. In such a case, the Screening/ Baseline visit and the EOS visit of Study TAK-771-3004 should be on the same day. If those visits happen on separate dates for a compelling reason, the Screening/Baseline visit in this study must be within 6 days at a maximum (it should be aligned with the timepoint of SC infusion) from the EOS visit in Study TAK-771-3004 and the assessments at both visits can still be combined. After confirming the eligibility, proficiency of the subject (and/or, as applicable, a caregiver who may assist the subject with self-administration) in self-infusion procedures will be verified by the investigator/designee using a proficiency checklist. If a subject (and/or a caregiver) had already been verified to be proficient to have self-infusion in the preceding Study TAK-771-3004, the initial administration of TAK-771 in this study can be self-infusion at home.

Treatment Period

Subjects will continue TAK-771 administration at the same dose and frequency they had in the Study TAK-771-3004 until the commercial TAK-771 becomes available at each study site or study termination (estimated duration: approximately 3 years). The dose of TAK-771 will be adjusted to maintain the target IgG trough level of ≥5 g/L and the dosing intervals will be either 3 or 4 weeks, changeable on a case-by-case basis if necessary.

Mandatory study site visits are scheduled every 12 weeks for clinical and laboratory examination. Infusions between the mandatory study site visits are recommended to be home treatments for subjects whose proficiency in self-infusion procedures is verified. The study subject should be well trained for self-infusion process before they will do self-infusion at home. Investigator should confirm that the subject has enough knowledge and skill for self-infusion and need to record it When infusions are self-administered at home, the infusion related data will be recorded in subject diary and assessments to be conducted on the day of administration (ie, vital signs and body weight) will also be conducted at home and recorded in the diary. Subjects who have not been confirmed to be proficient enough to have self-administration need to visit study site every 3 or 4 weeks for the study drug administration until the self-administration proficiency is verified. In such a case, the infusion related data will be recorded in the subject's source document and electronic case report form (eCRF) at study site. Other assessments to be conducted on the day of administration will also be measured/collected at study site and recorded in the subject's source documents and eCRFs.

End-of-Study/Early Termination Visit

All study subjects completing or exiting the study should complete the EOS/ET procedures at the EOS/ET visit.

A schematic of the study design is provided in Figure 1.

4.2 Scientific Rationale for Study Design

This is a Phase 3, prospective, multicenter, open-label, non-controlled, single-arm extension study enrolling patients with PID who successfully complete Study TAK-771-3004 and wish to continue TAK-771 administration. The study is designed to collect important data regarding safety of TAK-771 in Japanese patients with PID in the long-term continuous infusion.

4.3 Justification for Dose

For all subjects, the dosing regimen for TAK-771 in Study TAK-771-3004 was the same as the subject's previous monthly equivalent IVIG dose or SCIG when administered at a dosing frequency of every 3 or 4 weeks. The dose and dosing intervals in this study will be the same as those established in Study TAK-771-3004, and the dose can be adjusted to maintain the target IgG trough level of ≥5 g/L.

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 3 years. The study will be continued until the commercial TAK-771 becomes available in each study site.

The study completion date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s).

All AEs/SAEs which had been reported until EOS/ET visit will be followed until resolution, medically stabilized, or 30 days after EOS/ET visit, whichever comes first.

4.5 Sites and Regions

The study will be conducted at up to 10 sites in Japan.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written and/or electronic informed consent/assent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Subject has completed or is about to complete Study TAK-771-3004.
2. Written and/or electronic informed consent is obtained from either the subject or the subject's legally authorized representative prior to any study-related procedures and study product administration. If a subject is <18 years of age, written and/or electronic informed consent should also be obtained from the subject's legally authorized representative in addition to written informed assent by a subject if appropriate.
3. Subject is willing and able to comply with the requirements of the protocol.

5.2 Exclusion Criteria

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

1. Subject has developed a new serious medical condition during Study TAK-771-3004 such that the subject’s safety or medical care would be impacted by participation in the study.
2. Subject is willing to participate in other clinical trials.
3. Women of childbearing potential who meet any one of the following criteria:
   a. Subject presents with a positive pregnancy test.
   b. Subject does not agree to employ adequate birth-control measures (eg, intrauterine device, condom [for male partner], or birth-control pills) throughout the course of the study. See Section 5.4.1 and Appendix 4 for adequate birth-control measures.

5.3 Restrictions

Not applicable

5.4 Reproductive Potential

There are limited data available on the use of TAK-771 during pregnancy. Study 161301 (pregnancy registry) reported that TAK-771 given during pregnancy was not associated with labor and delivery complications. Two minor birth defects (cleft lip without cleft palate and talipes calcaneovalgus) were reported in 2 infants born of parents who were in the TAK-771 Arm and assessed as unrelated with treatment. Please see the IB addendum for the detailed information.

There are limited safety data available on the use of TAK-771 in breast-feeding women.

The effects of TAK-771 on fertility have not been established.

5.4.1 Female Contraception

Sexually active females of childbearing potential should use an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If used, hormonal contraceptives should be administered according to the package insert. Any female of childbearing potential who is not currently sexually active must agree to use acceptable contraception, as defined below, if she becomes sexually active during the study and for 30 days following the last dose of investigational product.Female subjects should be either:

- Premenarchal and either Tanner stage 1 or less than age 9 years, or
- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years), or
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Of childbearing potential with a negative urine pregnancy test at Screening/Baseline visit. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following:

- Intrauterine devices plus condoms
- Hormonal contraceptives (oral), stabilized for at least 30 days prior to the Screening/Baseline visit, plus condoms. Note: If the subject becomes sexually active during the study, she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

See Appendix 4 for contraceptive guidance.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is TAK-771 (10% IGI with rHuPH20).

Immune Globulin Infusion 10% (Human) - 10% IGI

The 10% IGI component of TAK-771 manufactured from human plasma by employing a modified Cohn-Oncley cold alcohol fractionation process, as well as cation and anion exchange chromatography. Screening against potentially infectious agents (such as human immunodeficiency virus [HIV], hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], hepatitis E virus [HEV], and Parvovirus B19 [B19V]) begins with the donor selection process and continues throughout plasma collection and preparation. To further improve the margin of safety, three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent treatment, nanofiltration, and incubation at a low pH and elevated temperature in the final formulation.

The finished medicinal product, 10% IGI, is a purified, functionally intact IgG solution formulated with 0.25 M glycine (for a stabilizing effect) at 10% w/v protein concentration and a pH of 4.6 to 5.1.

The preparation is an isotonic solution containing approximately 100 mg of protein per mL, of which at least 98% is IgG with an IgG subclass distribution representative of native human plasma. The product contains no preservatives.

Recombinant Human Hyaluronidase - rHuPH20

rHuPH20 drug product is supplied as a sterile, clear, colorless, ready-for-use solution in the label strength of 160 U/mL, containing the additional excipients sodium chloride, sodium phosphate, human albumin, ethylenediaminetetraacetic acid (EDTA) disodium, calcium chloride, and sodium hydroxide and/or hydrochloric acid added for pH adjustment. rHuPH20 solution contains 0.1% human albumin with an approximate pH of 7.4 and osmolality of 290 to 350 mOsm. rHuPH20 solution is preservative-free. rHuPH20 solution provides for high margins of safety with respect to viruses, due to comprehensive virus testing at the Master Cell Bank, Working Cell Bank and bulk harvest stage, effective virus reduction during the purification process, and the use of pharmaceutical grade human albumin as an excipient with no other materials of human or animal origin involved in the manufacturing process.

Additional information is provided in the current IB.

6.1.2 Blinding the Treatment Assignment

Not applicable

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

This is an open-label, non-controlled study where all subjects will be enrolled to receive TAK-771. Individual subject numbers are automatically assigned to all subjects via the interactive response technology (IRT) as they consent to take part in the study. Within each study site (numbered uniquely within a protocol), the subject number is assigned according to the sequence of subject presentation for study participation.

Interactive response technology will be used for study drug supply management, inventory management, supply ordering, study drug expiration tracking, temperature excursion reporting, and return of study drug.

Details for the handling of study drug will be described in the pharmacy manual.

6.2.2 Allocation of Subjects to Treatment

Individual subject treatment is automatically assigned by the IRT. Subjects will be assigned to receive the next available medication ID number allocated to each study site. The medication ID number will be entered onto the eCRF.

6.2.3 Dosing

In principle, the dose as well as the dosing frequency of rHuPH20 and IGSC 10% will be as same as those established in Study TAK-771-3004.

