Title: A Phase 3, Open-label, Non-controlled, Multi-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with Primary Immunodeficiency Diseases (PID)

NCT Number: NCT04346108

Protocol Approve Date: 27-OCT-2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

PROTOCOL: TAK-664-3001

TITLE:	A Phase 3, Open-label, Non-controlled, Multi-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with Primary Immunodeficiency Diseases (PID)
SHORT TITLE:	Pharmacokinetics, Safety and Tolerability, and Efficacy Evaluation of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with PID
STUDY PHASE:	Phase 3
ACRONYM:	TAK-664-3001
DRUG:	IGSC, 20% / SHP664 / TAK-664 Immune Globulin Subcutaneous (Human), 20% Solution
IND NUMBER:	Non-IND
EUDRACT NUMBER:	Non-EUDRACT
SPONSOR:	Baxalta US Inc.* 300 Shire Way, Lexington, MA 02421 AND Baxalta Innovations GmbH* Industriestrasse 67, A-1221 Vienna *Baxalta is now part of Shire (Shire, a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited)
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter
PROTOCOL HISTORY:	**Protocol Amendment 2: 27 OCT 2020** **Replaces:** **Amendment 1: 06 DEC 2019** **Original Protocol: 25 SEP 2019**

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature:	Date:
PPD Senior Medical Director, Clinical Medicine Plasma-Derived Therapies Business Unit Research & Development	

Investigator's Acknowledgement

I have read this protocol for Study TAK-664-3001.

Title: A Phase 3, Open-label, Non-controlled, Multi-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with Primary Immunodeficiency Diseases (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 of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **27 Oct 2020**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Minor grammatical, editorial and/or administrative changes have been made.	To improve the readability and/or clarity of the protocol.	Throughout the document
Reviewed the wording "investigational product (IP)" and, if necessary, changed to "study drug (IGIV or IGSC)" or "IGIV"	To clarify IP according to the definition in Section 6.1 and 6.2	Throughout the document
Additional explanation for Shire	To clarify the corporate structure	Cover Page
Removal of Shire medical monitor	To revise the medical monitor processes.	Emergency Contact Information Appendix 3.4 Appendix 3.5 Appendix 3.8
Changed the address of Shire (email address POC@shire.com and telephone number) to email address of Takeda (CTMCOMPLAINT@TAKEDA.com) to report product quality complaints	To clarify the corporate structure	Product Quality Complaints
Changed the wording "the PMDA-approved IGSC product (Hizentra®)" to "the approved IGSC product (Hizentra®)"	To delete the unnecessary wording	Synopsis Section 9.3
Changed the wording for the time limit for the screening period to "Screening: 2 to 8 weeks before the IGIV treatment period"	Allow longer screening time period	Synopsis Section 4.1
Additional explanation for training for self-administration of SC infusions at home	To clarify that training for self-administration is performed by the investigator/designee	Synopsis Section 4.1
PK start is planned for SC infusion number 21 (which is at Week 21). If it is not possible to start at infusion 21, the infusion ± 1 week from infusion number 21 may be taken to start the PK. This infusion must be performed as a site infusion visit. Removal of the wording "at infusion 21" in the schema (Figure 2 in Section 1.2).	Allow some flexibility within this timeline	Synopsis Figure 2 in Section 1.2 Table 3 in Section 1.3 Section 4.1 Table 9 in Appendix 2
Changed the wording within exclusion criteria #3 "Subject has creatinine clearance (CLcr) value that is < 60% of normal for age and gender." to "Subject has presence of renal function impairment defined by estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2."	To minimize potential for error resulting from manual calculation of kidney function, an absolute cutoff is provided.	Synopsis Section 5.2

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **27 Oct 2020**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Adjust and align the wording in inclusion criteria # 5 and the relevant sections to "Subject has been receiving a consistent dose of IGIV over a period of at least 3 months prior to screening equivalent to approximately 200 - 600 mg/kg BW per 3-4 week period, as according to the product package insert.	Adjustment of wording to more closely align with IGIV product label in Japan.	Synopsis Section 4.3 Section 5.1 Section 6.4.3
Changed the wording about dosing in Epoch 2 "between 50 and 200 mg/kg of IGSC" to "approximately 50 - 200 mg/kg of IGSC" and in Epoch 3 "between 100 and 400 mg/kg of IGSC" to "approximately 100 - 400 mg/kg of IGSC".	Adjustment of wording	Synopsis Section 6.4.3
Addition of Extension Study option following completion of Study TAK-664-3001, with additional explanation including additional infusions if needed on a case by case basis, until the Extension Study is available for enrollment. Removal of the sentence "no aftercare is planned for this study" in Section 8.1.4.	Add Extension Study option and clarity for when the Extension Study is implemented	Synopsis Section 4.4 Section 5.2 Section 8.1.4
Changed the wording stating tolerability event to "An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to a TEAE related to study drug (IGIV or IGSC) infusion. A tolerability event is considered to have occurred if an infusion was not tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable."	To refine the definition of tolerability event with re-consideration	Synopsis Section 3.2.2 Section 9.7
Changed the wording "EQ-5D" to "EQ-5D-3L"	To clarify a version of the EQ-5D	Synopsis Section 3.2.2 Section 8.2.5.3 Section 9.8.1
Changed the wording "Treatment Preference (EOS, Epoch 2 and Epoch 3)" to "Treatment Preference (EOS/Early Termination)"	To align with the time point of treatment preference assessments in Table 4	Synopsis Section 3.2.2 Section 9.8.1

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **27 Oct 2020**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Addition in the tables of assessment of healthcare resource utilization to each epoch which were already in the text.	To clarify that healthcare resource utilization was assessed in each epoch	Table 1 to Table 4 in Section 1.3 Section 8.1.2.1 Section 8.1.2.2 Section 8.1.2.3 Section 8.1.2.4
Addition of the wording; "Dosing/Visit date should be 28 days (±1 day) after the last dose/visit." or 21 days accordingly.	Add more clarity for infusion interval	Table 1 to Table 4 in Section 1.3
Additional explanation for follow-up contacts with the subject/caregiver by the investigator/designee to each epoch.	To add post infusion follow-up in the start of each epoch.	Table 1 to Table 4 in Section 1.3 Section 8.1
Additional explanation in the tables for end of study procedures.	Add more clarity for assessments in case early discontinuation is occurred during Epoch 1	Table 1 and 2 in Section 1.3
Removal of the wording stating follow-up period and, if necessary, addition of "EOS/Early Termination Visit"	To align with the explanation for follow-up period in Section 8.1.3	Section 4.4 Section 6.8 Section 6.8.2 Appendix 3.2 Appendix 3.5 Appendix 3.8
Changed the wording for pregnancy test to "urine human chorionic gonadotropin (hCG) or serum beta-hCG (β-hCG) pregnancy test"	To correct the clinical test items for pregnancy test	Section 5.4.1 Appendix 3.8
Changed the wording "The dose (in mg IgG per kg BW) should remain stable throughout the study." to "For the duration of the study:"	Additional explanation for when the absolute dose can be increased	Section 6.4.3
Addition of section 6.4.4 Infusions /Description of Treatment	To clarify the procedures of infusion including infusion volumes, rates and training for home infusions	Section 6.4.4
Removal of the wording "Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording."	To align with instruction manual of thermometer	Section 6.5.3

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **27 Oct 2020**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Changed the wording for the collection period of prior therapy to "within/from 30 days prior to the date the informed consent document is signed" Changed the wording for the collection period of concomitant therapy to "between/from the date the informed consent document is signed until the EOS/Early Termination Visit"	To clarify for collection period of prior therapy and concomitant therapy	Section 6.8 Section 6.8.1 Section 6.8.2 Section 8.2.1.2
Addition of the wording for prohibited treatment; "Immunosuppressive drugs following transplantation"	To clarify that patients undergoing HSCT cannot be included in the study	Section 6.8.4
Additional explanation to capture study product treatment related information in each epoch	To align with Table 1, 2, 3, and CRF	Section 8.1.2.1 Section 8.1.2.2 Section 8.1.2.3
Addition of clarification of Early Termination procedures to the section of EOS.	Add more clarity for procedures and assessments at the Early Termination Visit	Section 8.1.2.4
Changed the wording "End-of-Study Visit" to "EOS/Early Termination visit"	To align with Table 4 and Section 8.1.2.4	Section 8.1.2.2 Section 8.2.5.3 Section 8.2.5.4 Section 8.1.5.5
Removal of the wording "including severity (mild, moderate, or severe as defined in Appendix 3)"	Severity of medical history is not collected.	Section 8.2.1.2
Changed the wording "intent-to treat population" to "All-Treated Set"	To align with the statistical analysis set in Section 9.4	Section 8.2.3.1
Changed the wording for assessment of ANC to "absolute neutrophil counts (ANCs) will be determined by laboratory calculation."	Add more clarity for ANC calculation	Section 8.2.4.4.1
Additional explanation for urine pregnancy test	To clarify that urine pregnancy test is performed at the study site	Section 8.2.4.4.2 Section 8.2.4.5
Removal of the wording "and urine hemosiderin"	To correct the duplicate notation	Section 8.2.4.4.4
Addition of the wording; "compared to the previous visit"	Add more clarity for shift of hemoglobin level	Section 8.2.4.4.4
Changed the wording for infusion related data	To align with the subject diary and CRF	Section 8.2.8

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **27 Oct 2020**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Changed the wording for overall summary of TEAE to "related TEAE"	Definition of overall summary for TEAE was reviewed and the current description "TEAE related to IP" is changed to "related TEAE".	Section 9.7.1.3
Additional explanation for period for data storage specified by the regulation	The records regarding the administration of the investigational drug (IGSC, 20%) must be maintained for 20 years because this drug is equivalent to the specified biological products.	Appendix 1.3
Addition of subsection "Alternative Approaches to Monitoring Due to COVID-19 or Other Unavoidable Circumstances"	Allow implementation of remote monitoring	Appendix 1.4
Time point for urinalysis at Visit 3 was added to the table to align urine sample procedures.	To align with Table 6	Table 7 in Appendix 2
Removal of the wording "medicinal product"	To correct the duplicate notation	Appendix 3.1
Changed the wording for AEs/SAEs to "All AEs/SAEs which had been reported until EOS/Early Termination Visit must be followed until closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline) or until 30 days after EOS/Early Termination Visit, whichever comes first."	Add more clarity the period for follow-up of AEs/SAEs	Appendix 3.2
Additional explanation for the categorization of "possibly related", "probably related", and "unlikely related	Relationship to study drug was categorized according to the CRF.	Appendix 3.3 (text and Table 11)

See Appendix 8 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to the Shire Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO) medical monitor using the details below.

CRO local medical monitor:

PPD

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

CRO local medical monitor (during business hours 9:00 AM through 5:00 PM Japan):

PPD

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

PPD

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, 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 Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product 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 (e.g., 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 using the "Product Complaint Data Collection Form" via the email address:

CTMCOMPLAINT@TAKEDA.com

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-664-3001	**Drug:** IGSC, 20%
Title of the study: A Phase 3, Open-label, Non-controlled, Multi-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with Primary Immunodeficiency Diseases (PID)	
Short title: Pharmacokinetics, Safety and Tolerability, and Efficacy Evaluation of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with PID	
Study phase: Phase 3	
Number of subjects (total and per treatment arm): The planned total sample size for this study is 16 subjects. Of the 16 subjects to be enrolled, 12 subjects are expected to complete Epoch 2 of the study, assuming a conservative dropout rate of 25% (overall dropout rates assumed for previous IGSC, 20% PID studies and other PID studies are generally 10%-15%). Subjects who prematurely discontinue the study will not be replaced. The number of subjects expected to complete Epoch 2 (12) is considered adequate for the evaluation of serum trough levels, safety and tolerability, and efficacy of IGSC, 20%, as well as for the assessment of disease activity and health-related quality of life (HRQoL). This study is not designed for statistical hypothesis testing and therefore the sample size is not based on statistical considerations such as study power, but instead mainly on consideration of the small size of the Japanese patient population with PID, a group of rare diseases. In Japan, the estimated prevalence of PIDs is 2 to 3 per 100,000 people and the estimated number of people affected is 2,900-3,500. Of the number of PID patients (2,900-3,500), an estimated 1,450-1,750 would be potential targets for immunoglobulin replacement therapy. In clinical practice, most patients requiring a switch to subcutaneous immunoglobulin (IGSC) (as is required by the study design) are already being treated with the approved IGSC product (Hizentra®). For example, in the Hizentra® New Drug Application (NDA) review report, the estimated number of patients who could receive immunoglobulin replacement therapy was 1,155, which is lower than the estimated 1,450-1,750 patients. Therefore, the number of potentially eligible patients for the planned study is extremely limited, making it infeasible to enroll a large sample size. Based on feasibility and the Sponsor's clinical experience with immunoglobulin G (IgG) products, a total sample size of 16 subjects (12 completers) is considered adequate for providing reliable estimates of trough levels (study primary objective), as well as reliable estimates of safety and tolerability, efficacy, disease activity and HRQoL (secondary objectives).	
Investigator(s): multicenter study	
Site(s) and region(s): Japan – 10-15 sites planned	
Study period (planned): Approximately 2 years	**Clinical phase:** Phase 3

Objectives:

Primary:

To assess serum trough IgG concentrations following weekly administration of IGSC, 20% (Epoch 2) and serum trough IgG concentration after biweekly administration of IGSC, 20% (Epoch 3), in Japanese subjects with PID.