Subcutaneous infusion of rHuPH20 solution will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution at the same location. The recommended site(s) for SC infusion are the middle to upper abdomen and thighs. If more than one site are used, the infusion sites should be rotated by choosing opposite sides of the body. Avoid bony prominences, or scarred areas. The product should not be infused at or around an infected or acutely inflamed area due to the potential risk of spreading a localized infection.

rHuPH20 and 10% IGI solutions for administration must be prepared according to separate written procedures which will be provided in infusion manuals.

6.2.3.1 rHuPH20

Dose: 80 U/g IgG (rHuPH20 drug product: 160 U/mL)

Dosing Frequency: Same as 10% IGI

Mode of Administration: The infusion rate that was tolerated in Study TAK-771-3004 and as recommended by the investigator will be followed in this extension study. It should not exceed 300 mL/h/site.

6.2.3.2 10% IGI

Dose: The amount of IgG will be maintained as equivalent to that of preceding Study TAK-771-3004, which is assumed to be optimal dose for maintaining the target trough IgG level ≥5g/dL.

Dosing Frequency: Every 3 or 4 weeks. The same dosing intervals as the preceding Study TAK-771-3004 should be maintained.

Mode of Administration: SC infusion, to be administered via an infusion pump (Sapphire™ Multi-Therapy, See Section 6.8) at infusion rates and volumes determined by the investigator according to the weight and tolerability at 1 or 2 infusion sites (or 3 infusion sites alternatively) per infusion day.

6.2.3.2.1 Maximum Infusion Rate

For subjects weighing ≥40 kg, the infusion rate may be increased up to 300 mL/h per infusion site if tolerated. For subjects weighing <40 kg, infusion rates can be increased up to 160 mL/h per infusion site.

6.2.3.2.2 Volume of Infusion Per Site

10% IGI solution may be administered at a volume of up to 600 mL per infusion site for subjects ≥40 kg or up to 300 mL per infusion site for subjects <40 kg, as tolerated. On a given infusion day, the maximum infusion volume should not exceed 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg. The TAK-771 dose may be administered over multiple days as divided doses with 48 to 72 hours between doses only if a subject's total IgG dose on a given day exceeds the maximum infusion volume, or exceeds the SC maximum infusion volume the subject can tolerate.

6.2.3.3 Location of the Infusion Procedures

After confirming the eligibility, subject's (and/or caregiver's) proficiency in self-infusion procedures will be verified by the investigator/designee using a proficiency checklist. If a subject (and/or a caregiver) had already been verified to be proficient to have self-infusion in the preceding Study TAK-771-3004, the initial administration of TAK-771 in this study can be self-infusion at home.

For a subject (and/or a caregiver) who is not proficient enough, SC infusions will be administered at the study site and training will be provided on self-infusion procedures. After the training, evaluation and verification of subject's (and/or caregiver's) proficiency in self-infusion procedures using proficiency checklist are completed, self-administration at home will be allowed at the discretion of investigator.

On the days of mandatory study site visits, subjects whose proficiency in self-infusion procedures is verified can choose to have the infusion at home or at study site. The investigator/designee should advise subjects to have site visit prior to the self-administration at home, as blood sample needs to be collected before the administration of investigational product.

6.2.3.4 Monitoring Subject Treatment Compliance

Subcutaneous infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse) or, if applicable, can be administered by the subject and/or a caregiver. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee, must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at sites, home or other suitable locations. A healthcare professional (eg, infusion nurse) may be present to observe the subject's self-administration. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The proficiency check will not be required when the subject has self-administration of SC infusions at home. The proficiency check is also not required at every study visit after the subject started self-infusion at home unless the investigator suspects the subject's proficiency.

If subjects perform self-administration at home, information (date/time of infusion, infusion site, infusion rate/volume, AE) will be recorded in a subject's diary.

6.2.4 Unblinding the Treatment Assignment

Not Applicable

6.2.5 Dose Modification

The dose (in milligrams IgG per kg body weight) should remain stable throughout the study. In order to maintain the same dose in mg/kg when there has been an increase in body weight (kg), it will be necessary to increase the absolute dose (in g or mg) administered.

The dose of TAK-771 should be based on the most current weight measurement (taken at a site visit) - if the subject´s weight has increased by more than 5% compared to that the current dose of TAK-771 was determined based on, the absolute dose (in g or mg) should be adjusted at the next possible infusion. If there is a weight decrease, regardless of the percentage, the dose of TAK-771 should not be changed. Body weight self-measured at home will not be used to determine the need of dose modification.

Serum trough levels of IgG ≥5 g/L are targeted to be maintained throughout the study. If levels fall below 5 g/L, the subject's dose must be adjusted to maintain minimum trough levels of 5 g/L. If the dose is adjusted because IgG levels are below 5 g/L, a trough level should be reevaluated at the next infusion and the dose should be readjusted if necessary. The dose in mg/kg may be adjusted during the study if clinically indicated (eg, increased incidence of infections, low IgG trough level [<5 g/L]) at the investigator's discretion.

If such an event arises, the sponsor should be informed, the rationale for such dose adjustment should be documented in the subject's source documents, and the adjusted dose should be entered in the eCRFs.

6.2.6 Dosing Frequency Modification

Dosing frequency of TAK-771 should be the same as those established in the preceding Study TAK-771-3004, ie, subjects who have been treated at 3-week intervals in Study TAK-771-3004 should maintain the 3-week dosing interval in this study and subjects who have been treated at 4-week intervals in Study TAK-771-3004 should maintain the 4-week dosing interval in this study. Dosing frequency can be changed only if the investigator judged necessary due to medical reasons or to improve subject's tolerability, from 3-week intervals to 4-week intervals and vice versa, and such a change is allowed to be executed only at mandatory visits scheduled every 12 weeks. If such an event arises, the sponsor should be informed, and the change in dosing frequency and the reason for such change should be documented in the eCRFs.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Labeling

The product will be labeled according to the regulatory requirements for clinical studies.

6.3.2 Packaging

rHuPH20 drug product (160 U/mL) will be supplied as a clear, colorless, ready-for-use sterile liquid preparation in single-use glass vials. The appearance of rHuPH20 should be clear and colorless. Do not use IGI, 10% or rHuPH20 if either solution is cloudy or has particulates.

10% IGI will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials. 10% IGI is a clear or slightly opalescent and colorless or pale-yellow solution. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

TAK-771 must be stored under refrigerated conditions (2° to 8°C). Do not freeze the product. Do not use if expiration date is exceeded.

The head of the study site has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited task may be delegated to investigational product manager, but this delegation must be documented. Investigational products are distributed by the investigational product manager. The investigational product manager will enter the unique subject identifier on the investigational product vial/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigational product manager is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; 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 investigational product 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 investigational product that could affect the integrity of the product(s), such as fumigation of a storage room.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's investigational product manager who assigned by the head of the study site is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Investigational product will be shipped to the site once all required regulatory documents are reviewed by the sponsor and determined to be in accordance with applicable regulatory requirements. The investigational product manager will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigational product manager will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The head of the study site has overall responsibility for dispensing investigational product. Tasks may be delegated to a qualified designee (eg, the investigational product manager and a pharmacist are desirable) who is adequately trained in the protocol. This delegation must be documented in the applicable study delegation of authority form.

The site may use an alternative method for dispensing. If permitted by country or local regulations and institutional review boards (IRBs)/ethics committees (ECs), the investigational product can be shipped from the site directly to the subject's home address. Subjects must be provided with instructions on how to receive, store, and ultimately return investigational/sponsor-supplied treatments.

The investigational product manager/designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. One or multiple dose supply(ies) of investigational product will be dispensed to subjects, if self-administration is permitted per protocol, at each of the applicable study visits at which the

subject is required to be at the site. Each subject will be given the investigational product according to protocol. The investigational product manager is to keep a current record of the inventory and dispensing of all clinical supplies. All administered/dispensed medication will be documented in the subject's source documents and/or other investigational product record. The investigational product manager is responsible for ensuring the retrieval of all study supplies from subjects. Due to the health/safety concerns with returning the investigational product container, the investigational product manager must request that subjects keep the empty investigational product packaging after use and return it for drug accountability purposes.

No investigational product stock or returned inventory from the study sponsor may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local and national laws must be adhered to for the transfer.

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

With the written agreement of the sponsor, at the end of the study or as instructed by the sponsor, all unused stock, and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational product must be in accordance with local and national laws.

If the sponsor has not provided written agreement for destruction at the site or a local facility then, at the end of the study or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by the investigational product manager and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned/destroyed. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the investigational product, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

6.6 Subject Compliance

Subjects must be instructed how to have unused investigational product and empty/used investigational product packaging assessed for drug accountability. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The investigational product manager/pharmacist will record details on the drug accountability form.