Secondary:

- To assess serum trough IgG concentrations following every 3-week or every 4-week administration of IGIV (Epoch 1) in Japanese subjects with PID.
- To characterize the pharmacokinetic (PK) profiles of IGSC, 20% in Japanese subjects with PID following weekly subcutaneous (SC) administration (Epoch 2).
- To evaluate the safety and tolerability of IGSC, 20% (Epoch 2, Epoch 3) and of intravenous immunoglobulin (IGIV) (Epoch 1) in Japanese subjects with PID.
- To evaluate the efficacy of IGSC, 20% (Epoch 2, Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID.
- To assess quality of life aspects, treatment satisfaction, and treatment preference of Japanese subjects with PID (Epoch 1, Epoch 2, Epoch 3).

Endpoints/outcome measures corresponding to the primary and secondary objectives are defined in the statistical analysis section of this Synopsis.

Rationale: Approximately 2,900-3,500 people are diagnosed with PID in Japan, and the number of diagnosed patients is increasing. Furthermore, in Japan, the administration route for IG replacement therapy is mostly intravenous. This study (TAK-664-3001) evaluates serum trough IgG levels, safety and tolerability, and efficacy of IGSC, 20% (subcutaneous administration), and assesses disease activity and HRQoL in Epoch 1, Epoch 2 and Epoch 3, in subjects with PID in Japan. It aims to demonstrate maintenance of total IgG trough levels on IGSC, 20% (Epoch 2, Epoch 3) relative to IGIV (Epoch 1). The results from this study will extend/support the data obtained from two global (USA and EU) pivotal studies for IGSC, 20% in PID, to Japanese patients with PID. Data from this study will be used to support regulatory submission for the approval of IGSC, 20% in Japan.

Investigational product (IP), dose, and mode of administration:

This study comprises 3 Epochs (Parts):

Epoch 1 (13 weeks): IGIV: IGIV will be administered via IV infusions every 3 or 4 weeks, as per local product label, at the same dose as during pre-study period (equivalent to approximately 200 - 600 mg/kg BW at 3- or 4- week intervals).

Epoch 2 (24 weeks): approximately 50 - 200 mg/kg of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%), will be administered subcutaneously once a week. The dose in Epoch 2 will be adjusted so that it is an equivalent weekly dose of the dose administered in Epoch 1.

- Epoch 2, Period 1 (dose adjustment period, the first 12 weeks): IGSC, 20% is a 20% (weight per volume [w/v]) liquid formulation of human IGSC. Subjects will receive weekly SC infusions of IGSC, 20% at a weekly dosage calculated based on the dosage of pre-study IGIV treatment. The dose of IGSC, 20% (in mg/kg) will be adjusted if needed to maintain the IgG trough level ≥5 g/L.
- Epoch 2, Period 2 (including IgG trough evaluation period, the second 12 weeks): weekly SC administration of IGSC at the dosage established during the dose adjustment period.

Epoch 3 (12 weeks): approximately 100 - 400 mg/kg of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%), will be administered subcutaneously once every 2 weeks in a subset of 7 subjects. The dose in Epoch 3 will be twice the dose in Epoch 2.

Methodology: This is a phase 3, open-label, non-controlled, 3-epoch, multi-dose, multi-center study to evaluate serum trough levels of IgG, PK, efficacy, safety and tolerability of IGSC, 20% (Epoch 2 and Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID, as well as to assess disease activity and health-related quality of life (HRQoL). A total of 16 subjects will be enrolled, of whom 12 subjects are expected to complete the study. The Enrolled Set is defined in Section 9.4.

A schematic of the study design is provided in Figure 1. Each subject will receive IGIV treatment in Epoch 1 for a total of 13 weeks, and then switch to weekly SC treatment with IGSC, 20% in Epoch 2 for a total of 24 weeks; a subset of 7 subjects (of whom 5 subjects are expected to complete, assuming 25% dropout) will continue into Epoch 3 for a total of 12 weeks of biweekly SC treatment with IGSC, 20%.

The study consists of the following evaluation periods:

- Screening: 2 to 8 weeks before the IGIV treatment period
- Epoch 1: IGIV treatment period: 13 weeks

  All subjects will receive either 4 IGIV infusions at 4-week intervals, or 5 IGIV infusions at 3-week intervals, during Epoch 1.

- Epoch 2: IGSC treatment period: 24 weeks (total); PK, safety, tolerability, efficacy and HRQoL per Schedule of Activities in Section 1.3
  - Epoch 2, IGSC treatment period 1: 12 weeks of weekly IGSC, 20% dose adjustment period (infusion training will be performed during this period)

    All subjects from Epoch 1 will receive IGSC, 20% infusion every week during Epoch 2, as illustrated in Figure 1. If self-infusion is planned, self-infusion training must be provided at the study sites, i.e. weekly visits for self-infusion training are acceptable during the first 8 weeks of the treatment period. It is preferable that subsequent infusions between scheduled site infusion visits be performed at home, by the subject/caregiver, if in the opinion of the investigator, such treatment is safe and appropriate. In that case, the investigator/designee must have trained the subject or caregiver (documented the training), and must be satisfied that the subject or caregiver is capable of self-administration of SC infusions at home, before the subject or caregiver will be permitted to conduct the SC infusion at home.

    The dose of IGSC, 20% infusion will be adjusted if necessary, to maintain the target IgG trough level ≥5 g/L.
  - Epoch 2, IGSC treatment period 2: 12 weeks of weekly IGSC, 20% efficacy evaluation period (serum IgG trough levels and PK assessment)

    All subjects will continue to receive IGSC, 20% infusion every week (see Figure 1) at the dose established in the preceding study period. IgG trough level sampling for the efficacy assessments will be performed during the efficacy evaluation period. The IgG trough level will be assessed at Epoch 2 Week/Infusion numbers 17, 21 and 25 for all subjects.

A PK assessment will be performed in 5-7 subjects aged 12 years and older, within the last month on weekly IGSC treatment (in Epoch 2 period 2, see Figure 1). The following PK parameters will be assessed: area under the curve (AUC), apparent clearance (CL/F), maximum concentration (C_{max}), minimum concentration (C_{min}), and time to maximum concentration (T_{max}). PK serial sampling will start at Epoch 2 SC infusion number 21 ± 1. If the PK assessment cannot start at SC infusion number 21 (which is at Week 21), it may alternatively start at the infusion ± 1 week from infusion number 21, however the infusion at the start of the PK must be performed as a site infusion visit.

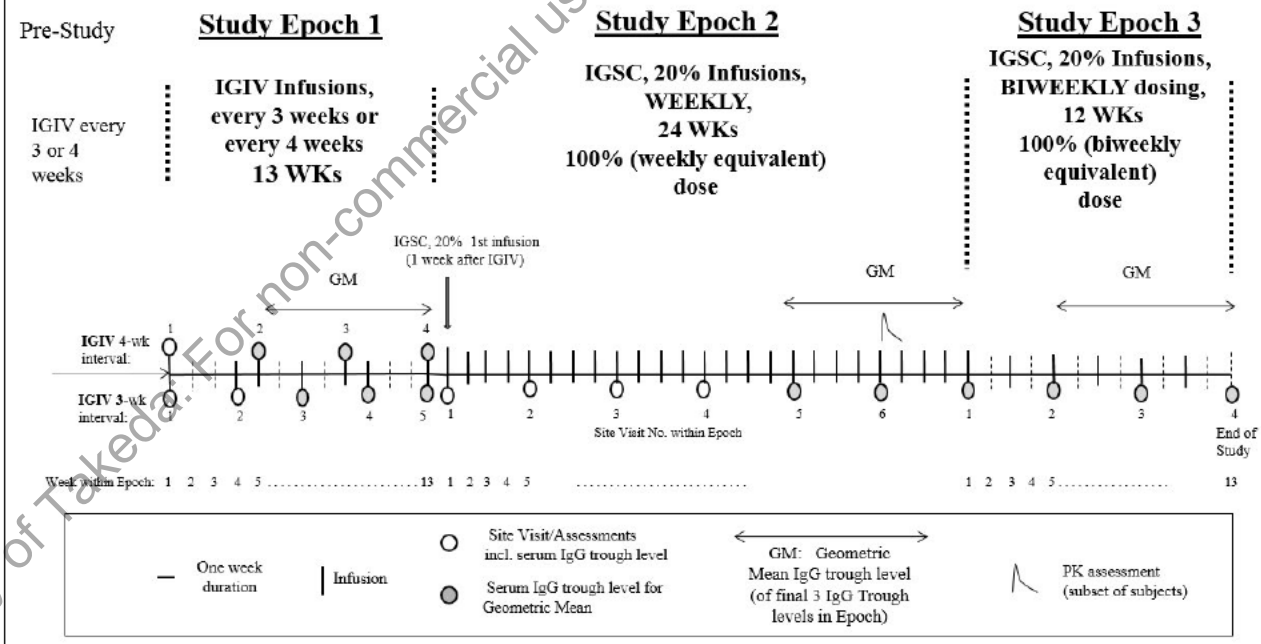
Serum samples will be collected at the following time points:

- Pre-infusion (i.e., trough level of previous infusion within 1 hour before infusion) (Day 0 of PK)
- Day 1 (± 6 hours, from infusion start time of Day 0)
- Day 3 (± 6 hours, from infusion start time of Day 0)
- Day 5 (± 6 hours, from infusion start time of Day 0)
- Day 7 (± 6 hours, from infusion start time of Day 0, pre-infusion to the next SC infusion)

- Epoch 3: IGSC, 20% treatment period: 12 weeks of biweekly IGSC, 20%; PK (serum IgG trough only), safety, tolerability and efficacy and HRQoL, per Schedule of Activities in Section 1.3

  At the discretion of the investigator and with agreement of the subject, a subset of 7 subjects in Epoch 2 treatment period 2 will continue for an additional 12 weeks of biweekly SC treatment with IGSC, 20%, in Epoch 3, at an equivalent dose (the dose in Epoch 3 will be twice the dose in Epoch 2). The serum IgG trough level will be assessed in Epoch 3 at Weeks 5, 9 and 13 for all subjects.

Figure 1. Study Design



Abbreviations: IGIV = intravenous immunoglobulin, IGSC = subcutaneous immunoglobulin, WKs = weeks, GM = geometric mean, IgG = immunoglobulin G, PK = pharmacokinetic

Inclusion and Exclusion Criteria:

Inclusion Criteria:

Each subject must meet all the following criteria to enroll in the study:

1. Be of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
2. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving antibody formation and requiring gammaglobulin replacement, as defined according to the International Union of Immunological Societies (IUIS) Committee 2017 (Picard et al., 2018). The diagnosis must be confirmed by the Medical Director prior to treatment with IGIV.
3. Subject is 2 years or older at the time of screening.
4. Written 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.
5. Subject has been receiving a consistent dose of IGIV over a period of at least 3 months prior to screening equivalent to approximately 200 - 600 mg/kg BW per 3 - 4 week period, as according to the product package insert.
6. Subject has a serum trough level of IgG ≥5 g/L at screening.
7. Subject has not had a serious bacterial infection within the 3 months prior to screening.
8. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from the study:

1. Subject has a known history of or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2.
2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
    a. Persistent alanine aminotransferase (ALT) and aspartate amino transferase (AST) >2.5 times the upper limit of normal (ULN) for the testing laboratory
    b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] ≤500/mm^3)
3. Subject has presence of renal function impairment defined by estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2.
4. Subject has been diagnosed with or has a malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix), unless the disease-free period prior to screening exceeds 5 years.
5. Subject is receiving anti-coagulation therapy or has a history of thrombotic episodes (including deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening or a history of thrombophilia.
6. Subject has abnormal protein loss (protein losing enteropathy, nephrotic syndrome).

7. Subject has anemia that would preclude phlebotomy for laboratory studies according to standard practice at the site.
8. Subject has an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IV immunoglobulin, SC immunoglobulin, and/or Immune Serum Globulin (ISG) infusions.
9. Subject has immunoglobulin A (IgA) deficiency (IgA less than 0.07g/L), known anti IgA antibodies, and a history of hypersensitivity.
10. Subject is on preventative (prophylactic) systemic antibacterial antibiotics at doses sufficient to treat or prevent bacterial infections, and cannot stop these antibiotics at the time of screening.
11. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening.
12. Subject has a bleeding disorder, or a platelet count less than 20,000/μL, or, in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of subcutaneous therapy.
13. Subject has total protein >9 g/dL or myeloma, or macroglobulinemia (IgM) or paraproteinemia.
14. Women of childbearing potential meeting any one of the following criteria:
    a. Subject presents with a positive pregnancy test.
    b. Subject is breast feeding.
    c. Subject intends to begin nursing during the course of the study.
    d. Subject does not agree to employ adequate birth-control measures (e.g. intrauterine device, diaphragm or condom [for male partner] with spermicidal jelly or foam, or birth control pills/patches) throughout the course of the study.
15. Subject has participated in another clinical study and has been exposed to an IP or device within 30 days prior to study enrollment.
16. Subject is scheduled to participate in another non-observational (interventional) clinical study involving an IP or device during the course of the study (exception: an extension study of TAK-664-3001).
17. Subject has severe dermatitis that would preclude adequate sites for safe product administration.

Maximum duration of subject participation in the study:

- Screening: 2 to 8 weeks before the IGIV treatment period
- Epoch 1: IGIV treatment period: 13 weeks
- Epoch 2: IGSC, 20% treatment period 1: 12 weeks
- Epoch 2: IGSC, 20% treatment period 2: 12 weeks
- Epoch 3: IGSC, 20%: 12 weeks

Endpoints and statistical analysis:

Analysis Populations /Analysis Sets:

Analysis of serum trough levels of IgG, efficacy, safety and tolerability, and disease activity and HRQoL data will be based on the following analysis sets (analysis populations), as defined:

- Enrolled Set: All screened subjects for whom an enrollment number has been assigned. Screened subjects will consist of all subjects who have signed informed consent. Background summaries (e.g., subject disposition) will be based on the Enrolled Set.
- All-Treated Set: All enrolled subjects who received at least 1 dose of study drug (IGIV or IGSC). Analysis of efficacy, safety and tolerability, and disease activity and HRQoL will be based on the All-Treated Set. Since this study is non-randomized, the Safety Set (defined as all dosed subjects) and Full Analysis Set (defined as all randomized and dosed) are identical, and therefore simply referred to as All-Treated Set for this study.
- Pharmacokinetic Analysis Set (PKAS): All-Treated Set who have had at least 1 evaluable serum IgG concentration value and have had no major protocol deviations or events that would affect the serum IgG concentration analysis results. Analysis of PK data (serum IgG trough concentrations and PK profiles) will be based on the PKAS.