For study procedures that are to be performed under the direct supervision of the investigator/healthcare professional (eg, infusion nurse) at the study site or infusion center, no separate procedures will be used to monitor subject compliance. The procedure to monitor treatment compliance is provided in Section 6.2.3.4.

6.7 Prior and Concomitant Therapy

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received from the first dose of investigational product in this study and through the final study contact must be recorded in the subject's source documents and appropriate eCRF.

6.7.1 Prior Treatment

No prior treatment information will be collected in this study.

6.7.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product in this study and completion/termination of this study, inclusively. Concomitant treatment information must be recorded in the subject's source documents and appropriate eCRF. If a subject has concomitant treatment for AEs that occurred in Study TAK-771-3004 and is still ongoing in this study, it will be recorded as a concomitant treatment in this study. In case a new treatment is started between EOS visit in Study TAK-771-3004 and the first dose of investigational product in this study, it will be considered as a concomitant treatment in this study.

6.7.3 Permitted Treatment

Treatments not listed in Section 6.7.4 are considered allowable.

6.7.4 Prohibited Treatment

The following medications are not permitted during the course of the study:

- Requirement for all antibiotic therapy must be documented as an AE. Prophylactic treatment with systemic antibacterial antibiotics is not allowed during the study, EXCEPT:
  - Use of antibiotics for a period of up to 72 hours if required due to trauma or a scheduled procedure
  - Use of anti-viral/fungal/protozoal drug for infections which are not treated by IG (eg, trimethoprim/sulfamethoxazole twice a week)
  - Low-dose continuous administration of macrolides which are used for anti-inflammatory effects (eg, For adults (≥15 years old): erythromycin 400 mg/day; clarithromycin 200 mg/day, for children (<15 years old): erythromycin 10 mg/kg/day; clarithromycin 5 mg/kg/day)

  Note: The use of systemic prophylactic antibacterial antibiotics by a subject will be considered a protocol deviation (except for trauma or a scheduled procedure as described above). However, prophylaxis for viral, fungal or protozoal infections (eg, trimethoprim/sulfamethoxazole twice a week for pneumocystis) which are not treated by IG can be used and should be recorded as concomitant medication.
- Other IgG products
- Hyper immune serum
- Immunosuppressive drugs following transplantation

6.8 Devices Used in Clinical Trial

In this study, 'Device Used in Clinical Trial' is defined as below:

Device name	Sapphire™ Multi-Therapy
Type	Infusion pump
Manufacturer	Q Core Medical Ltd.

6.8.1 Marketing approval

Sapphire Multi-Therapy has not yet been approved for marketing in Japan.

Administration of TAK-771 using Sapphire Multi-Therapy has already been evaluated for the compatibility with the drug and the mechanical suitability by Sponsor in Europe and the US where TAK-771 had been approved and marketed.

6.8.2 Indications for Use in This Study

Sapphire Multi-Therapy will be used for administration of TAK-771 and to adjust the administration rate and volume of TAK-771 for SC infusion.

6.8.3 Usage Instructions and Warnings

For the usage instructions and warnings of Sapphire Multi-Therapy, see the User Manual (Q Core Medical, 2021) that will be provided to investigators.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If investigational product is discontinued, regardless of the reason, the evaluations listed for EOS/ET visit will be performed as completely as possible. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the subject's source documents. The reason for discontinuation, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the subject's source documents and appropriate eCRFs.

Subjects who prematurely discontinue the study will not be replaced.

7.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source documents and appropriate eCRFs. If a subject is discontinued for more than 1 reason, each reason should be documented in the subject's source documents and the most clinically relevant reason should be indicated.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other

7.3 Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the study site, 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.

7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject 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 acknowledgement of receipt request) asking that the subject be assessed for final safety evaluations and return any unused investigational product.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Periods

The study consists of signing informed (e)Consent, Screening/Baseline visit, treatment period (approximately 3 years at a maximum) and EOS/ET visit.

Tabulated schedules of study procedures are provided in Table 1. Study assessments are detailed in Section 8.2.

8.1.1 Screening/Baseline Visit

Informed consent is expected to be obtained prior to or at the last visit of Study TAK-771-3004. The subjects will undergo screening procedures for determination of eligibility after the informed consent has been obtained. Data obtained in Study TAK-771-3004 may be utilized for eligibility assessments in some cases. The assessments at the Screening/Baseline visit can be combined with the EOS visit assessments in Study TAK-771-3004. In such a case, the EOS visit in Study TAK-771-3004 and the Screening/Baseline visit in this study should be on the same day. If those visits happen on separate dates for a compelling reason, the Screening/Baseline visit in this study must be within 6 days at a maximum (it should be aligned with the timepoint of administration) from the EOS visit in Study TAK-771-3004 and the assessments at both visits can still be combined. The following procedures will be performed and documented:

- Availability of signed informed (e)Consent
- Assessment of eligibility
- Demographic and other baseline characteristics
- Body height and weight
- Physical examination
- Concomitant medication and non-drug therapies
- Clinical laboratory assessments (See Appendix 2)
- Serum IgG
  Not for the eligibility judgement but for the assessment of dosage appropriateness for maintaining the target IgG trough level of IgG ≥5 g/L, the last 2 values measured in Study TAK-771-3004 will be used.
- Pregnancy test
- Vital signs (See Section 8.2.2.4)
- Adverse events
- Self-administration proficiency

A screen failure is a subject who has given informed (e)Consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been administered investigational product(s) in this study. Subjects cannot be rescreened once they have been designated as a screen failure.

8.1.2 Treatment Period

Eligible subjects can continue TAK-771 administration until the commercial TAK-771 becomes available at each study site or study termination (estimated duration: approximately 3 years).

The number of infusion visits and study site visits during the treatment period will depend on where the injection of TAK-771 is administered. Infusions between mandatory study site visits are recommended to be home treatments.

Mandatory study site visits (physical examinations, vital signs, etc.) are planned to be performed every 12 weeks as shown in Table 1. The following procedures will be performed and documented at study site:

- Body height (every 48 weeks; or every 24 weeks for subjects <18 years of age) and weight
- Physical examination
- Concomitant medication and non-drug therapies
- Clinical laboratory assessments (See Appendix 2)
- Serum IgG
- Pregnancy test (every 24 weeks)
- Vital signs (See Section 8.2.2.4)
- Adverse events
- Collection/review of subject diaries
- Healthcare Resource Utilization (See Section 8.2.3.3)

On the days of study drug administration other than at the mandatory study site visits, the following assessments will be performed.

- Body weight
- Concomitant medication and non-drug therapies
- Vital signs (See Section 8.2.2.4)
- Adverse events
- Healthcare Resource Utilization (See Section 8.2.3.3)

Subjects who have not been confirmed to be proficient enough to have self-administration at home need to visit study site every 3 or 4 weeks for the study drug administration until his or her (and/or caregiver's) proficiency is verified. In such a case, the assessments scheduled on the days of study drug administration will be performed at the study site and recorded in the eCRF. For those who are allowed to have self-administration at home, such procedures and assessments should be performed at home and recorded in the subject diary.

8.1.3 End-of-Study/Early Termination Visit

All subjects completing or exiting the study should complete the EOS/ET procedures. The visit will be 21 days after the last dose for 3-week dosing intervals and 28 days after the last dose for 4-week dosing intervals.

The following procedures and assessments will be performed at the study site:

- Body weight
- Physical examination
- Concomitant medication and non-drug therapies
- Clinical laboratory assessments (See Appendix 2)
- Serum IgG
- Pregnancy test
- Vital signs (See Section 8.2.2.4)
- Adverse events
- Collection/review of subject diaries
- Healthcare Resource Utilization (See Section 8.2.3.3)
- Treatment preference assessments (see Section 8.2.5.1)

8.1.4 Follow-up Period

There is no follow-up period in this study.

8.1.5 Additional Care of Subjects after the Study

This study is planned to be continued until TAK-771 becomes available commercially.
No aftercare is planned for this study.

8.2 Study Assessments

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including gender, date of birth, ethnicity, and race that were collected in the preceding Study TAK-771-3004 will be used. Subject's dosing intervals (3- or 4-week intervals) in the preceding Study TAK-771-3004 derived from the data collected in Study TAK-771-3004 will be used in this study as other baseline characteristics.

8.2.1.1 Medical and Medication History

Medical and medication history collected in the preceding Study TAK-771-3004 will be used in this study.

8.2.2 Safety

8.2.2.1 Physical Examination

A physical examination will be performed by the investigator on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At study visits including Screening/Baseline visit, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Appendix 3), 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 subject's source document.

8.2.2.2 Body Height and Weight

Body height will be measured at Screening/Baseline visit, distinct study visits (every 48 weeks; or every 24 weeks for subjects <18 years of age) and recorded in the subject's source documents and appropriate eCRF.