Primary Endpoint:

Total serum trough levels of IgG (total serum trough IgG antibodies) measured during Period 2 of Study Epoch 2 (weekly administration of IGSC, 20%) and during Epoch 3 (biweekly administration of IGSC, 20%).

Secondary Endpoints:

Endpoints cover PK, safety and tolerability, efficacy, and disease activity and HRQoL.

Pharmacokinetic endpoints and parameters in Epoch 1, Epoch 2 and Epoch 3, as indicated:

- Total serum trough levels of IgG (total serum trough IgG antibodies) measured during Epoch 1 (every 3 weeks or every 4 weeks administration of IGIV)
- PK parameters for total serum levels of IgG and for IgG subclasses (Epoch 2): AUC, CL/F, C_{max}, C_{min}, and T_{max}
- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae [HIB], Hepatitis B Virus [HBV]) (Epoch 1, Epoch 2, Epoch 3)

Safety and Tolerability Endpoint(s):

Safety endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3:

- Occurrence of treatment-emergent adverse events (TEAEs), including but not limited to: study drug (IGIV or IGSC)-related and non-related*, serious, nonserious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs

  * Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to study drug (IGIV or IGSC) will be considered a related adverse event (AE), and any AE recorded as "unlikely related" or "not related" will be considered an unrelated AE.

- Clinical laboratory outcomes: raw (actual) values and change from baseline

  Clinically significant, treatment-emergent changes in clinical laboratory measurements will be recorded in the study database (internal or external) as TEAEs.

- Vital signs: raw (actual) values and change from baseline and change from pre-infusion to post-infusion

Baseline is defined as the last non-missing value before the initial dose of study drug (IGIV or IGSC).

Tolerability endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3:

- Occurrence of tolerability events related to the infusion of study drug (IGIV or IGSC)

  An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to a TEAE related to study drug (IGIV or IGSC) infusion.

  A tolerability event is considered to have occurred if an infusion was not tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable.

Efficacy endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3:

- Annual rate of validated acute serious bacterial infections per subject
- Annual rate of all infections per subject
- 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

Disease activity and HRQoL endpoints in Epoch 1, Epoch 2 and Epoch 3:

- QoL: PEDS-QL (Varni et al., 1999), SF-36 (Ware and Sherbourne, 1992), EQ-5D-3L Health Questionnaire (Shaw et al., 2005)
- Treatment Satisfaction (Life Quality Index, TSQM-9) (Daly et al., 1991)
- Treatment Preference (End-of-Study [EOS]/Early Termination)

Endpoint details will be provided in the study Statistical Analysis Plan (SAP).

Statistical analysis

Statistical details will be provided in the SAP.

The primary objective of this study is to assess serum trough IgG concentrations following weekly administration of IGSC, 20% and serum trough IgG concentration after biweekly administration of IGSC, 20%, in Japanese subjects with PID, covering Epoch 2 and Epoch 3.

The secondary objectives focus on PK, safety and tolerability, efficacy, and disease activity and HRQoL and cover Epoch 1, Epoch 2 and Epoch 3 (see Section 3.1).

PK analysis will be based on the PKAS, and safety and tolerability, efficacy, and disease activity and HRQoL analyses on the All-Treated Set.

Study endpoint data (serum IgG trough levels, safety and tolerability, and efficacy, as well as disease activity and HRQoL) will be analyzed using descriptive statistics. No statistical hypothesis testing will be performed, and no interim analysis is planned.

Statistical summaries will be presented, as appropriate, by epoch, by treatment period, by treatment period and visit/timepoint, and overall.

Baseline is defined as the last non-missing value before initial dose of study drug (IGIV or IGSC). 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 (SD), minimum value, maximum value. Categorical endpoints/outcome measures (e.g., adverse events) will be summarized in terms of number and percent of subjects and number of occurrences in each category.

For serum IgG trough levels, descriptive statistics will also include geometric mean (GM) and the corresponding 2-sided 95% confidence interval (CI). No formal statistical comparison (hypothesis testing) of treatments will be performed. CIs are for descriptive purposes. Caution should be exhibited in their interpretation as this study is not designed for hypothesis testing.

For disease activity and HRQoL data, raw (actual) and change from baseline values will be summarized descriptively, and summaries will be provided by treatment period and pre-defined age group.

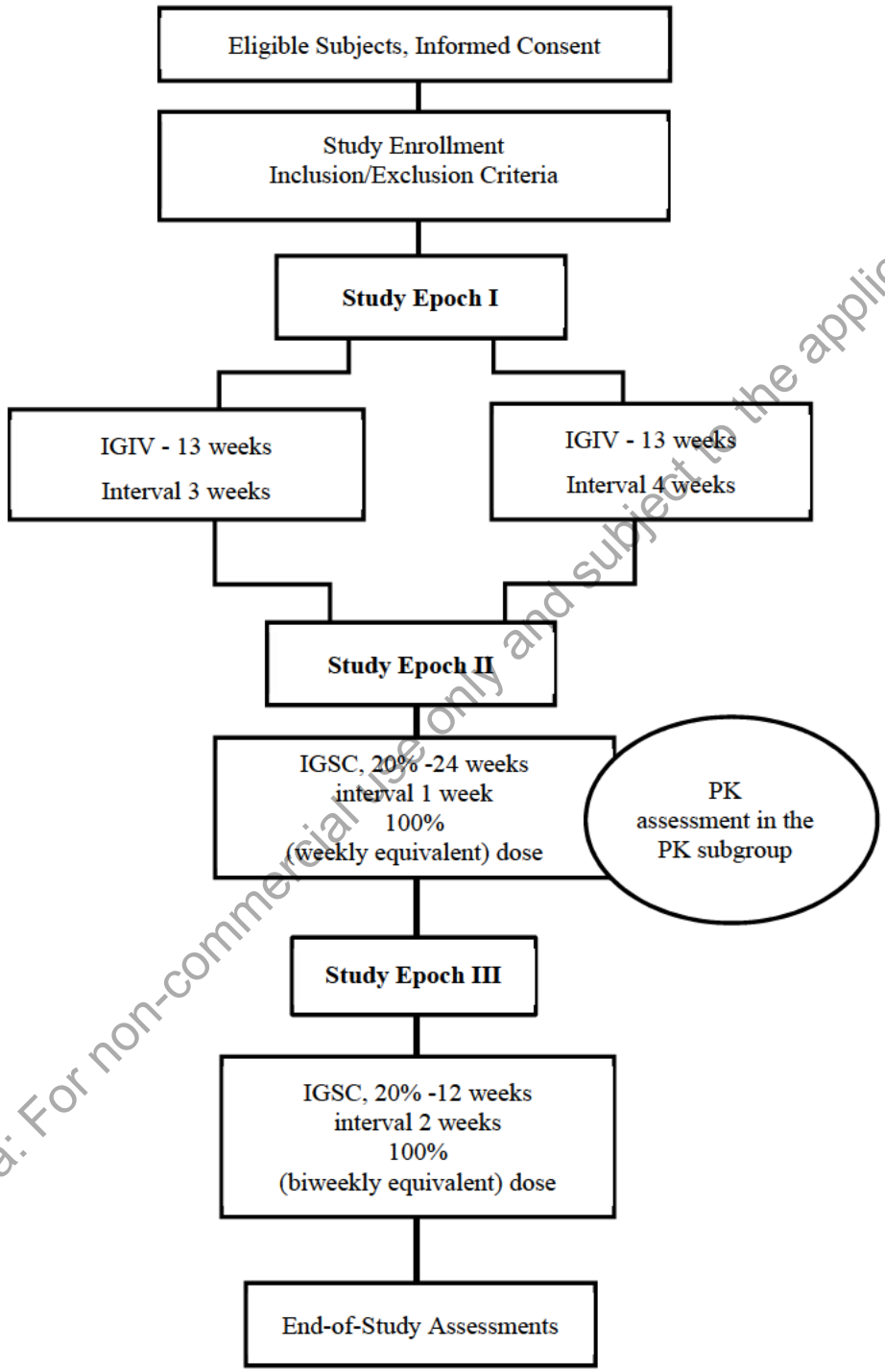
For the QoL endpoint: 2-7 years (PEDS-QL, observer: parent), 8-13 years (PEDS-QL, observer: subject), and 14 years and older (SF 36, observer: subject); EQ-5D-3L Health Questionnaire: 2-11 years EQ-5D-3L (observer: parent) and 12 years and older EQ-5D-3L (observer: subject).

For the Treatment Satisfaction (Life Quality Index) endpoint: 2-13 years (observer: parent) and 14 years and older (observer: subject). Treatment Satisfaction Questionnaire for Medication (TSQM-9): 2-12 years (observer: parent) and 13 years and older (observer: subject).

For the Treatment Preference endpoint: 2-13 years (observer: parent) and 14 years and older (observer: subject).

1.2 Schema

Figure 2. Study Schematic Diagram



Abbreviations: IGIV = intravenous immunoglobulin, IGSC = subcutaneous immunoglobulin, IgG = immunoglobulin G, PK = pharmacokinetics

1.3 Schedule of Activities

Table 1. Schedule of Study Procedures and Assessments
SCREENING and STUDY EPOCH 1
IV Treatment 3-Week (± 1 Day)[a] Treatment Interval

Procedure/Assessment	Screening/ Baseline Visit	Visit No./Week in Study Epoch 1[e]					(One Week Later Start Study Epoch 2)
		Visit 1 Week 1	Visit 2 Week 4	Visit 3 Week 7	Visit 4 Week 10	Visit 5 Week 13	
Location	Site	Site	Site	Site	Site	Site	
Informed Consent	X						
Eligibility Criteria	X						
Medical History	X						
Physical Exam	X	X			X		
Vital Signs	X	X	X	X	X	X	
Laboratory Assessments[b]	X[c]	X	X	X	X	X	
Concomitant Medication and Non-Drug Therapies	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	
Collection/Review Diaries		X	X	X	X	X	
Study Product Treatment		X[d]	X[d]	X[d]	X	X	
Quality of Life Assessments		X					
Treatment Satisfaction Assessment		X					
Healthcare Resource Utilization		X	X	X	X	X	

[a] For the treatment interval. Dosing date should be 21 days (±1 day) after the last dose.
[b] For laboratory assessments specific to the visits, see Table 6. At an infusion visit the assessments are to be taken pre-infusion, unless specified otherwise.
[c] Including retention samples to be taken at screening or prior to the first infusion. For subject 12 years or older approximately 2.5 mL serum and 2 mL plasma. For children younger than 12 years of age, approximately 2 mL plasma will be obtained.
[d] Follow-up contact with the subject/caregiver by the investigator/designee will be necessary 3-5 days after completion of the first 3 infusions of each epoch in order to document AEs that may have occurred.
[e] Any early discontinuation during Epoch 1 should complete End-of-Study procedures as described in Table 4, but excluding the quality of life, treatment satisfaction and treatment preference assessments

Table 2. Schedule of Study Procedures and Assessments
SCREENING and STUDY EPOCH 1
IV Treatment 4-Week (± 1 Day)[a] Treatment Interval

Procedure/Assessment	Screening/ Baseline Visit	Visit No./Week in Study Epoch 1[e]				(One Week Later Start Study Epoch 2)
		Visit 1 Week 1	Visit 2 Week 5	Visit 3 Week 9	Visit 4 Week 13	
Location	Site	Site	Site	Site	Site	
Informed Consent	X					
Eligibility Criteria	X					
Medical History	X					
Physical Exam	X	X		X		
Vital Signs	X	X	X	X	X	
Laboratory Assessments[b]	X[c]	X	X	X	X	
Concomitant Medication and Non-Drug Therapies	X	X	X	X	X	
Adverse Events		X	X	X	X	
Collection/Review Diaries		X	X	X	X	
Study Product Treatment		X[d]	X[d]	X[d]	X	
Quality of Life Assessments		X				
Treatment Satisfaction Assessment		X				
Healthcare Resource Utilization		X	X	X	X	

[a] For the treatment interval. Dosing date should be 28 days (±1 day) after the last dose.
[b] For laboratory assessments specific to the visits, see Table 7. At an infusion visit the assessments are to be taken pre-infusion, unless specified otherwise.
[c] Including retention samples to be taken at screening or prior to the first infusion. For subject 12 years or older approximately 2.5 mL serum and 2 mL plasma. For children younger than 12 years of age, approximately 2 mL plasma will be obtained.
[d] Follow-up contact with the subject/caregiver by the investigator/designee will be necessary 3-5 days after completion of the first 3 infusions of each epoch in order to document AEs that may have occurred.
[e] Any early discontinuation during Epoch 1 should complete End-of-Study procedures as described in Table 4, but excluding the quality of life, treatment satisfaction and treatment preference assessments

Table 3. Schedule of Study Procedures and Assessments
STUDY EPOCH 2
SC Treatment 7 Day (± 1 Day)[a] Treatment Interval

Procedure/Assessment	Visit No./Week in Study Epoch 2[g]						
	Treatment at Study Site[b]						Treatment at Home[d]
Location	Site Visit 1 Week 1	Site Visit 2 Week 5	Site Visit 3 Week 9	Site Visit 4 Week 13	Site Visit 5 Week 17	Site Visit 6 Week 21	Home
Informed Consent							
Inclusion/Exclusion							
Medical History							
Physical Exam[e]	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	
Laboratory Assessments[c]	X[f]	X	X	X	X	X	
Concomitant Medication and Non-Drug Therapies	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Collection/Review Diaries[e]	X	X	X	X	X	X	
Study Product Treatment	X[h]	X	X	X	X	X	X[h]
Quality of Life Assessments	X						
Treatment Satisfaction Assessment	X						
Healthcare Resource Utilization	X	X	X	X	X	X	X

[a] Visit date should be 28 days (±1 day) after the last visit. For the treatment interval prior to the start of the PK the window of ±1 day does NOT apply.
[b] Mandatory site visit at least once every 4 weeks. If additional site visits occur for study product treatment, PE, Lab assessments, and Diary review are not mandatory.
[c] For laboratory assessments specific to the mandatory site visits, see Table 8. At an infusion visit the assessments are to be taken pre-infusion unless specified otherwise. PK starts (pre-infusion) at site visit 6. If it is not possible to start at Visit 6, PK can be started at 1 week before or after Visit 6, but the subject need to visit the site for IP treatment.
[d] Infusions between mandatory site visits are to be home treatments, if possible - if investigator confirms (and documents) that subject/caregiver is capable of administering infusions.
[e] At mandatory site visits only.
[f] Including retention samples to be taken prior to the first infusion. For subject 12 years or older approximately 2.5 mL serum and 2 mL plasma. For children younger than 12 years of age, approximately 2 mL plasma will be obtained.
[g] All study subjects completing or exiting the study should complete the End of Study/Early Termination Procedures as described in Table 4.
[h] Follow-up contact with the subject/caregiver by the investigator/designee (irrespective of whether the infusion was performed at the study site or at home) will be necessary 3-5 days after completion of the first 3 infusions of each epoch in order to document AEs that may have occurred.