Body weight will be measured once per administration. At Screening/Baseline visit, each study visit, and the EOS/ET visit, it will be measured at study site and recorded in the subject's source documents and the appropriate eCRF. When subjects have self-infusion at home, subjects (and/or caregiver) should measure body weight by themselves and record the values on subject diary.

8.2.2.3 Adverse Events

At Screening/Baseline visit and each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the completion of EOS visit in Study TAK-771-3004 and all of AEs collected in this study will be considered as TEAEs in this study.

Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.2.2.4 Vital Signs

Vital signs include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute.

Vital signs will be measured once per administration. At Screening/Baseline visit and each study visits including the EOS/ET visit, vital signs will be measured at study site and the values are to be recorded on the subject's source documents and the appropriate eCRF. If an AE occurs, vital signs should be measured and recorded multiple times. When subjects have self-infusion at home and an AE occurs, subjects (and/or caregivers) should measure vital signs by themselves and record the values on the subject diary. In case vital signs are measured at study site at a mandatory study visit but a subject chooses to have a self-infusion at home after the visit within the allowance period, the subject should record vital signs self-measured at home before the self-infusion. Guidance for self-measurement and documentation of vital signs will be given to subjects (and/or caregiver) by the investigator/designee. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result 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.

The investigator will assess whether a change from baseline values in Study TAK-771-3004 in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.2.2.5 Clinical 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 should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are clinically significant or not. 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.

A complete list of the clinical laboratory tests to be performed is provided in Appendix 2.

8.2.2.5.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [ie, red blood cell count], and leukocytes [ie, white blood cell {WBC} count]) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. In addition, absolute neutrophil counts (ANCs) will be determined by laboratory calculation.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, alanine aminotransferase (ALT), serum total bilirubin, aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine, creatinine phosphokinase (CK), glucose, haptoglobin, lipase.

Blood will be obtained for assessment of hematology and clinical chemistry at predose at Screening/Baseline and each mandatory study visit, and at EOS/ET visit. These assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, processed through a central laboratory.

8.2.2.5.2 Anti-rHuPH20 Antibodies

Blood samples for the detection of anti-rHuPH20 binding and neutralizing antibodies will be collected at predose at Screening/Baseline and distinct study visits, and at EOS/ET visit. For a schedule of blood sample drawings, see Appendix 2. Blood samples for the detection of anti-rHuPH20 binding and neutralizing antibodies will be collected and processed according to directions provided in the laboratory manual. At each collection timepoint, plasma samples will be collected into separate tubes labeled for binding antibodies and neutralizing antibodies. All subjects will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection assay (also known as the Screening and Confirmatory Binding Assay). Samples with binding antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies using a validated assay based on neutralization of rHuPH20 activity at the central laboratory.

The test results (titers, and binding or neutralizing) will be assessed for clinical significance by the investigator in the Electronic Data Capture (EDC) database but are not to be reported as AEs.

8.2.2.5.3 Immunogenicity Panel

The following tests conducted at Baseline visit predose in Study TAK-771-3004 are considered as baseline data in this study: 50% hemolytic complement activity of serum (CH50), serum complement component 3 (C3), serum complement component 4 (C4), complement 1q (C1q) binding assay, and circulating immune complex (CIC) Raji cell assay.

All subjects will have anti-rHuPH20 antibody testing in pre-identified central laboratories for anti-rHuPH20 binding antibodies, and neutralizing antibodies will also be measured for subjects with an anti-rHuPH20 binding antibody titer ≥160 (Section 8.2.2.5.2).

If a subject has a positive titer ≥10,000 at any time during the study, characterization of antibodies may be performed (include antibodies cross reacting with Hyal 1, 2, and 4). When there is more than one samples from a same subject has a positive titer ≥10,000, the cross-reactivity analyses for each subject at the peak titer sample will be analyzed, not more than a one-time point from the same subject in a given study. If the cross-reactivity data is going to be included in any interim Safety Data Analysis deliverable/milestone, the highest titer sample of the subject observed by the time of data cut-off for interim analysis will be used for analysis. At any time during the course of the study, subjects who have (a) two consecutive anti-rHuPH20 binding antibody titers of ≥1:160 which are elevated from the subject's titers at baseline in the preceding Study TAK-771-3004, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin or rHuPH20 will be asked to return to the study site as soon as possible to undergo an additional panel of testing. That panel assesses CH50, serum C3, serum C4, C1q binding assay and CIC Raji cell assay.

For a schedule of laboratory test blood drawings, see Appendix 2.

8.2.2.5.4 Urinalysis

Urinalysis includes: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination. Urine samples will be collected at predose at Screening/Baseline visit and each mandatory study visit, and at EOS/ET visit.

For a schedule of laboratory test sample drawings, see Appendix 2. These assessments will be performed at the central laboratory.

A urine pregnancy test will be performed at the study site for females of childbearing potential as indicated in Appendix 2 (see also Section 5.4 and Section 8.2.2.6).

8.2.2.5.5 Specialty Tests

Specialty tests include: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for HCV, and PCR for HIV-1/2. For a schedule of laboratory test blood drawings, see Appendix 2. These assessments will be performed at the central laboratory. If the test is performed at EOS visit in the preceding Study TAK-771-3004, it will not be assessed at Screening/Baseline visit in this study.

Additional specialty tests may be performed if required to establish the etiology of an AE or of abnormal laboratory results, such as tests for HIV, HAV, HBV*, HCV, HEV, or B19V (see also Section 8.2.2.5.7.2).

*Note: Test for HBV is not equal to HBsAg test; HBsAg will be assessed in scheduled specialty tests and additional test for HBV will be conducted for confirmation if required.

8.2.2.5.6 Hemolysis Tests

Scheduled tests will only be performed in subjects aged 12 years and older, in order to avoid multiple blood drawings in small children.

Tests for hemolysis:

1. If hemolysis tests are scheduled when routine hematology and clinical chemistry are already being assessed at the visit, then tests for hemolysis will consist of:
   - direct antiglobulin test (Coombs-test or AGT)
   - urine hemosiderin
2. If hemolysis tests are scheduled when routine hematology and clinical chemistry are Not being assessed at the visit, then tests for hemolysis will consist of:
   - direct antiglobulin test (Coombs-test or AGT)
   - urine hemosiderin
   - hemoglobin
   - lactate dehydrogenase
   - serum haptoglobin

In addition, these assessments (item 2 above) should be performed within 72 hours of being informed of the hemoglobin level, if there is a decrease of hemoglobin ≥2 g/dL compared to the previous visit, unless there is a clear alternative explanation (which has been documented on the subject's source documents and appropriate eCRF).

For a schedule of laboratory test blood drawings, see Appendix 2.

8.2.2.5.7 Assessment of Laboratory Values

8.2.2.5.7.1 Toxicity Grading Scale

The investigator will be asked to assess each abnormal laboratory value as described in Section 8.2.2.5.7.2. In addition, the sponsor will evaluate laboratory values for abnormalities according to a 5-point (Grades 0-4) toxicity grading scale provided in Appendix 6.

The Common Toxicity Criteria of the (Eastern Cooperative Oncology Group 2006) will be used to grade the following laboratory values: ALP, ALT, AST, BUN, hemoglobin, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and WBC count. Grading for LDH will use the same thresholds as defined for ALT and AST. Sodium and potassium will be graded using the thresholds taken from the WHO toxicity grading system (World Health Organization 2003).

8.2.2.5.7.2 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value (with the exception of total IgG) is to be recorded on the laboratory form. For each abnormal laboratory value, the investigator will determine whether the value is also considered an AE (see definition in Appendix 3). If yes, the signs, symptoms, or medical diagnosis will be recorded on the AE eCRF. If the abnormal value was not deemed an AE because it was due to a lab error, was due to a pre-existing disease (described in Appendix 3.1), was not clinically significant, was a symptom of a new/worsened condition already recorded as an AE, or was due to another issue that will be specified, the investigator will record the justification on the laboratory form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result 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. Any positive seroconversion result for HIV, HAV, HBV, HCV, HEV, or B19V shall be re-tested and confirmed.

8.2.2.6 Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at the Screening/Baseline visit as well as distinct study visits (every 24 weeks), and EOS/ET visit. If the pregnancy test is performed at the EOS visit in the preceding Study TAK-771-3004, it can be used to determine the pregnancy status at the Screening/Baseline visit of this study and there will be no need to repeat the test in this study.

All pregnancies are reported from the time the informed (e)Consent is signed until EOS/ET visit. See Appendix 3.8 for the pregnancy reporting.