Table 4. Schedule of Study Procedures and Assessments
STUDY EPOCH 3
SC Treatment 14 Day (± 1 Day)[a] Treatment Interval

Procedure/Assessment	Visit No./Week in Study Epoch 3				
	Treatment at Study Site[b]				Treatment at Home[d]
Location	**Site Visit 1 Week 1**	**Site Visit 2 Week 5**	**Site Visit 3 Week 9**	**End-of-Study/Early Termination Visit[f] Site Visit 4 Week 13**	**Home**
Informed Consent					
Inclusion/Exclusion					
Medical History					
Physical Exam[e]	X	X	X	X	
Vital Signs	X	X	X	X	
Laboratory Assessments[c]	X	X	X	X	X
Concomitant Medication and Non-Drug Therapies	X	X	X	X	X
Adverse Events	X	X	X	X	X
Collection/Review Diaries	X	X	X	X	
Study Product Treatment	X[g]	X[g]	X		X[g]
Quality of Life Assessments	X			X	
Treatment Satisfaction Assessment	X			X	
Treatment Preference Assessment				X	
Healthcare Resource Utilization	X	X	X	X	X

[a] For the treatment interval. Visit date should be 28 days (±1 day) after the last visit.
[b] Mandatory site visit at least once every 4 weeks.
[c] For laboratory assessments specific to the mandatory site visits, see Table 10. At an infusion visit the assessments are to be taken pre-infusion unless specified otherwise.
[d] Infusions between mandatory site visits are to be home treatments, if possible - if investigator confirms (and documents) that subject/caregiver is capable of administering infusions
[e] At mandatory site visits only.
[f] All study subjects completing or exiting the study should complete the End of Study/Early Termination Procedures as described above.
[g] Follow-up contact with the subject/caregiver by the investigator/designee (irrespective of whether the infusion was performed at the study site or at home) will be necessary 3-5 days after completion of the first 3 infusions of each epoch in order to document AEs that may have occurred.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Primary immunodeficiency diseases (PID) 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) (Picard et al., 2018) distinguishes 9 PID categories according to common disease phenotypes.

Therapeutic options for the treatment of infections in PID with antibody production defects include standard antibiotic treatment and administration of IgG as a replacement therapy. Antibody replacement can be administered either intravenously (IV) or subcutaneously (SC) (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 IV administration, though in the past several years, SC administration has gained popularity. When given weekly or every other week, IGSC leads to higher trough serum IgG concentrations than monthly IV infusions (Berger, 2011, Gardulf et al., 1995, Gardulf et al., 1991).

Immunoglobulin replacement therapy administered by the subcutaneous route (IGSC) is considered to be effective, safe and is also well accepted by subjects 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 IGSC is the lower incidence of systemic adverse events compared to IGIV (Berger, 2013, Suez et al., 2016). The immunoglobulin preparations currently approved for SC use in the US, Canada and the European Union (EU) are formulated at 10% to 20% (only the 20% IGSC formulation Hizentra® is available in Japan). 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).

2.2 Product Background and Clinical Information

A major disadvantage of conventional SC administration is that only small volumes can be infused at each site, necessitating the use of multiple sites on a weekly or biweekly (every-other-week) basis. Generally, using a 16% solution, approximately 20 mL can be infused per site; an adult patient receiving 400 mg/kg BW every 4 weeks thus would require at least 3 sites per week or 12 sites per month. Even though weekly or biweekly administration has the added advantage of maintaining better trough levels than monthly IV infusions, the requirement of multiple needle insertions has been a deterrent for many patients.

The pharmacokinetics of SC administration are different from that of IV infusions, and bioavailability of immunoglobulin administered subcutaneously may be less 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).

IGSC, 20%, a new immunoglobulin preparation for SC use, is formulated as a 20% solution. The manufacturing process for IGSC, 20% shares common manufacturing steps with IGI, 10%, with the exception of the final ultra-/diafiltration and formulation steps. The IgG subclass distribution is within the normal range for human serum, and the product comprises antibodies to specific bacterial and viral pathogens. The preparation retains all Fab and Fc mediated functions of the native IgG molecule. The higher protein concentration leads to smaller infusion volumes compared with less concentrated products.

The clinical development program of IGSC, 20% is based on the EMEA Guidelines for normal human normal immunoglobulin for SC and IV use (Committee for Human Medicinal Products, 2010, Committee for Proprietary Medicinal Products, 2002) and the Food and Drug Administration (FDA) guidance to industry (Food and Drug Administration, 2008). The safety, tolerability, and efficacy of IGSC, 20% in primary immunodeficiency have been demonstrated in adult and pediatric patients in two phase 2/3 studies in Europe (Study 170903) (Borte et al., 2017) and in North America (Study 170904) (Suez et al., 2016).

Refer to the latest version of the IGSC, 20% investigator's brochure (IB) for detailed information on product properties and nonclinical and clinical studies.

2.3 Study Rationale

Approximately 2,900-3,500 people are diagnosed with PID in Japan, and the number of diagnosed patients is increasing. Furthermore, in Japan, the administration route for IG replacement therapy was historically mostly intravenous. This study (TAK-664-3001) evaluates serum trough IgG levels, safety and tolerability, and efficacy of IGSC, 20% (subcutaneous administration), and assesses disease activity and HRQoL in Epoch 1, Epoch 2 and Epoch 3, in subjects with PID in Japan. It aims to demonstrate maintenance of total IgG trough levels on IGSC, 20% (Epoch 2, Epoch 3) relative to IGIV (Epoch 1). The results from this study will extend/support the data obtained from two global (USA and EU) pivotal studies for IGSC, 20% in PID, to Japanese patients with PID. Data from this study will be used to support regulatory submission for the approval of IGSC, 20% in Japan.

2.4 Benefit/Risk Assessment

IGSC, 20% is a new immunoglobulin preparation supplied as a 20% solution for SC use that contains functionally intact IgG. The IgG subclass distribution for the final product is within the normal range for human serum and comprises antibodies to specific bacterial and viral pathogens. IGSC, 20% is a benefit to patients with poor vein access, to pediatric patients because of the low volume to be administered, and to those patients interested in home-based therapy since it can be self-administered. The higher concentration allows for a smaller infusion volume, which may reduce the number of infusion sites and/or duration of infusion.

Final results from Study 170904 and Study 170903 indicate that IGSC, 20% administered SC is efficacious and well tolerated in adult and pediatric subjects with PID. Results of the integrated safety analysis support the similarity of IGSC, 20% safety profile to the licensed IGI, 10% administered SC.

Tolerability was demonstrated by the high rate of IGSC, 20% infusions completed without interruption (>99.9%). In Study 170904, a median maximum infusion rate of 60 mL/hr per site and a median maximum infusion volume of 39.5 mL per site were tolerated without an increase in the rate of local or systemic AEs.

Efficacy was demonstrated by the low annual rate of validated acute serious bacterial infections (ASBI), meeting the predefined criteria of 1 or less validated ASBI per year in subjects with PID treated with IGSC, 20% either at the same weekly-equivalent dose as with the previously used IG product (170903) or at a dose adjusted to achieve the bioavailability of IGIV 10% (170904). The low total infection rates and the maintenance of protective trough levels of total IgG and pathogen-specific antibodies in both studies conducted with IGSC, 20% are further evidence of the effectiveness of IGSC, 20% treatment as replacement therapy in subjects with PID.

Quality of life assessments and other patient-outcome assessments suggest that subjects appreciate the treatment convenience offered by IGSC, 20% preparation.

Immunoglobulin preparations have been used extensively in clinical practice for more than 25 years, to treat a variety of disorders, including PID. The incidence of systemic reactions following administration of currently available SC preparations is much less than with IV administration as documented in numerous studies (Chapel et al., 2000, Gardulf et al., 1995). The safety profile of IGSC, 20% was consistent with expected adverse reactions for GAMMAGARD LIQUID administered SC. Across IGSC, 20% studies, the incidence of related systemic AEs was low (0.029 events/infusion). Headache, the most common systemic adverse reaction during the IGSC, 20% development program occurred in 1% to less than 10% of subjects.

Potential risks with IGSC, 20% replacement therapy such as hypersensitivity, transmission of infectious agents, hemolysis, thrombotic and thromboembolic events, renal adverse reaction and aseptic meningitis syndrome were not observed during clinical development with IGSC, 20%. Therefore, the benefits of IGSC, 20% for treatment of patients with PID outweigh the risks.

Always refer to the latest version of the IGSC, 20% IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of IGSC, 20%.

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 (Integrated Addendum to ICH E6[R1]: Guideline for Good Clinical Practice E6[R2] Current Step 4 version, 9 November 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

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

The primary objective of the study is to assess serum trough IgG concentrations following weekly administration of IGSC, 20% (Epoch 2) and serum trough IgG concentration after biweekly administration of IGSC, 20% (Epoch 3), in Japanese subjects with PID.

3.1.2 Secondary Objectives

The secondary objectives of this study are listed below:

- To assess serum trough IgG concentrations following every 3-week or every 4-week administration of IGIV (Epoch 1) in Japanese subjects with PID.
- To characterize the PK profiles of IGSC, 20% in Japanese subjects with PID following weekly SC administration (Epoch 2).
- To evaluate the safety and tolerability of IGSC, 20% (Epoch 2, Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID.
- To evaluate the efficacy of IGSC, 20% (Epoch 2, Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID.
- To assess quality of life aspects, treatment satisfaction, and treatment preference of Japanese subjects with PID (Epoch 1, Epoch 2, Epoch 3).

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the total serum trough levels of IgG (total serum trough IgG antibodies) measured during Period 2 of Study Epoch 2 (weekly administration of IGSC, 20%) and during Epoch 3 (biweekly administration of IGSC, 20%).

For a detailed description of endpoints and the planned statistical analysis, refer to Section 9.

3.2.2 Secondary Endpoints

Endpoints cover PK, safety and tolerability, efficacy, and disease activity and HRQoL.

Pharmacokinetic endpoints and parameters in Epoch 1, Epoch 2 and Epoch 3, as indicated:

- Total serum trough levels of IgG (total serum trough IgG antibodies) measured during Epoch 1 (every 3 weeks or every 4 weeks administration of IGIV)

- PK parameters for total serum levels of IgG and for IgG subclasses (Epoch 2): AUC, CL/F, C_{max}, C_{min}, and T_{max}
- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, HIB, HBV) (Epoch 1, Epoch 2, Epoch 3)

Safety and Tolerability Endpoint(s):

Safety endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3:

- Occurrence of TEAEs, including but not limited to: study drug (IGIV or IGSC)-related and non-related*, serious, nonserious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs

  * Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to study drug (IGIV or IGSC) will be considered a related AE, and any AE recorded as "unlikely related" or "not related" will be considered an unrelated AE.

- Clinical laboratory outcomes: raw (actual) values and change from baseline

  Clinically significant, treatment-emergent changes in clinical laboratory measurements will be recorded in the study database (internal or external) as TEAEs.

- Vital signs: raw (actual) values and change from baseline and change from pre-infusion to post-infusion

Baseline is defined as the last non-missing value before the initial dose of study drug (IGIV or IGSC).

Tolerability endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3:

- Occurrence of tolerability events related to the infusion of study drug (IGIV or IGSC)

  An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to a TEAE related to study drug (IGIV or IGSC) infusion.

  A tolerability event is considered to have occurred if an infusion was not tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable.

Efficacy endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3:

- Annual rate of validated acute serious bacterial infections per subject
- Annual rate of all infections per subject

- 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

Disease activity and HRQoL endpoints in Epoch 1, Epoch 2 and Epoch 3:

- QoL: PEDS-QL (Varni et al., 1999), SF-36 (Ware and Sherbourne, 1992), EQ-5D-3L Health Questionnaire (Shaw et al., 2005)
- Treatment Satisfaction (Life Quality Index, TSQM-9) (Daly et al., 1991)
- Treatment Preference (EOS/Early Termination)

Endpoint details will be provided in the study SAP.

Table 5. Objectives and Endpoints

Objective	Endpoint(s)
Primary	
• To assess serum trough IgG concentrations following weekly administration of IGSC, 20% (Epoch 2) and serum trough IgG concentration after biweekly administration of IGSC, 20% (Epoch 3) in Japanese subjects with PID.	• Total serum trough levels of IgG (total serum trough IgG antibodies) measured during Period 2 of Study Epoch 2 (weekly administration of IGSC, 20%), and during Epoch 3 (biweekly administration of IGSC, 20%)
Secondary	
• To assess serum trough IgG concentrations following every 3-week or every 4-week administration of IGIV (Epoch 1) in Japanese subjects with PID. • To characterize the PK profiles of IGSC, 20% in Japanese subjects with PID following weekly SC administration (Epoch 2).	• Total serum trough levels of IgG (total serum trough IgG antibodies) measured during Epoch 1 (every 3 weeks or every 4 weeks administration of IGIV) • PK parameters for total serum levels of IgG and for IgG subclasses (Epoch 2): AUC, CL/F, C_{max}, C_{min}, and T_{max} • Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, HIB, HBV) (Epoch 1, Epoch 2, Epoch 3)

Table 5. Objectives and Endpoints

Objective	Endpoint(s)
• To evaluate the safety and tolerability of IGSC, 20% (Epoch 2, Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID.	• Occurrence of TEAEs, including but not limited to: study drug (IGIV or IGSC)-related and non-related*, serious, nonserious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs *Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to study drug (IGIV or IGSC) will be considered a related AE, and any AE recorded as "unlikely related" or "not related" will be considered an unrelated AE. • Clinical laboratory outcomes: raw (actual) values and change from baseline • Vital signs: raw (actual) values and change from baseline, and change from pre-infusion to post-infusion • Occurrence of tolerability events related to the infusion of study drug (IGIV or IGSC)
• To evaluate the efficacy of IGSC, 20% (Epoch 2, Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID.	• Annual rate of validated acute serious bacterial infections per subject • Annual rate of all infections per subject • 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 quality of life aspects, treatment satisfaction, and treatment preference of Japanese subjects with PID (Epoch 1, Epoch 2, Epoch 3).	• QoL: PEDS-QL, SF-36, EQ-5D-3L Health Questionnaire • Treatment Satisfaction (Life Quality Index, TSQM-9) • Treatment Preference (EOS/Early Termination)

4. STUDY DESIGN

4.1 Overall Design

This is a phase 3, open-label, non-controlled, 3-epoch, multi-dose, multi-center study to evaluate serum trough levels of IgG, PK, efficacy, safety and tolerability of IGSC, 20% (Epoch 2 and Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID, as well as to assess disease activity and HQoL. A total of 16 subjects will be enrolled, of whom 12 subjects are expected to complete Epoch 2 of the study.

A schematic of the study design is provided in Figure 1. Each subject will receive IGIV treatment in Epoch 1 for a total of 13 weeks, then switch to weekly SC treatment with IGSC, 20% in Epoch 2 for a total of 24 weeks; a subset of 7 subjects (of whom 5 subjects are expected to complete, assuming 25% dropout) will continue into Epoch 3 for a total of 12 weeks of biweekly SC treatment with IGSC, 20%.

The study consists of the following evaluation periods:

- Screening: 2 to 8 weeks before the IGIV treatment period
- Epoch 1: IGIV treatment period: 13 weeks
- All subjects will receive either 4 IGIV infusions at 4-week intervals, or 5 IGIV infusions at 3-week intervals, during Epoch 1.
- Epoch 2: IGSC treatment period: 24 weeks (total); PK, safety, tolerability, efficacy and HRQoL, per Schedule of Activities in Section 1.3
  - Epoch 2, IGSC treatment period 1: 12 weeks of weekly IGSC, 20% dose adjustment period (infusion training will be performed during this period)

    All subjects from Epoch 1 will receive IGSC, 20% infusion every week during Epoch 2, as illustrated in Figure 1. If self-infusion is planned, self-infusion training must be provided at the study sites, i.e. weekly visits for self-infusion training are acceptable during the first 8 weeks of the treatment period. It is preferable that subsequent infusions between scheduled site infusion visits be performed at home, by the subject/caregiver, if in the opinion of the investigator, such treatment is safe and appropriate. In that case, the investigator/designee must have trained the subject or caregiver (documented the training), and must be satisfied that the subject or caregiver is capable of self-administration of SC infusions at home, before the subject or caregiver will be permitted to conduct the SC infusion at home.

    The dose of IGSC, 20% infusion will be adjusted if necessary, to maintain the target IgG trough level ≥5 g/L.

- Epoch 2, IGSC treatment period 2: 12 weeks of weekly IGSC, 20% efficacy evaluation period (serum IgG trough levels and PK assessment)

  All subjects will continue to receive IGSC, 20% infusion every week (see Figure 1) at the dose established in the preceding study period. IgG trough level sampling for the efficacy assessments will be performed during the efficacy evaluation period. The IgG trough level will be assessed at Epoch 2, Week/Infusion numbers 17, 21 and 25 for all subjects.

  A PK assessment will be performed in 5-7 subjects aged 12 years and older, within the last month on weekly IGSC treatment (in Epoch 2 period 2, see Figure 1). The following PK parameters will be assessed: AUC, CL/F, C_{max}, C_{min}, and T_{max}. PK serial sampling will start at Epoch 2 SC infusion number 21 ± 1. If the PK assessment cannot start at SC infusion number 21 (which is at Week 21), it may alternatively start at the infusion ± 1 week from infusion number 21, however the infusion at the start of the PK must be performed as a site infusion visit.

  Serum samples will be collected at the following time points:

  - Pre-infusion (i.e., trough level of previous infusion within 1 hour before infusion) (Day 0 of PK)
  - Day 1 (± 6 hours, from infusion start time of Day 0)
  - Day 3 (± 6 hours, from infusion start time of Day 0)
  - Day 5 (± 6 hours, from infusion start time of Day 0)
  - Day 7 (± 6 hours, from infusion start time of Day 0, pre-infusion to the next SC infusion)

- Epoch 3: IGSC, 20% treatment period: 12 weeks of biweekly IGSC, 20%; PK (serum IgG trough only), safety, tolerability, efficacy and HRQoL, per Schedule of Activities in Section 1.3

  At the discretion of the investigator and with agreement of the subject, a subset of 7 subjects in Epoch 2 treatment period 2 will continue for an additional 12 weeks of biweekly SC treatment with IGSC, 20%, in Epoch 3, at an equivalent dose (the dose in Epoch 3 will be twice the dose in Epoch 2). The serum IgG trough level will be assessed in Epoch 3 at Weeks 5, 9 and 13 for all subjects.

4.2 Scientific Rationale for Study Design

This phase 3, open-label study is designed to evaluate serum trough levels of IgG, efficacy, and safety and tolerability of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with PID, as well as to assess disease activity and HRQoL. The clinical data in Japanese subjects with PID from study TAK-664-3001 will be evaluated with the clinical data of 122 subjects from the overseas pivotal clinical studies (Study 170903 and Study 170904).

4.3 Justification for Dose

For all study subjects, the immunoglobulin dose during the pre-study period (equivalent to approximately 200 - 600 mg/kg BW at 3- or 4-week intervals, as according to the product package insert) will be maintained upon study entry into study TAK-664-3001. In replacement therapy, the dose may need to be individualized for each patient dependent on the serum trough levels of IgG and clinical response. The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 g/L and aim to be within the reference interval of serum IgG for age.

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 55 weeks. The study will be completed in approximately 2 years. Subjects who wish to enroll in the Extension Study, and complete Study TAK-664-3001 prior to the approval and implementation of the Extension Study, may extend participation in Epoch 2 or Epoch 3 at the same dose and treatment interval as they were last receiving (for a maximum of 4 months), to enable roll-over. The EOS visit will be postponed for such subjects until they enroll in the Extension Study.

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

4.5 Sites and Regions

The study will be conducted in Japan at approximately 10 to 15 sites.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written 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. Be of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
2. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving antibody formation and requiring gammaglobulin replacement, as defined according to the IUIS Committee 2017 (Picard et al., 2018). The diagnosis must be confirmed by the Medical Director prior to treatment with IGIV.
3. Subject is 2 years or older at the time of screening.
4. Written 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.
5. Subject has been receiving a consistent dose of IGIV over a period of at least 3 months prior to screening equivalent to approximately 200 - 600 mg/kg BW per 3-4 week period, as according to the product package insert.
6. Subject has a serum trough level of IgG ≥5 g/L at screening.
7. Subject has not had a serious bacterial infection within the 3 months prior to screening.
8. 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 a known history of or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2.
2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
    a. Persistent alanine aminotransferase (ALT) and aspartate amino transferase (AST) >2.5 times the upper limit of normal (ULN) for the testing laboratory

b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] $\leq 500/mm^3$)

3. Subject has presence of renal function impairment defined by estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2.
4. Subject has been diagnosed with or has a malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix), unless the disease-free period prior to screening exceeds 5 years.
5. Subject is receiving anti-coagulation therapy or has a history of thrombotic episodes (including deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening or a history of thrombophilia.
6. Subject has abnormal protein loss (protein losing enteropathy, nephrotic syndrome).
7. Subject has anemia that would preclude phlebotomy for laboratory studies according to standard practice at the site.
8. Subject has an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IV immunoglobulin, SC immunoglobulin, and/or Immune Serum Globulin (ISG) infusions.
9. Subject has immunoglobulin A (IgA) deficiency (IgA less than 0.07g/L), known anti IgA antibodies, and a history of hypersensitivity.
10. Subject is on preventative (prophylactic) systemic antibacterial antibiotics at doses sufficient to treat or prevent bacterial infections, and cannot stop these antibiotics at the time of screening.
11. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening.
12. Subject has a bleeding disorder, or a platelet count less than 20,000/µL, or, in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of subcutaneous therapy.
13. Subject has total protein >9 g/dL or myeloma, or macroglobulinemia (IgM) or paraproteinemia.
14. Women of childbearing potential meeting any one of the following criteria:
    a. Subject presents with a positive pregnancy test.
    b. Subject is breast feeding.
    c. Subject intends to begin nursing during the course of the study.

d. Subject does not agree to employ adequate birth-control measures (e.g. intrauterine device, diaphragm or condom [for male partner] with spermicidal jelly or foam, or birth control pills/patches) throughout the course of the study.

15. Subject has participated in another clinical study and has been exposed to an IP or device within 30 days prior to study enrollment.
16. Subject is scheduled to participate in another non-observational (interventional) clinical study involving an IP or device during the course of the study (exception: an extension study of TAK-664-3001).
17. Subject has severe dermatitis that would preclude adequate sites for safe product administration.

5.3 Restrictions

Not applicable.

5.4 Reproductive Potential

There are no adequate data from the use of IGSC, 20% in pregnant or lactating women.

Maternally administered IGIV products have been shown to cross the placenta, increasingly during the third trimester.

The effects of IGSC, 20% 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 IP. 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 IP.

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)
- 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 human chorionic gonadotropin (hCG) or serum beta-hCG (β-hCG) pregnancy test at the Screening 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
- Double-barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit (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.

6. STUDY INTERVENTION

6.1 Investigational Product

The IP Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) is a liquid formulation of IgG. At least 95% (EU specifications) / 96% (US specifications) of the protein in the study drug is gamma globulin. The product is isotonic and has a pH of 4.6 to 5.1 (diluted at 1% in saline). It contains 18.0 to 22.0 g of protein per 100 mL and approximately 0.2-0.3 M glycine. The liquid preparation is clear and colorless or pale yellow or light brown. It contains no preservatives.

Additional information is provided in the current Investigator's Brochure.

Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) will be provided by the sponsor and will be labeled as IP.

6.2 IGIV (Non-Investigational Product)

The IGIV product administered during Epoch 1 is an approved IV immunoglobulin procured locally, which is administered as per local product label. Additional information is provided in the appropriate product package label. IGIV will not be managed by interactive response technology (IRT) and will not be provided by the sponsor as IP.

The IGIV used in Epoch 1 will be the same IGIV preparation being administered to the patient prior to enrollment in the study and will be sourced by the sites. The lot number of IGIV used for the study should be recorded in eCRF by clinical site personnel.

6.3 Blinding the Treatment Assignment

Not applicable.

6.4 Administration

6.4.1 Interactive Response Technology for Investigational Product Management

This is an open-label, non-controlled study where all subjects will be enrolled to receive IGSC, 20%. Individual subject numbers are automatically assigned to all subjects via the IRT as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned according to the sequence of subject presentation for study participation.

IRT will be used for IP supply management in Epoch 2 and Epoch 3 (not Epoch 1), inventory management, supply ordering, IP expiration tracking, temperature excursion reporting, and return of IP.

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

6.4.2 Allocation of Subject Numbers

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

Once a unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

6.4.3 Dosing

In Epoch 1, IGIV will be administered via IV infusions every 3 or 4 weeks, as per local product label, at the same dose as during pre-study period (equivalent to approximately 200 - 600 mg/kg at 3- or 4-week intervals).

In Epoch 2 (24 weeks), approximately 50 - 200 mg/kg of IGSC, 20% will be administered subcutaneously once a week. The dose in Epoch 2 will be adjusted so that it is an equivalent weekly dose of the dose administered in Epoch 1.

- In Epoch 2, Period 1 (dose adjustment period, the first 12 weeks), the dose will be adjusted, if needed, to maintain an IgG trough level ≥5 g/L.
- In Epoch, 2 Period 2 (including IgG trough evaluation period, the second 12 weeks), the dose established during the dose adjustment period will be administered.

In Epoch 3, approximately 100 - 400 mg/kg of IGSC, 20% will be administered subcutaneously once every 2 weeks in a sub-set of 7 subjects. The dose in Epoch 3 will be twice the dose in Epoch 2.