8.2.3 Efficacy

8.2.3.1 Validated Acute Serious Bacterial Infection Rate

Infections will be reported as AEs and the number and types of infections will be determined. Acute serious bacterial infections will include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that are caused by a recognized bacterial pathogen. The diagnostic criteria for ASBIs are included in Appendix 5.

The validated ASBI rate will be calculated as the mean number of validated ASBIs per subject per year.

8.2.3.2 Infections

All infections will be reported as AEs and the number and types of infections will be determined. The annual rate of all infections per subject will be calculated as the mean number of infections per subject per year.

8.2.3.3 Healthcare Resource Utilization

The following will be collected using subject electronic diaries or other source data options throughout the study and will be transcribed to eCRFs.

- Days not able to attend school/work or to perform normal daily activities due to illness/infection
- Days on antibiotics
- Admissions to a hospital as an inpatient and the number of days in hospital
- Acute (urgent or unscheduled) physician visits due to illness/infection

8.2.4 Pharmacokinetics

8.2.4.1 Serum IgG Trough Levels

Serum IgG trough levels (total serum levels of IgG) will be determined according to the schedule described in Appendix 2 by using standard assay methods for the determination of total IgG concentration.

At enrollment, the last 2 values measured in Study TAK-771-3004 will be used to assess the appropriateness of the dosage to maintain the target IgG trough level of IgG ≥5 g/L.

The blood drawing for the IgG trough level determination must always take place before the infusion is administered.

8.2.4.2 Specific Antibodies

Specific antibody tests (quantitative method) to Clostridium tetani toxoid, Haemophilus influenzae (HIB) and HBV will be performed at EOS/ET visit (see Appendix 2), and analyzed for changes from the baseline in the preceding Study TAK-771-3004.

8.2.5 Other

8.2.5.1 Treatment Preference

Treatment preference will be assessed at the EOS/ET visit.

Treatment preference will be analyzed separately for the age groups of 2 to 13 years (observer: parent) and 14 years and older (observer: subject). Age will be defined as the age at screening in Study TAK-771-3004.

8.2.6 Volume of Blood to Be Drawn from Each Subject

The volume of blood to be drawn from each subject for laboratory assessments for the duration of the study will be specified in the laboratory manual.

8.2.7 Subject Diary

An electronic subject diary will be used in this study to record the following information throughout the study period:

- Occurrence of AEs (including infections). The investigator will provide guidance for the subject/caregiver regarding identification and documentation of AEs.
- Vital signs and body weight self-measured when subjects have self-infusion at home. Vital signs should also be self-measured multiple times when an AE occurs. The investigator will provide guidance for the subject/caregiver regarding self-measurement and documentation of vital signs. In case vital signs are measured at study site at a mandatory study visit but a subject chooses to have a self-infusion at home after the visit within the allowance period, the subject should record vital signs self-measured at home before the self-infusion.
- Concomitant medication use
- Days not able to attend school/work or to perform normal daily activities due to illness/infection
- Number of hospitalizations, indication for the hospitalization (infection or noninfection) and days hospitalized
- Number of acute physician visits (office and emergency room) due to infection or other illnesses
- Infusion related data of self-administration at home, the data to be collected are specified in Section 8.2.8.

The subject diary will serve as a subject's source document. Subject and/or caregiver will be trained on use of the diary. The electronic diary will be used and remain with 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.

If any abnormalities in physical condition or vital signs are recorded and the investigator judged necessary, subject will be contacted by the investigator/designee to follow up on AEs that may have occurred. When infusion related data is not entered timely manner (deviated from the allowance of ±3 days from the scheduled day of administration), the investigator/designee will contact the subject to ensure the adherence of infusion schedule and appropriate, timely entry of data into the subject diary.

Untoward events recorded in the diary will be reported as AEs in the eCRF according to the investigator's discretion and clinical judgement. Any entry on the eCRF that does not correspond with an entry in the subject diary will be explained by the investigator in the subject's source documentation.

8.2.8 Product Administration

TAK-771 infusion related data will be collected and recorded in the eCRF. The data to be collected includes but not limited to: lot number, start and stop time, infusion site, maximum infusion rate achieved (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The Statistical Analysis Plan (SAP) will provide the statistical methods and definitions for the analysis of the safety, efficacy, and PK data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock. Specifications for the corresponding tables, figures, and listings (TFLs) will be provided separately, in the study TFL shells document.

Analysis will be performed with pooled data from this study and the preceding Study TAK-771-3004.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513) version 9.4 or higher.

9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

Interim analysis will be performed within approximately 2 months from the regulatory submission for the approval of TAK-771 in Japan to present the most up-to-date data on the long-term safety of TAK-771 in Japanese subjects with PID to the Pharmaceuticals and Medical Devices Agency (PMDA) to support the data submitted for the approval. No adaptive design or data monitoring committee (DMC) is planned for this study.

9.3 Sample Size and Power Considerations

A sample size of approximately 10 subjects is the estimated number of subjects who can enroll from the previous Study TAK-771-3004. Of the 15 subjects to be enrolled in Study TAK-771-3004, 12 subjects are expected to complete treatment period of Study TAK-771-3004, assuming a dropout rate of 20%.

This study is not designed for hypothesis testing and therefore the sample size is not based on statistical considerations such as study power.

9.4 Statistical Analysis Set(s)

Analysis of safety and tolerability, efficacy, and PK data will be based on the following analysis sets (analysis populations), as defined:

- Enrolled Set: All enrolled subjects who have signed informed (e)Consent in Study TAK-771-3004 and are assigned a subject identifier.
- Safety Analysis Set (SAS): All enrolled subjects who received investigational drug in Study TAK-771-3004 at least once. Analysis of safety, tolerability, and product administration will be based on the SAS.
- Safety Analysis Set for Extension Study (EXSAS): All enrolled subjects who received investigational drug in TAK-771-3005 at least once. Some of the analyses for SAS will be based on the EXSAS as well. The data after the start of Study TAK-771-3005 will be included in these analyses.
- Full Analysis Set (FAS): All enrolled subjects who received investigational drug in Study TAK-771-3004 at least once. Analysis of efficacy will be based on the FAS.
- Pharmacokinetic Analysis Set (PKAS): All enrolled subjects who received investigational drug at least once in Study TAK-771-3004, have had at least 1 evaluable serum IgG concentration, and no major protocol deviations or events that would affect the serum IgG concentration analysis results. Analysis of serum IgG trough concentrations will be based on the PKAS.

9.5 Safety Analyses

Assessments of safety and tolerability are the primary and exploratory objectives of this study, respectively. Safety and tolerability endpoints (defined below) will be summarized descriptively using the SAS (for pooled analysis) and EXSAS (for the data after the start of Study TAK-771-3005). Continuous endpoints/outcome measures (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation, minimum value, maximum value, 1st quartile (Q1) and 3rd quartile (Q3). Categorical endpoints/outcome measures will be summarized in terms of number and percent of subjects and number of occurrences of events in each category.

Safety Endpoints

Primary

- Occurrence of TEAEs, including but not limited to: any TEAEs, local/systemic TEAEs, related/non-related TEAEs, serious/non-serious TEAEs, severe TEAEs, severe related TEAEs, serious related TEAEs, infusion-associated TEAEs, TEAEs leading to premature discontinuation from study, and TEAEs leading to death

- Development of positive titer (≥1:160) binding antibodies, and development of neutralizing antibodies, to rHuPH20
  Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of ≥1:160
  Number and percentage of subjects who develop neutralizing antibodies to rHuPH20

Exploratory

- Changes in clinical laboratory parameters
  Changes from baseline in the preceding Study TAK-771-3004 in clinical laboratory measurements
- Changes in vital signs and body weight.
  Change from baseline in the preceding Study TAK-771-3004 in vital signs and body weight
- Relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs (assessed only when at least 5 subjects have elevated titers cumulatively from the preceding Study TAK-771-3004)

Tolerability endpoints

- Occurrence of tolerability events related to the infusion of TAK-771
  A tolerability event is considered to have occurred if an infusion was not tolerable, which is defined as any changes in dosing of TAK-771 such as reduction of infusion rate, interruption or discontinuation of TAK-771 due to TEAEs related to TAK-771.
- Ability to maintain a regular treatment interval of 3 or 4 weeks

The detailed definition of maintenance of treatment intervals will be described in SAP.

9.5.1 Analysis of Adverse Events

9.5.1.1 Definitions

Treatment-emergent adverse events are defined as AEs with onset after date-time of first dose of investigational drug or medical conditions present prior to the start of investigational drug but increased in severity or relationship after date-time of first dose of investigational drug. Because all participants in this study have completed the first dose of investigational product in preceding Study TAK-771-3004, all of AEs collected in this study will be considered as TEAEs. Adverse events in this study will be collected from the completion of EOS visit in Study TAK-771-3004 until EOS/ET visit of this study.