For the duration of the study: In order to maintain the same dose in mg/kg when there has been an increase in BW (kg), it will be necessary to increase the absolute dose (in g or mg) administered. The IGSC, 20% dose 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%, 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 IGSC, 20% dose should not be changed.

6.4.4 Infusions/Description of Treatment

Infusion Volumes

For subjects with a BW >= 40 kg, up to 60 mL should be administered per infusion site if well tolerated. For subjects with a BW <40 kg it is recommended that for the initial two infusions the volume be limited to 20 mL per infusion site, but if well tolerated the volume should be increased to a maximum of 60 mL for subsequent infusions.

Infusion Rates

For the initial two infusions, the infusion rate should be approximately 10-20 mL/h/site, and appropriate pump tubing set should be used. Especially for the first infusion, the pump tubing set for approximately 10 mL/h/site is recommended. For subsequent infusions, if well tolerated, the pump tubing set up to 60 ml/h/site can be used. It is suggested to complete the administration within 2 hours due to the potential formation of particles caused by siliconized syringes.

Multiple infusion sites can be used for infusion simultaneously as determined by the subject and investigator. Infusions will be conducted with a pump.

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.

Infusion Parameters	**First 2 Infusions**		**Subsequent Infusions**	
	Patients <40 kg	**Patients ≥ 40kg**	**Patients < 40kg**	**Patients ≥ 40kg**
Volume (mL/site)	≤20	≤60	≤60	
Rate (mL/h/site)	10-20		≤60	

Site of Administration

The infusion site should be selected in an area that is free of tenderness, erythema, or induration, and the overlying skin should be intact. It is recommended that the infusion sites be rotated to avoid any single infusion site being used repeatedly within a short time interval. In addition, when two or more SC infusion sites are to be used during an infusion, each site should be at least 10 cm (4 inches) apart.

Multiple infusion sites can be used simultaneously. The number of infusion sites will depend on the subject's total dose in mL; there is no maximum to the number of infusion sites. To calculate the number of sites to be used, divide the total volume to be infused by the maximum volume/site to be infused. Up to 10% overage per site is permitted, if necessary, to avoid starting a new site for only a few milliliters. For example, if the dose is 124 mL, and 2 sites are to be used, the dose per site can be 62 mL per site rather than using 3 sites.

6.4.5 Unblinding the Treatment Assignment

Not applicable.

6.4.6 Dose Modification

In Epoch 2, Period 1 (dose adjustment period), subjects will receive weekly SC infusions of IGSC, 20% at a weekly dosage calculated based on the dosage in Epoch 1 (which is based on pre-study IGIV treatment). The dose of IGSC, 20% (in mg/kg) will be adjusted if needed to maintain IgG trough level ≥5 g/L.

In Epoch 2, Period 2, the dosage established during the dose adjustment period (Period 1) will be administered.

In Epoch 3, the dose will be twice the dose in Epoch 2.

The dose in mg/kg may be increased during the study if clinically indicated (e.g. 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 patient file, and the adjusted dose should be entered in the case report forms (CRFs).

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

6.5.1 Packaging

IGSC, 20% is supplied in single-dose glass vials that nominally contain 4 g and 8 g of protein per vial.

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

6.5.2 Labeling

Labels containing study information and pack identification are applied to the IP vial and carton. The product will be labeled according to the valid regulatory requirements for clinical studies.

6.5.3 Storage

The investigator has overall responsibility for ensuring that IP is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. IGSC 20% is distributed or administered by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the IP vial/carton labels as they are distributed or administered.

IP must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the IP is maintained within an established temperature range. The investigator 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. 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 IP 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 IP that could affect the integrity of the product(s), e.g., fumigation of a storage room.

All IP for the sponsor's studies must be stored in a securely locked, substantially constructed room or cabinet according to all applicable local, state, and/or national laws. Limited, controlled access to these IPs must be maintained, as well as chain of custody, for all IP movement.

6.6 Drug Accountability

Investigators will be provided with sufficient amounts of the IP to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the IP, documenting shipment content and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing IP. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer/dispense the IP only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the IP carrying his/her treatment assignment. All administered/dispensed medication will be documented in the subject's source and/or other IP record. The investigator is responsible for ensuring the retrieval of all study supplies from subjects.

Due to the health/safety concerns with returning the IP container, the investigator must request that subjects keep the empty IP packaging after use and return it to the site for drug accountability purposes.

No IP stock or returned inventory from a Shire-sponsored study 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, state, 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.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned IP, and empty/used IP packaging are to be sent to a nominated contractor on behalf of the sponsor. IP being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel 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. Validated electronic return systems (i.e., IRT) do not require a shipment form. Returned IP must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any IP prior to shipment. Shipment of all returned IP must comply with local, state, and national laws.

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

6.7 Subject Compliance

Subjects must be instructed to bring unused IP and empty/used IP packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused IP that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.8 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 within 30 days prior to the date the informed consent document is signed until the EOS/Early Termination Visit, and must be recorded in the subject's source document.

6.8.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days prior to the date the informed consent document is signed. Prior treatment information must be recorded in the subject's source document.

6.8.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the date the informed consent document is signed until the EOS/Early Termination Visit. Concomitant treatment information must be recorded in the subject's source document.

6.8.3 Permitted Treatment

Treatments not listed in Section 6.8.4 are considered allowable.

6.8.4 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 for a period of up to 72 hours if required due to trauma or a scheduled procedure). 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 (e.g. trimethoprim/sulfamethoxazole twice a week for pneumocystis) which are not treated by immunoglobulin can be used and should be recorded as concomitant medication.
- Other IgG products after first exposure to study drug.
- Hyper immune serum
- Immunosuppressive drugs following transplantation

Pre-medication on the Day of Product Administration:

- IV-Product Administration
  Subjects who are prone to AEs occurring in conjunction with infusions of IGIV products are often pre-medicated with antihistamines, antipyretics, and/or steroids. In this study, however, pre-medications should be avoided, if possible, for both IV and SC infusions. Subjects should only receive pre-medication (acetaminophen/non-steroidal anti-inflammatory drugs [NSAIDs], corticosteroids, and antihistamines) prior to IV infusions if the same AE(s) were seen prior to the study with 2 or more IGIV preparations. In addition, should an AE occur during or following 2 or more infusions during this study, pre-medications can be used for subsequent IV or SC infusions. The use of these medications must be recorded in the concomitant medication record. Reactions that occur during the IV infusions do not necessitate automatic pretreatment for the SC infusions.
- SC-Product Administration
  In this study, subjects should not receive pre-medication for SC infusions unless an adverse reaction of at least moderate severity, not resolving with a reduction in the infusion rate, occurs during or after at least 2 infusions. Should this occur, subjects may be pretreated with antipyretics, corticosteroids or antihistamines at the discretion of the investigator. Topical local anesthetics may be used if the needle insertion was intolerable in prior infusions. Subjects who have a history of using topical anesthetics may use these topical anesthetics for SC infusions. The use of such pre-medications must be recorded on the concomitant medication record.

Treatments not listed above are considered allowable.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If study drug (IGIV or IGSC) is discontinued, regardless of the reason, the subject will discontinue participation in the study. Whenever possible, all discontinued subjects should also undergo the protocol-specified evaluations at EOS/Early Termination Visit. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the study drug (IGIV or IGSC), and the total amount of study drug (IGIV or IGSC) administered must be recorded in the source documents.

Subjects who discontinue 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 document. If a subject is discontinued for more than 1 reason, each reason should be documented in the source 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 institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (e.g., 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 (office visit or telephone contact). 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 return to the site for final safety evaluations and return any unused IP.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Periods

The study will consist of 3 epochs. A tabulated schedule of study procedures and assessments is provided for Study Epoch 1 in Table 1 (IV treatment 3-week treatment interval) and Table 2 (IV treatment 4-week treatment interval), for Study Epoch 2 in Table 3, and for Study Epoch 3 in Table 4. Clinical laboratory assessments are detailed in Section 8.2.

Follow-up contact with the subject/caregiver by the investigator/designee (irrespective of whether the infusion was performed at the study site or at home) will be necessary 3-5 days after completion of the first 3 infusions of each epoch in order to ensure that the documentation of AEs that may have occurred is being completed correctly.

8.1.1 Screening / Baseline Visit

Any subject who provides informed consent (i.e., signs and dates the informed consent form [ICF]) is considered a subject in the study.

The written informed consent for all procedures and assessments for the conduct of the study must be obtained prior to any study related procedure.

Every single subject who enters the study will get a unique subject identification code (SIC).

The following procedures and assessments will be performed at the Screening / Baseline Visit (see Table 1 and Table 2):

- Availability of signed informed consent
- Assessment of eligibility
- Medical history
- Physical exam
- Vital signs (see Section 8.2.4.3)
- Clinical laboratory assessments (see Table 6 for Epoch 1 3-week interval treatment and Table 7 for Epoch 1 4-week interval treatment)
- Retention samples should be taken at screening or prior to the first infusion. For subjects 12 years or older approximately 2.5 mL serum and 2 mL plasma will be taken and stored frozen at –70°C or below at the central lab in the event further testing is needed. For children younger than 12 years of age, approximately 2 mL of plasma will be obtained.
- Concomitant medication and non-drug therapies

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been administered study drug (IGIV or IGSC). The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All relevant screening data will be collected and reported, regardless of screening outcome.

Subjects who fail to meet eligibility criteria may be re-screened; they will be assigned a different SIC at re-screening.

8.1.2 Treatment Period

8.1.2.1 Study Epoch 1

During Epoch 1, subjects will receive either 5 IGIV infusions at 3-week intervals or 4 IGIV infusions at 4-week intervals.

The following procedures and assessments will be performed at the study site (detailed scheduled provided in Table 1 for 3-week interval treatment and in Table 2 for 4-week interval treatment):

- Physical exam
- Vital signs (see Section 8.2.4.3)
- Clinical laboratory assessments (see Table 6 for 3-week interval treatment and Table 7 for 4-week interval treatment)
- Concomitant medication and non-drug therapies
- Adverse events
- Collection/review of patient diaries
- Quality of life and treatment satisfaction assessments (see Section 8.2.5.3 and Section 8.2.5.4)
- Healthcare Resource Utilization
- Study Product Treatment
  Collection of Infusion related data e.g.: lot number, start and stop time, infusion site, infusion rate (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.

8.1.2.2 Study Epoch 2

During Epoch 2, subjects will receive weekly IGSC, 20% infusions.

The following procedures and assessments will be performed at the study site or during treatment at home, if applicable (detailed schedule provided in Table 3):

- Physical exam
- Vital signs (see Section 8.2.4.3)
- Clinical laboratory assessments (see Table 8)
- Concomitant medication and non-drug therapies
- Adverse events
- Collection/review of patient diaries
- Quality of life and treatment satisfaction assessments (see Section 8.2.5.3 and Section 8.2.5.4). (Treatment Preference at the EOS/Early Termination Visit, for subjects completing the study in Epoch 2.)
- Healthcare Resource Utilization
- Study Product Treatment
  Collection of Infusion related data e.g.: Med ID number (six digit), start and stop time, infusion site, infusion rate (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.

8.1.2.3 Study Epoch 3

During Epoch 3, subjects will receive biweekly IGSC, 20% infusions.

The following procedures and assessments will be performed at the study site or during treatment at home, if applicable (detailed schedule provided in Table 4):

- Physical exam
- Vital signs (see Section 8.2.4.3)
- Clinical laboratory assessments (see Table 10)
- Concomitant medication and non-drug therapies
- Adverse events
- Collection/review of patient diaries

- Quality of life, treatment satisfaction and treatment preference assessments (see Section 8.2.5.3, Section 8.2.5.4 and Section 8.2.5.5)
- Healthcare Resource Utilization
- Study Product Treatment
  Collection of Infusion related data e.g.: Med ID number (six digit), start and stop time, infusion site, infusion rate (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.

8.1.2.4 End-of-Study Visit/Early Termination Visit

The EOS Visit will be conducted 1 week following the last IP infusion (subject in Epoch 2) or 2 weeks following the last IP infusion (subject in Epoch 3). The following procedures and assessments should also be completed in the event of an early termination visit (if the subject need to terminate the study before study completion).

The following procedures and assessments will be performed at the study site (see Table 4):

- Physical exam
- Vital signs (see Section 8.2.4.3)
- Clinical laboratory assessments (see Table 10)
- Concomitant medication and non-drug therapies
- Adverse events
- Collection/review of patient diaries
- Quality of life, treatment satisfaction and treatment preference assessments (see Section 8.2.5.3, Section 8.2.5.4 and Section 8.2.5.5)
- Healthcare Resource Utilization

8.1.3 Follow-up Period

There is no follow-up period.

8.1.4 Additional Care of Subjects after the Study

An extension study is planned, to offer continuation of treatment and for the additional collection of treatment-related data. The subjects who complete Epoch 2 or Epoch 3 can be enrolled in the Extension Study.

8.2 Study Assessments

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including gender, age, and race will be collected prior to the subject receiving the first dose of study drug (IGIV or IGSC).

8.2.1.1 Height and Weight

Height and weight will be measured and recorded in the subject's source documents.

8.2.1.2 Medical and Medication History

Medical and medication history will be collected and recorded in the subject's source documents.

At screening, the subject's medical history will be described for the following body systems or surgery, and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from 30 days prior to the date the informed consent document is signed until completion/termination will be recorded on the concomitant medications and non-drug therapies electronic case report forms (eCRFs).

8.2.2 Pharmacokinetics

8.2.2.1 Serum IgG Trough Levels

Serum IgG trough levels (total serum levels of IgG and IgG subclasses IgG1, IgG2, IgG3, and IgG4) will be determined according to the schedule described in Appendix 2 by using standard assay methods for the determination of total IgG concentration and IgG subclasses.

The blood drawing for the IgG determination will always take place before the infusion is administered.

8.2.2.2 Pharmacokinetic Profiles

PK parameters for total serum levels of IgG and for IgG subclasses (IgG1, IgG2, IgG3, and IgG4) will be evaluated during Study Epoch 2 in a subset of 5-7 subjects aged 12 years and older only.

The following parameters will be assessed: AUC, CL/F, C_{max}, C_{min}, and T_{max}.

For a schedule of pharmacokinetic testing see Appendix 2.

8.2.2.3 Specific Antibodies

Specific antibody tests (quantitative method) to Clostridium tetani toxoid, HIB and HBV will be performed.

For a schedule of specific antibody testing see Appendix 2.

8.2.3 Efficacy

8.2.3.1 Acute Serious Bacterial Infection Rate

Infections will be reported as AEs and the number and types of infections will be determined. ASBIs 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 ASBI rate will be calculated as the mean number of acute serious bacterial infections per subject per year in the All-Treated Set.

8.2.3.2 Infections

1. The annual rate of all infections per subject.
   All infections will be reported as AEs and the number and types of infections will be determined.
2. Days not able to attend school/work or to perform normal daily activities due to illness/infection.
   Days not able to attend school/work or to perform normal daily activities due to illness/infection, will be collected using diaries or other source data options throughout the study and will be transcribed to CRFs.
3. Days on antibiotics
   Days on antibiotics will be collected using diaries or other source data options throughout the study and will be transcribed to CRFs.
4. Number of hospitalizations due to illness/infection and length of stay (in days)
   Admissions to a hospital as an in-patient and the number of days in hospital will be collected using diaries or other source data options throughout the study and will be transcribed to CRFs.
5. Number of acute (urgent or unscheduled) physician visits due to illness/infection
   Acute (urgent or unscheduled) physician visits due to illness/infection, will be collected using diaries or other source data options throughout the study and will be transcribed to CRFs.

8.2.4 Safety

8.2.4.1 Physical Examination

At screening and subsequent scheduled study visits at the site (as described in Section 1.3, Section 8.1.1 and Section 8.1.2), a physical examination will be performed 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 screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting 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 source record.

8.2.4.2 Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.2.4.3 Vital Signs

Vital signs will include height (in or cm), weight (lb or kg), body temperature (°C or °F), 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 as described below:

1. Screening
   All vital signs
2. Infusion at Study Site
   - Within 30 min prior to infusion.
     All vital signs except height. Weight can be taken at any time at the site visit.
   - 30 (± 10) min after initiation of infusion
     All vital signs except height and weight
   - During the infusion if a systemic AE occurs, to be assessed as needed:
     All vital signs except height and weight

- Within 30 min of completion of the infusion
  All vital signs except height and weight

3. Infusion at home
   No assessment of vital signs
4. End-of-Study
   All vital signs

Vital sign values are to be recorded on the appropriate eCRF. 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 (as determined at the Screening / Baseline Visit) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.2.4.4 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 not clinically significant or clinically significant. 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.

8.2.4.4.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count {WBC}]) with differential (i.e., 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, ALT, serum total bilirubin, AST, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine, creatinine phosphokinase (CPK), glucose, haptoglobin, lipase.

IgG and IgG subclasses (IgG1, IgG2, IgG3, and IgG4) will be measured for assessment of trough levels.

IgG and IgG subclasses will also be measured for PK purposes. This will only be performed in subjects aged 12 years and older.

Blood will be obtained for assessment of hematology and clinical chemistry including IgG and IgG subclasses at screening/baseline, distinct study visits, and at study completion/termination. For a schedule of laboratory test blood drawings, see Appendix 2. These assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, processed through a central laboratory.

8.2.4.4.2 Urinalysis

Urinalysis includes: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

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 8.2.4.5).

8.2.4.4.3 Specialty Tests

Specialty tests include: HBsAg, 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.

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 (hepatitis E virus), or B19V (Parvovirus B19) (see also Section 8.2.4.4.5.2).

8.2.4.4.4 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 antiglobin 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 antiglobin test (Coombs-test or AGT)
   - urine hemosiderin
   - hemoglobin
   - LDH
   - 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 appropriate eCRF).

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

8.2.4.4.5 Assessment of Laboratory Values

8.2.4.4.5.1 Toxicity Grading Scale

The investigator will be asked to assess each abnormal laboratory value as described in Section 8.2.4.4.5.2. 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).

8.2.4.4.5.2 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value (with the exception of total IgG, IgG subclasses and specific antibodies) 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 sign, symptom, 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 preexisting 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.

8.2.4.5 Pregnancy Test

A urine pregnancy test will be performed at the study site for females of childbearing potential as indicated in Appendix 2.

8.2.5 Other

8.2.5.1 Pharmacodynamics

Not applicable.

8.2.5.2 Genetics

Not applicable.

8.2.5.3 Health-related Quality of Life (QoL)

A quality of life assessment will be performed as part of visits 1 during Epoch 1, Epoch 2 and Epoch 3 and at the EOS/Early Termination Visit.

Quality of life will be analyzed separately for the age groups 2-7 years (PEDS-QL, observer: parent), 8-13 years (PEDS-QL, observer: subject), and 14 years and older (SF-36, observer: subject). Additionally, all subjects will complete the EQ-5D-3L Health Questionnaire, analyzed separately for the age groups: 2-11 years EQ-5D-3L (observer: parent) and 12 years and older EQ-5D-3L (observer: subject). Age will be defined as the age at screening. The observer should remain constant for the duration of subject participation. In the event that the language/age group is not available, the assessment in the closest language/age group will be used.

8.2.5.4 Treatment Satisfaction

Treatment satisfaction (Life Quality Index; LQI) will be assessed as part of visits 1 during Epoch 1, Epoch 2 and Epoch 3 and at the EOS/Early Termination Visit.

Treatment satisfaction (Life Quality Index; LQI) will be analyzed separately for the age groups 2-13 years (observer: parent) and 14 years and older (observer: subject). Age will be defined as the age at screening. The observer should remain constant for the duration of subject participation.

All subjects will complete the Treatment Satisfaction Questionnaire for Medication (TSQM-9), analyzed separately for the age groups: 2-12 years (observer: parent) and 13 years and older (observer: subject). Age will be defined as the age at screening. The observer should remain constant for the duration of subject participation. In the event that the language/age group is not available, the assessment in the closest language/age group will be used.

8.2.5.5 Treatment Preference

Treatment preference will be assessed at the EOS/Early Termination Visit.

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

8.2.5.6 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) and number of acute (urgent or unscheduled) physician visits due to illness/infection will be collected as described in Section 8.2.3.2.

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 will be specified in the laboratory manual.

8.2.7 Retention of Bioavailability and Bioequivalence Testing Samples

Retention samples should be taken at screening or prior to the first infusion. For subjects 12 years or older approximately 2.5 mL serum and 2 mL plasma will be taken and stored frozen at –70°C or below at the central lab in the event further testing is needed. For children younger than 12 years of age, approximately 2 mL of plasma will be obtained.

8.2.8 Subject Diary

A subject diary will be provided to each subject at enrollment to record the following information in addition to the information specified in Section 8.1.2, throughout the study period:

- Occurrence of AEs (including infections). The investigator will provide guidance for the subject/caregiver regarding identification and documentation of AEs
- Concomitant medication use
- Days not able to attend school/work or to perform normal daily activities due to illness/infection

- Non-study-required out-patient visits (including urgent care visits to see healthcare providers), and hospitalizations, due to illness/infection
- Infusion related data e.g.: Med Number (six digit), start and stop time, infusion site, infusion rate (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.

The subject diary will serve as a source record and remain at the study site. Entries in the subject diaries will be transcribed or entered into the appropriate collection device. Any entry on the eCRF that does not correspond with an entry in the subject diary will be explained by the investigator in source documentation.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

Statistical analysis process details will be provided in the study SAP.

In this study, each subject will receive IGIV treatment in Epoch 1 for a total of 13 weeks, then switch to weekly SC treatment with IGSC, 20% in Epoch 2 for a total of 24 weeks. A subset of 7 subjects in Epoch 2 treatment period 2 will continue for an additional 12 weeks of biweekly SC treatment with IGSC, 20%, in Epoch 3, at the dose from Epoch 2.

The primary objective of this study is to assess serum trough IgG concentrations following weekly administration of IGSC, 20% and serum trough IgG concentration after biweekly administration of IGSC, 20%, in Japanese subjects with PID, covering Epoch 2 and Epoch 3.

The secondary objectives focus on PK, safety and tolerability, efficacy, and disease activity and HRQoL and cover Epoch 1, Epoch 2 and Epoch 3 (see Section 3.1).

PK analysis will be based on the PKAS, and safety and tolerability, efficacy, and disease activity and HRQoL analyses on the All-Treated Set.

Study endpoint data (serum IgG trough levels, safety and tolerability, and efficacy, as well as disease activity and HRQoL) will be analyzed using descriptive statistics. No statistical hypothesis testing will be performed, and no interim analysis is planned.

Baseline is defined as the last non-missing value before initial dose of study drug (IGIV or IGSC).

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 (SD), minimum value, maximum value. Categorical endpoints/outcome measures (e.g., adverse events) will be summarized in terms of number and percent of subjects and number of occurrences in each category.

Study data will be summarized by the sponsor or the sponsor-designated contract research organization, using SAS®, Version 9.4 or higher.

Summaries will be provided, *as appropriate*, by epoch, by treatment period, by treatment period and visit/timepoint, and overall. TEAEs will not be presented by visit/timepoint. Study visits/timepoints are displayed in the study procedures and assessments in Section 1.3.

As noted above in this section, the analysis process will be detailed in the study SAP, meaning the study SAP will provide a technical and detailed elaboration of the analyses of study endpoints and further document the planned summary of other study information, including but is not limited to: subject disposition, demographics and baseline characteristics, exposure to study drug (IGIV or IGSC), and prior and concomitant medications. In addition, the SAP will also include a description of how missing, unused and spurious data will be addressed.

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

There are no statistical stopping criteria (go/no-go decision criteria) for this study.

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

Not applicable. No interim analysis, adaptive design, or data monitoring committee (DMC) is planned for this study.

9.3 Sample Size and Power Considerations

The planned total sample size for this study is 16 subjects.

Of the 16 subjects to be enrolled, 12 subjects are expected to complete Epoch 2 of the study, assuming a conservative dropout rate of 25% (overall dropout rates assumed for previous IGSC, 20% PID studies and other PID studies are generally 10%-15%). Subjects who prematurely discontinue the study will not be replaced. The number of subjects expected to complete Epoch 2 (12) is considered adequate for the evaluation of serum trough levels, safety and tolerability, and efficacy of IGSC, 20%, as well as for the assessment of disease activity and HRQoL.

This study is not designed for statistical hypothesis testing and therefore the sample size is not based on statistical considerations such as study power, but instead mainly on consideration of the small size of the Japanese patient population with PID, a group of rare diseases. In Japan, the estimated prevalence of PIDs is 2 to 3 per 100,000 people and the estimated number of people affected is 2,900-3,500. Of the number of PID patients (2,900-3,500), an estimated 1,450-1,750 would be potential targets for immunoglobulin replacement therapy. In clinical practice, most patients requiring a switch to IGSC (as is required by the study design) are already being treated with the approved IGSC product (Hizentra®). For example, in the Hizentra® NDA review report, the estimated number of patients who could receive immunoglobulin replacement therapy was 1,155, which is lower than the estimated 1,450-1,750 patients.

Therefore, the number of potentially eligible patients for the planned study is extremely limited, making it infeasible to enroll a large sample size. Based on feasibility and the Sponsor's clinical experience with IgG products, a total sample size of 16 subjects (12 completers) is considered adequate for providing reliable estimates of trough levels (study primary objective), as well as reliable estimates of safety and tolerability, efficacy, disease activity and HRQoL (secondary objectives).

9.4 Statistical Analysis Set(s)

Analysis of serum trough levels of IgG, efficacy, safety and tolerability, and disease activity and HRQoL data will be based on the following analysis sets (analysis populations), as defined:

- Enrolled Set: All screened subjects for whom an enrollment number has been assigned. Screened subjects will consist of all subjects who have signed informed consent. Background summaries (e.g., subject disposition) will be based on the Enrolled Set.
- All-Treated Set: All enrolled subjects who received at least 1 dose of study drug (IGIV or IGSC).
  Analysis of efficacy, safety and tolerability, and disease activity and HRQoL will be based on the All-Treated Set. Since this study is non-randomized, the Safety Set (defined as all dosed subjects) and Full Analysis Set (defined as all randomized and dosed) are identical, and therefore simply referred to as All-Treated Set for this study.
- Pharmacokinetic Analysis Set (PKAS): All-Treated Set who have had at least 1 evaluable serum IgG concentration value and have had no major protocol deviations or events that would affect the serum IgG concentration analysis results.
  Analysis of PK data (serum IgG trough concentrations and PK profiles) will be based on the PKAS.

9.5 Pharmacokinetic Analyses

The primary objective of the study is to assess serum trough IgG concentrations following weekly administration of IGSC, 20% (Epoch 2) and serum trough IgG concentration after biweekly administration of IGSC, 20% (Epoch 3), in Japanese subjects with PID. All PK data will be analyzed using descriptive statistics. Descriptive statistics will also include geometric mean (GM) and the corresponding 2-sided 95% confidence interval (CI). No formal statistical comparison (hypothesis testing) of treatments will be performed. Note that CIs are for descriptive purposes, and therefore caution should be exhibited in their interpretation as this study is not designed for hypothesis testing.

Analysis details will be provided in the study SAP.

9.5.1 Primary Pharmacokinetic Endpoint

The primary PK endpoint is the total serum trough levels of IgG (total serum trough IgG antibodies) measured during Period 2 of Study Epoch 2 (weekly administration of IGSC, 20%), and Study Epoch 3 (biweekly administration of IGSC, 20%).