Related TEAEs, defined as TEAEs causally related to investigational product.

Detailed definitions of AEs are provided in Appendix 3.1.

9.5.1.2 Handling of Recurrent Adverse Events and Other Adverse Event Situations

Multiple Severities and Relationships: Subject with multiple severities of the same AE, the maximum severity (most serious severity) will be used in analysis, and similarly with multiple relationships of the same AE, the worst relationship will be used. If a subject experiences multiple severities of the same AE (eg, 3 occurrences: 1 mild, 1 moderate, 1 severe) all categorized under the same causality assessment (eg, all related to investigational drug), the AE with the maximum severity (AE that is severe) will be used in analysis.

Related AEs: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), 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. Relationship (causality) to study procedures should also be determined for all AEs. The relationship should be assessed as "Related" if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as "Not Related".

Recurrent AEs: If more than 1 AE occurs within the same preferred term (PT) for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational drug. For example, if a subject experienced a mild headache not related to the investigational drug, and a moderate headache related to investigational drug, then the subject will be counted once for headache using the moderate headache related to investigational drug.

Details on data handling conventions will be provided in the study SAP.

9.5.1.3 Occurrence and Number of Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or higher and then reported by MedDRA system organ class (SOC) and PT, and overall. Only TEAEs will be analyzed.

Note: Hereafter, TEAE and AE are used interchangeably.

The following summaries will be provided:

- Number and percentage of subjects with TEAEs by SOC and PT, and overall
- Number of TEAEs by SOC and PT, and overall

The following approaches will be used, where applicable:

- Overall summary: Overall summary will include, but not limited to: any TEAEs, local/systemic TEAEs, related/non-related TEAEs, severe TEAEs, severe related TEAEs, serious/non-serious TEAEs, serious related TEAEs, infusion-associated TEAEs, and TEAEs leading to premature discontinuation from study, and TEAEs leading to death.
- Summaries by SOC and PT: In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the Total column (ie, the Total column will be sorted in descending order after the sorting by SOC and PT).
- Summaries by PT only: In the summaries, PT will be sorted in decreasing frequency in the table Total column.
- If more than 1 TEAE occurs within the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational drug. For example, if a subject experienced a mild headache not related to the investigational drug, and a moderate headache related to investigational drug, then the subject will be counted once for headache using the moderate headache related to investigational drug.
- In AE incidence summaries, subjects with multiple events in the same category will be counted only once in the AE category. Subjects with events in more than one category will be counted once in each of the categories.
- In AE count summaries, multiple occurrences of the same AE will be counted multiple times.

9.5.1.4 Adverse Events per Infusion, per Subject, per Subject-Year

The following summaries will be provided:

- Number of AEs per infusion, by SOC and PT
- Number of AEs per subject, by SOC and PT
- Number of AEs per SY, by SOC and PT

Per infusion is number of events divided by total number of infusions administered; per subject is number of events divided by total number of subjects; per SY is number of events divided by total number of days of exposure, converted into years.

AEs per SY summary adjusts for differences in subjects' durations in the study.

For number of AEs, multiple occurrences of the same AE in the same subject will be counted multiple times.

Number of AEs and AEs per 1000 SYs will be provided for all AEs (if analyzable), by primary SOC and PT.

The following calculations apply, where applicable:

- AEs per infusion = number of AEs / total number of infusions administered to subjects in the analysis set
- AEs per subject = number of AEs / total number of subjects in the analysis set
- AEs per SY = number of AEs / total number of days of exposure, ie, the sum of duration of treatment for all subjects in the analysis set, converted into years
- AEs per 1000 SYs = 1000 x (Total Number of AEs in the study for all subjects / Total SYs in the study)

Total SYs will be calculated by summing subjects' durations in the study. Each subject's duration will be calculated as: (last date in this study – date of initial dose of investigational drug in Study TAK-771-3004 + 1) / 365.25. If the subject's last date is missing, then the date of last dose of investigational drug will be used if available.

9.5.2 Tolerability

The following summaries will be provided:

- Number (percentage) of subjects for whom the infusion rate was reduced for tolerability concerns or for AEs
- Number (percentage) of subjects for whom the infusion was interrupted for tolerability concerns or for AEs
- Number (percentage) of subjects for whom the infusion was stopped for tolerability concerns or for AEs
- Number (percentage) of subjects for whom the infusion rate was reduced or interrupted or stopped for tolerability concerns or for AEs
- Percentage of subjects who maintained a treatment interval of 3 or 4 weeks throughout the study participation
- Percentage of subjects who maintained a treatment interval of 3 or 4 weeks for 48 weeks from the start of Epoch 2 in Study TAK-771-3004 through TAK-771-3005
- Maximum duration of maintaining a regular treatment interval of 3 or 4 weeks
  Maximum duration of maintaining a regular treatment interval is defined as the longest period of the same treatment interval that the subject was treated at, which does not have to be the interval the subject was assigned to at the initiation of study drug.

9.5.3 Clinical Laboratory Data

Baseline is defined as the last non-missing value before initial dose of study drug in Study TAK-771-3004.

Raw (actual) clinical laboratory values (in SI units) and changes in raw values from baseline in Study TAK-771-3004 at each post-baseline assessment time point will be summarized as continuous variables.

Shift from baseline in Study TAK-771-3004 (shift table) to each post-baseline assessment time point will be provided for categorical variables. Summaries of shift-from-baseline will be produced for each laboratory parameter that has a reference range, using the categories: low (below the lower limit of the reference range), normal (within the reference range), high (above the upper limit of the reference range), and missing. Missing data will not be imputed. In addition, shift-from-baseline summaries will be produced by toxicity grade.

9.5.4 Vital Signs and Body Weight

Raw (actual) vital signs and body weight, and changes in raw values from baseline in Study TAK-771-3004 at each post-baseline assessment time point will be summarized as appropriate.

9.5.5 Antibodies

Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of ≥1:160 will be summarized. Samples with anti-rHuPH20 binding antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies, and the number and percentage of subjects who develop neutralizing antibodies to rHuPH20 will be summarized.

Subjects are defined as having elevated anti-rHuPH20 antibody titers if they have two consecutive anti-rHuPH20 binding antibody titers of ≥1:160 which are elevated from the subject's titers at baseline in the preceding Study TAK-771-3004. If at least 5 subjects have elevated titers cumulatively from the preceding Study TAK-771-3004, then an exploratory analysis will be conducted to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

In addition, an exploratory analysis of any treatment-emergent abnormal titer or rises above baseline in the preceding Study TAK-771-3004 in anti-rHuPH20 antibody titer will be performed to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

9.6 Efficacy Analysis

Assessment of efficacy is an exploratory objective of the study. Efficacy endpoint data (defined below) will be analyzed using the FAS. Continuous endpoints/outcome measures (eg, change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation, minimum value, maximum value, Q1 and Q3.

- Annual rate of validated ASBIs per subject
- Annual rate of all infections per subject
- Healthcare Resource Utilization:
  - Days not able to attend school/work or to perform normal daily activities due to illness/infection
  - Days on antibiotics
  - Number of hospitalizations due to illness/infection and length of stay (in days)
  - Number of acute (urgent or unscheduled) physician visits due to illness/infection

9.7 Pharmacokinetic Analysis

Assessment of PK is an exploratory objective of the study. The PK endpoint is the serum trough levels of total IgG measured during the treatment period and will be summarized descriptively using the PKAS. For trough serum concentrations of IgG, descriptive statistics including geometric mean and the corresponding 2-sided 95% confidence interval will be presented. Confidence intervals are for descriptive purposes. Caution should be exhibited in their interpretation as this study is not designed for hypothesis testing. The same analysis will be performed for specific antibodies.

9.8 Other Analyses

9.8.1 Treatment Preferences

Assessment of treatment preferences is an exploratory objective of the study. Treatment preference endpoints will be summarized in terms of number and percent of subjects in each category using the FAS.

9.8.2 Product Administration

Mode of administration will be summarized descriptively using the FAS. The parameters may include but not limited to the following:

- Number of infusions per month
- Number of infusion sites per infusion

- Number of infusion sites per month
- Duration of individual infusion
- Maximum infusion rate/site
- Infusion volume/site

Endpoint details will be provided in the study SAP.

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APPENDIX 1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6 (ICH GCP, 1996; ICH E6 R2, 2016), Title 21 of the US CFR, EU Directive (2001/20/EC; 2005/28/EC), and all updates, as well as local ethical and legal requirements including J-GCP (as last amended by the Ordinance of Ministry of Health, Labour and Welfare No. 21 of January 29, 2021) and other relevant regulations in Japan.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study 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.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information. The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs 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.

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), Title 21 of the US CFR, EU Directive (2001/20/EC; 2005/28/EC), and applicable regulatory requirements and guidelines including J-GCP (as last amended by the Ordinance of Ministry of Health, Labour and Welfare No. 21 of January 29, 2021) and other relevant regulations in Japan.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available prior to commitment to participate in this 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.

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 sub-investigators are provided to the study sponsor (or designee) before starting the study.

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.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators 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 head of the study site, and provide them with a detailed written explanation. Upon study completion, the investigator will provide the sponsor and the head of the study site with final reports and summaries as required by national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, the head of the study site, or for multicenter studies, the coordinating principal investigator according to national provisions.

Documentation and Retention of Records

The investigator and the head of the study site agree to keep the records and documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated the informed (e)Consent/assent document , 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.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

Since the investigational drug (TAK-771) in this study is equivalent to the specified biological products, the records regarding the administration of 10% IGI at the study sites must be maintained for 20 years according to the regulation of the product of specified biological products "Explanation of the use of specified biological products to the target person and records and preservation of specified biological products" (Pharmaceutical Affairs No. 0515012 May 15, 2003).

Case Report Forms

Electronic case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log.

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

The clinical research associate (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.

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diary cards, and original clinical laboratory reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source documents relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The (e)Consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, data obtained using electronic devices and associated technologies [if applicable], etc).

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 PMDA, the US FDA, EMA, United Kingdom Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP/J-GCP requirements.

Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the PMDA, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

Financial Disclosure

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 investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Compliance to 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.

Appendix 1.4 Data Management Considerations

Data Collection

The investigators' authorized site personnel must enter the information required by the study eCRF Completion Guidelines or similar for all data requiring transcription of the source documents. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

Alternative Approaches to Monitoring Due to COVID-19 or Other Unavoidable Circumstances

In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact study procedures, data monitoring may be conducted remotely. The Remote Monitoring strategy is provided in the Clinical Operation Plan.

Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan or similar. 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.

Data Handling in Blinded Studies

Not applicable

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written and/or electronic informed consent and assent where applicable from all study subjects prior to any study-related procedures including screening assessments. All (e)Consent and assent documentation must be in accordance with applicable regulations and GCP:

The nature, scope, and possible consequences, including the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities, of the study will be explained to the subject, the subject's parent(s), or the subject's legally authorized representative(s) by the investigator (and study staff where required). 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 participant and site staff or investigator. Regardless of the consent format – written or eConsent – the investigational site is responsible for the consenting process.

After the subject has received and read (or been read) the subject information, the subject's parent(s) or legally authorized representative(s) and the subject (if applicable) are requested to sign and date the subject informed (e)Consent form or a certified translation if applicable. Subjects consenting via eConsent, where available, will electronically sign consent forms. (Paper consent forms will be used instead, if required by local regulations.)

A copy of the informed (e)Consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be provided to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed (e)Consent forms must remain in each subject's study file at the site (either in their original, signed paper form or as a certified copy if applicable for electronic signature) and must be available for verification at any time.

Within the subject's source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the (e)Consent form and assent form where applicable that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC'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/EC requires modification of the sample subject information and (e)Consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

Institutional Review Board or Ethics Committee

It is the responsibility of the head of the study site to submit this protocol, the informed (e)Consent/assent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent/assent documents and amendments to the protocol unless there is a subject safety issue. Substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

Investigational product supplies will not be released until the sponsor or designee has received written IRB/EC approval and contract with the study site has been finished.

The head of study site is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. The head of study site must also keep the local IRB/EC informed of any serious and significant AEs in accordance with IRB/EC procedures.

Privacy and Confidentiality

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

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records 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-771; national or local regulatory authorities; and the IRB(s)/EC(s) 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 initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and 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.

Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

Clinical Trial Registration

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 interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via e-mail/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

APPENDIX 2 CLINICAL LABORATORY AND PHARMACOKINETIC TESTS

Table A1. Schedule of Clinical Laboratory and Pharmacokinetic Assessments

Procedure/Assessment		Screening /Baseline Visit[a]	Treatment Period					EOS/ET Visit[b]
Visit No.			Visit 1	Visit 2	Visit 3	Visit 4	Following visits	
Week		Week 0	Week 12	Week 24	Week 36	Week 48	Every 12 weeks	
Visit allowance		-	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
PK assessments	Serum IgG trough levels	X[c]	X	X	X	X	X	X
	Specific antibodies							X
Clinical laboratory assessments[d]	Hematology	X	X	X	X	X	X	X
	Clinical Chemistry	X	X	X	X	X	X	X
	Specialty tests[e]	X						X
	Anti-rHuPH20 Antibodies (binding/neutralizing)[f]	X		X		X	(X)[g]	X
	Hemolysis test[h]	X						X
	Immunogenicity test[f]		← X →					
	Urinalysis	X	X	X	X	X	X	X

Abbreviations: EOS=end-of-study; ET=early termination; IgG=immunoglobulin G; PK= pharmacokinetic(s)

[a] The assessments at the Screening/Baseline visit can be combined with the EOS visit assessments in Study TAK-771-3004. In such a case, the EOS visit in Study TAK-771-3004 and the Screening/Baseline visit in this study should be on the same day. If those visits happen on separate dates for a compelling reason, the Screening/Baseline visit in this study must be within 6 days at a maximum (it should be aligned with the timepoint of SC infusion) from the EOS visit in Study TAK-771-3004 and the assessments at both visits can still be combined.

[b] The visit will be 21 days after the last dose for 3-week dosing intervals and 28 days after the last dose for 4-week dosing intervals.

[c] For the assessment of dosage appropriateness for maintaining the target IgG trough level of IgG ≥5 g/L, the last 2 values measured in Study TAK-771-3004 will be used.

[d] Blood/urine samples will be collected before infusion.

[e] Specialty tests include: HBsAg, PCR for HCV, and PCR for HIV-1/2. Additional specialty tests may be performed if required to establish the etiology of an AE or of abnormal laboratory results.

[f] For those subjects who have (a) two consecutive anti-rHuPH20 binding antibody titers of ≥1:160 which are elevated from the subject's titers at baseline in the preceding Study TAK-771-3004 and (b) a moderate or severe AE which may be a result of immune-mediated response will be asked to undergo an immunogenicity test (Section 8.2.2.5.3).

[g] Anti-rHuPH20 antibodies will be measured every 24 weeks after Week 48.

[h] Hemolysis test will be performed in subjects aged 12 years or older. It should be performed within 72 hours of being informed of the hemoglobin level if there is a decrease of hemoglobin ≥2 g/dL compared to the previous visit, unless there is a clear alternative explanation.

APPENDIX 3 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Appendix 3.1 Adverse Event Definitions

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causality is suspected (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A TEAE is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or any existing event that worsens in either intensity or frequency following exposure to the investigational product.

Serious Adverse Event

An SAE is any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not and at any dose):

- Results in death
- Is life-threatening. Note: 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 which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of hospitalization.
  Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.
  For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:

Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

- Reviewed and confirmed seroconversion for HIV, HAV, HBV, HCV, HEV, or B19V

The sponsor and IQVIA are responsible for notifying the relevant regulatory authorities of related, unexpected SAEs, and related expected fatal/life-threatening SAEs. In addition, the sponsor is responsible for notifying the investigator in active site/the heads of the active study sites (and IRBs/ECs, if applicable) of all related, unexpected SAEs occurring during all interventional studies across the TAK-771 program.

The investigator is responsible for notifying the head of the study site and the sponsor of all SAEs or significant safety findings that occur at his or her site, and responding to requests when the sponsor, the head of the study site or IRB requires more information.

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information 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 and/or prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected disease progression and are part of the efficacy or effectiveness data collected in the study. Significant worsening of symptoms should be recorded as an AE.

Pre-existing Condition/Events Initiated Before Enrollment to This Study

Pre-existing conditions prior to initiation of study medication are described in the medical history, which were collected in the preceding Study TAK-771-3004 and will be used in this study. When there is an increase in the severity, duration or frequency of a pre-existing condition in the medical history during the subject is participating in this study, the event must be described on the AE eCRF in this study. Adverse events which occurred in Study TAK-771-3004 and are ongoing at the end of Study TAK-771-3004 will be recoded as AEs in this study. When there is an increase in the severity, duration or frequency of an AE that is ongoing from Study TAK-771-3004 during the subject is participating in this study, the event must be considered as a new AE and described on the AE eCRF in this study.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, or vital sign measure can represent an AE if the change is clinically relevant or if, during administration of investigational product, 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 waning 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 investigational product, 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), or vital sign which 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 should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, or vital sign is clinically significant and represents an AE.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs in this study are collected from the completion of EOS visit in Study TAK-771-3004 until the EOS/ET visit in this study and recorded as TEAEs. This includes events occurring during the screening phase of this study, regardless of whether or not investigational product is administered in this study.

All AEs/SAEs which had been reported until EOS/ET visit in this study must be followed to closure (the subject's health has returned to his/her baseline status in this study or all variables have returned to baseline in this study or until 30 days after EOS/ET visit, whichever comes first), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates. An event that changes in severity is captured as a new event. However, worsening medical conditions, signs or symptoms present prior to initiation of investigational product in this study, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product in this study, and the dyspepsia becomes severe and more frequent after first dose in this study, a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the subject's source documents and appropriate eCRFs.

The medical assessment of severity is determined by using the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "Not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "Related". The causality assessment must be documented in the subject's source documents and appropriate eCRFs.

The following additional guidance may be helpful:

Table A2. Adverse Event Relationship Categorization

Related	The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Outcome Categorization

The outcome of AEs must be documented in the subject's source documents and appropriate eCRFs during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

If applicable, action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF.

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the IB which the sponsor has provided under separate cover to all investigators.

The latest scientific findings available for device-used-in-clinical-trial is the User Manual which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

An SAE should be reported by the investigator to the sponsor or CRO via EDC within 24 hours/1 business day of the SAE occurrence, along with any relevant information. If the event cannot be reported via EDC during the required period, it should be reported to Emergency Reception Center for Safety Information via e-mail or fax using an SAE Form in the same time frame. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

The investigator should submit the original copy of the SAE Form to the sponsor.

Emergency Reception Center for Safety Information:

BELLSYSTEM24, Inc.
E-mail: Takeda@e-medinfo.com
FAX: 0120-490-849
TEL: 0120-490-749

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs in this study (regardless of relationship to investigational product) are collected from the completion of EOS visit in Study TAK-771-3004 until the EOS/ET visit in this study and must be reported to the Emergency Reception Center for Safety Information within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Emergency Reception Center for Safety Information within 24 hours of the reported first becoming aware of the event.

Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after the first dose of the investigational product, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Appendix 3.7 Fatal Outcome

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 investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawal should not be selected solely as a result of the subject's death.

Appendix 3.8 Pregnancy

All pregnancies are reported from the time informed (e)Consent is signed until the EOS/ET visit.

Any report of pregnancy for any female study participant must be reported within 24 hours using the Clinical Study Pregnancy Report Form.

A copy of the Clinical Study Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant 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 and approximately 30 calendar days and 1-year post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the SAE 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 SAE Form as well as the Clinical Study 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.

Appendix 3.9 Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor whether or not they result in an AE/SAE as described in Appendix 3.1. The report should be made according to the SAE reporting procedure, not via EDC but via e-mail or fax.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

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

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical 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 investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

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

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

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

Appendix 3.10 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible IRB/EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities (PMDA) of related, unexpected SAEs.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the TAK-771 program.

The investigator is responsible for notifying the head of study site of SAEs or significant safety findings that occur at his or her site and the head of study site is responsible for notifying it to local IRB/EC in accordance with IRB/EC procedures (see Appendix 1.5).

APPENDIX 4 CONTRACEPTIVE GUIDANCE

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) **Bilateral tubal occlusion**
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the women of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Refraining from heterosexual intercourse Do not engage in heterosexual intercourse (ie, sexual abstinence) that is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment.

APPENDIX 5 DIAGNOSTIC CRITERIA/DISEASE CLASSIFICATION

Source: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; Guidance for Industry - Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency, June, 2008 (Food and Drug Administration 2008).

Note: Items in bold are considered essential diagnostic features.

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, oliguria, cutaneous vasodilation/ vasoconstriction
- *Laboratory tests*: **positive blood culture**[b], leukocytosis (WBC count >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis

[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 partial pressure of carbon dioxide ($PaCO_2$) <32 mm Hg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms. For pediatric patients, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (Goldstein et al. 2005).

[b] Indwelling catheter or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IVIG 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.

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

[(c)] A blood culture positive for growth of *Streptococcus pneumoniae*, *Neisseria meningitides*, or *HIB*, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis

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, involucre**

Infection: Bacterial Pneumonia[(d)]

Note: The *Diagnosis of Pneumonia* eCRF is to be completed for all diagnoses of pneumonia (not only for diagnoses of bacterial pneumonia).

- *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 (partial pressure of arterial oxygen [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 or previous CXR)**

(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.[i] However, for the purposes of counting serious infection episodes in a clinical study of IVIG, 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 age 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.

(e) We recommend a deep expectorated sputum Gram stain 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.

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 ALP concentration (hepatic abscess) pyuria in renal abscess
- *Imaging studies*: **typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan**

[i] Further evaluation, in particular laboratory evaluation (culture and white blood count with differential to evaluate for the presence of immature neutrophils) and CXRs, should be aggressively pursued whenever a bacterial pneumonia is suspected.

APPENDIX 6 SCALES AND ASSESSMENTS

Toxicity Grading Scale for Laboratory Values

Laboratory values will be evaluated for abnormalities according to the toxicity grading scale provided in Table A3. Grade refers to severity: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening. Grading for LDH will use the same thresholds as defined for ALT and AST. Parameters not included in Table A3 will not be graded.

Grading will be performed by the sponsor for the development of the final report.

Table A3. Grading of Laboratory Parameters

Analyte	Direction	WNL is Grade 0	No Grade 1	Unit Grades	Grade 0 Low	Grade 0 High	Grade 1 Low	Grade 1 High	Grade 2 Low	Grade 2 High	Grade 3 Low	Grade 3 High	Grade 4 Low	Grade 4 High	Source[1]
ALP	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
ALT	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
AST	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
BUN	Increase	NO	NO	ULN	0.0	1.4	1.5	2.5	2.6	5.0	5.1	10	10.1	.	ECOG
Hemoglobin	Decrease	YES	NO	g/dL	.	.	10.0	.	8.0	9.9	6.5	7.9	0.0	6.4	ECOG
Lymphocytes	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Neutrophils	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Platelet Count	Decrease	YES	NO	x10^3/uL	.	.	75.0	.	50.0	74.9	25	49.9	0.0	24.9	ECOG
Potassium	Decrease	NO	NO	mmol/L	3.5	.	3.0	3.4	2.5	2.9	2.0	2.4	0.0	1.9	WHO
Potassium	Increase	NO	NO	mmol/L	0.0	5.5	5.6	6.0	6.1	6.5	6.6	7.0	7.1	.	WHO
Serum Creatinine	Increase	YES	NO	ULN	.	.	.	1.4	1.5	3.0	3.1	6.0	6.1	.	ECOG
Sodium	Decrease	NO	NO	mmol/L	136	.	130	135	123	129	116	122	0.0	115	WHO
Sodium	Increase	NO	NO	mmol/L	0.0	145	146	150	151	157	158	165	166	.	WHO
Serum Total Bilirubin	Increase	YES	YES	ULN	.	.	.	.	.	1.4	1.5	3.0	3.1	.	ECOG
WBC	Decrease	NO	NO	x10^3/uL	4.0	.	3.0	3.9	2.0	2.9	1.0	1.9	0.0	0.9	ECOG

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, WBC=white blood cell, WNL=within normal limits, ULN=upper limit of normal, ECOG=Eastern Cooperative Oncology Group, WHO=World Health Organization

[1] For references see Section 8.2.2.5.7.1

APPENDIX 7 ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AGT	antiglobulin test
ALP	alkaline phosphatase
ALT	alanine aminotransferase (synonymous with SGPT)
ASBI	acute serious bacterial infection
AST	aspartate aminotransferase (synonymous with SGOT)
B19V	parvovirus B19
BUN	blood urea nitrogen
C1q	complement 1q
C3	complement component 3
C4	complement component 4
CFR	Code of Federal Regulations
CH50	50% hemolytic complement activity of serum
CIC	circulating immune complex
CRA	clinical research associate
CRO	contract research organization
cSCIG	conventional subcutaneous immunoglobulin
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOS	end-of-study
ET	early termination
EU	European Union
EXSAS	safety analysis set for extension study
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Definition
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIB	Haemophilus influenzae
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IG	immunoglobulin
IGI	immune globulin infusion
IgG	immunoglobulin G
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
PID	primary immunodeficiency disease
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
Q1	1st quartile
Q3	3rd quartile
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SC	subcutaneous
SCIG	subcutaneous immunoglobulin
SOC	system organ class

Abbreviation	Definition
SY	subject-year
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
US	United States
WBC	white blood cell
WHO	World Health Organization

APPENDIX 8 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Amendment 1	24 May 2022	Japan
Original Protocol	31 Jan 2022	Japan