9.5.2 Secondary Pharmacokinetic Endpoints

Secondary PK endpoints and parameters in Epoch 1, Epoch 2 and Epoch 3, as indicated:

- Total serum trough levels of IgG (total serum trough IgG antibodies) measured during Epoch 1 (every 3 weeks or every 4 weeks administration of IGIV)
- PK parameters estimated based on PK profiles in Epoch 2 using non-compartmental analysis for total serum levels of IgG and for IgG subclasses (Epoch 2): AUC, CL/F, C_{max}, C_{min}, and T_{max}
- Trough levels of specific antibodies to clinically relevant pathogens (e.g. Clostridium tetani toxoid, HIB, HBV) (Epoch 1, Epoch 2, Epoch 3)

9.6 Efficacy Analyses

Assessment of efficacy is a secondary objective of the study. Efficacy endpoint data (defined below) will be analyzed using descriptive statistics.

9.6.1 Efficacy Endpoints

Efficacy endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3:

- Annual rate of validated acute serious bacterial infections per subject
- Annual rate of all infections per subject
- 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

Days will be standardized to per week, per month, or per year to adjust for the differential durations of the epochs.

9.7 Safety Analyses

Assessment of safety and tolerability is a secondary objective of this study. Safety and tolerability endpoints (defined below) will be analyzed using descriptive statistics.

Safety and tolerability endpoints/outcome measures in Epoch 1, Epoch 2 and Epoch 3 include:

- Occurrence of TEAEs, including but not limited to: study drug (IGIV or IGSC)-related and non-related*, serious, nonserious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs

  * Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to study drug (IGIV or IGSC) will be considered a related AE, and any AE recorded as "unlikely related" or "not related" will be considered an unrelated AE.

- Occurrence of tolerability events related to the infusion of study drug (IGIV or IGSC)

  An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to a TEAE related to study drug (IGIV or IGSC) infusion.

  A tolerability event is considered to have occurred if an infusion was not tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable.

- Clinical laboratory outcomes: raw (actual) values and change from baseline

  Clinically significant, treatment-emergent changes in clinical laboratory measurements will be recorded in the study database (internal or external) as TEAEs.

- Vital signs: raw (actual) values and change from baseline and change from pre-infusion to post-infusion.

Baseline is defined as the last non-missing value before initial dose of study drug (IGIV or IGSC).

9.7.1 Analysis of Adverse Events

9.7.1.1 Definitions

TEAEs, defined as: AEs with onset after date-time of first dose of study drug (IGIV or IGSC), or medical conditions present prior to the start of study drug (IGIV or IGSC) but increased in severity or relationship after date-time of first dose of study drug (IGIV or IGSC).

Non-TEAEs, defined as: AEs with onset before date-time of first dose of study drug (IGIV or IGSC), or medical conditions present prior to the start of study drug (IGIV or IGSC) but did not increase in severity or relationship after date-time of first dose of study drug (IGIV or IGSC).

Related TEAEs, defined as causally related TEAEs.

9.7.1.2 Handling of Recurrent AEs and Other AE 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 (e.g., 3 occurrences: 1 mild, 1 moderate, 1 severe) all categorized under the same causality assessment (e.g., all related to study drug [IGIV or IGSC]), the AE with the maximum severity (AE that is severe) will be used in analysis.

Related AEs: Any AE that is recorded as "possibly related" or "probably related" to study drug (IGIV or IGSC) will be considered a "related" AE, and any AE recorded as "unlikely related" or "not related" will be considered an "unrelated" AE.

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 study drug (IGIV or IGSC). For example, if a subject experienced a mild headache not related to the IP, and a moderate headache related to IP, then the subject will be counted once for headache using the moderate headache related to IP.

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

9.7.1.3 Occurrence and Number of Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1 or higher and then reported by MedDRA system organ class (SOC) and PT, and overall. Only TEAEs will be analyzed. Non-TEAEs will be listed only.

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 TEAE, local TEAE, related TEAE, severe TEAE, severe related TEAE, serious TEAE, serious related TEAE, and TEAE leading to discontinuation for the epoch, and any TEAE 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 (i.e., 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 study drug (IGIV or IGSC). For example, if a subject experienced a mild headache not related to the IP, and a moderate headache related to IP, then the subject will be counted once for headache using the moderate headache related to IP.
- 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.

9.7.1.4 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 subject-year, 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 subject-year is number of events divided by total number of days of exposure, converted into years.

AEs per subject-year summary adjusts for differences in subjects' durations in the study and the potential differential dropout rates between epochs.

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 subject-years (SYs) will be provided for all AEs (if analyzable), by primary SOC and PT for each epoch and overall.

The following calculations apply, where applicable:

- AEs per infusion = number of AEs / total number of infusions administered to subjects in the analysis set
- AE per subject = number of AEs / total number of subjects in the analysis set
- AEs per subject-year = number of AEs / total number of days of exposure, i.e., the sum of duration of treatment for all subjects in the analysis set, converted into years
- AEs per 1000 SYs = 1000 × (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 study – date of initial dose of study drug (IGIV or IGSC) + 1) / 365.25. If the subject's last date is missing, then the date of last dose of study drug (IGIV or IGSC) will be used if available.

9.7.1.5 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

9.7.2 Clinical Laboratory Data

Baseline is defined as the last non-missing value before initial dose of study drug (IGIV or IGSC).

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

Shift from baseline (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.

9.7.3 Vital Signs

Raw (actual) vital signs, and changes in raw values from baseline at each post-baseline assessment time point, and change from pre-infusion to post-infusion, will be summarized as appropriate.

9.8 Other Analyses

9.8.1 Disease Activity and Health-related Quality of Life Analyses

All disease activity and HRQoL data will be listed in the subject data listing(s). All endpoints will be analyzed using descriptive statistics, as planned for the efficacy endpoints. Disease activity and HRQoL endpoints in Epoch 1, Epoch 2 and Epoch 3:

- QoL: PEDS-QL (Varni et al., 1999), SF-36 (Ware and Sherbourne, 1992), EQ-5D-3L Health Questionnaire (Shaw et al., 2005)
- Treatment Satisfaction (Life Quality Index, TSQM-9) (Daly et al., 1991)
- Treatment Preference (EOS/Early Termination)

Endpoint details will be provided in the study SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1 CCI [redacted]

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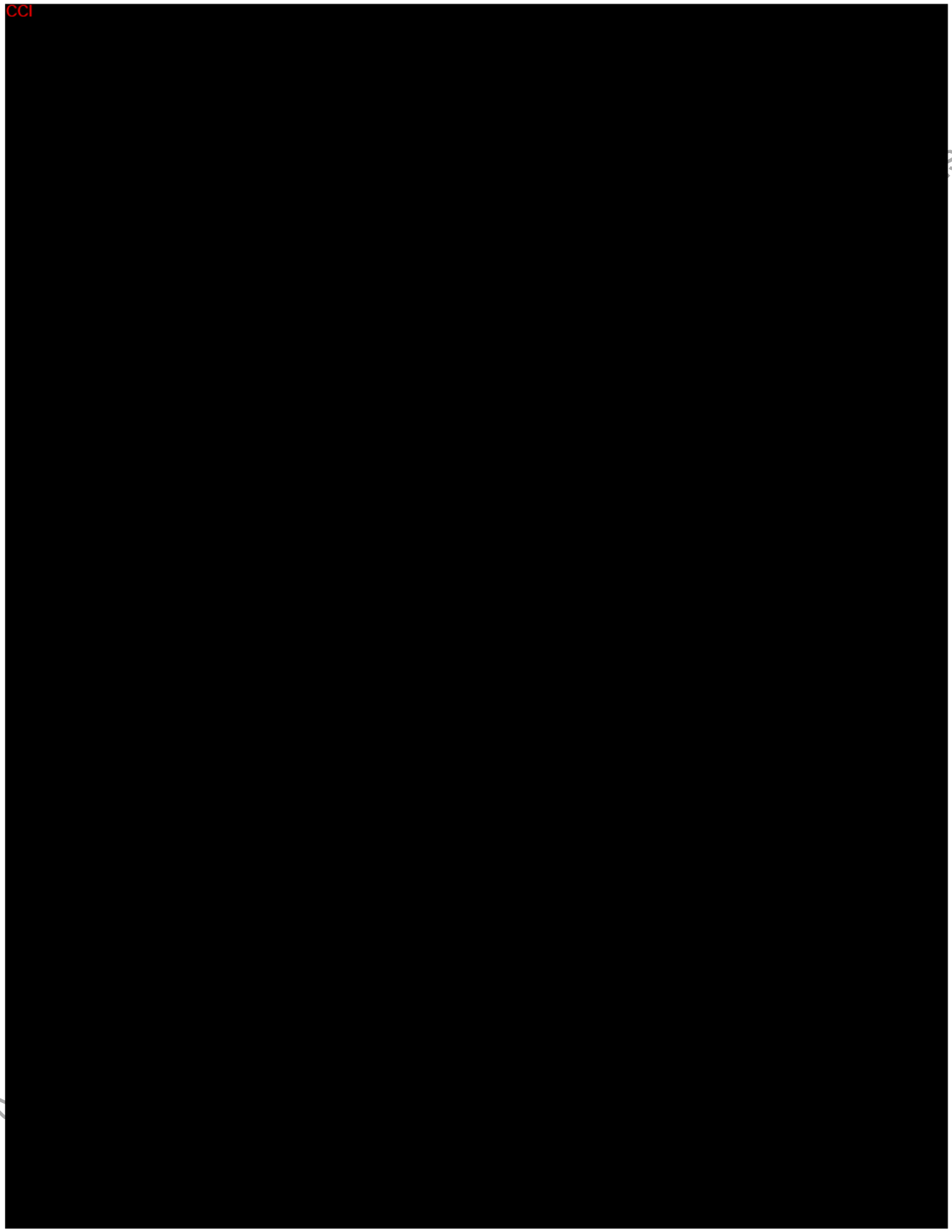

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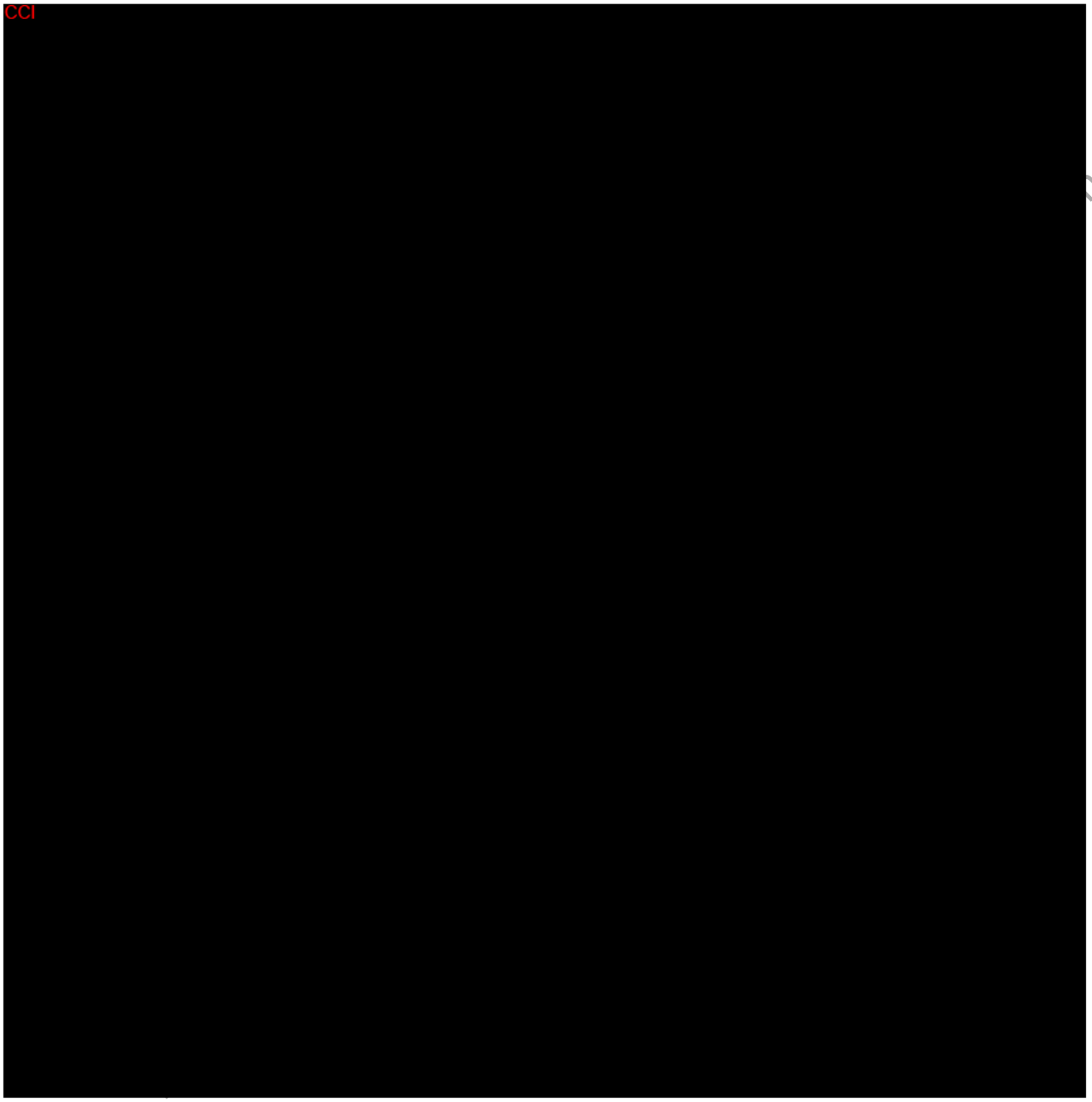

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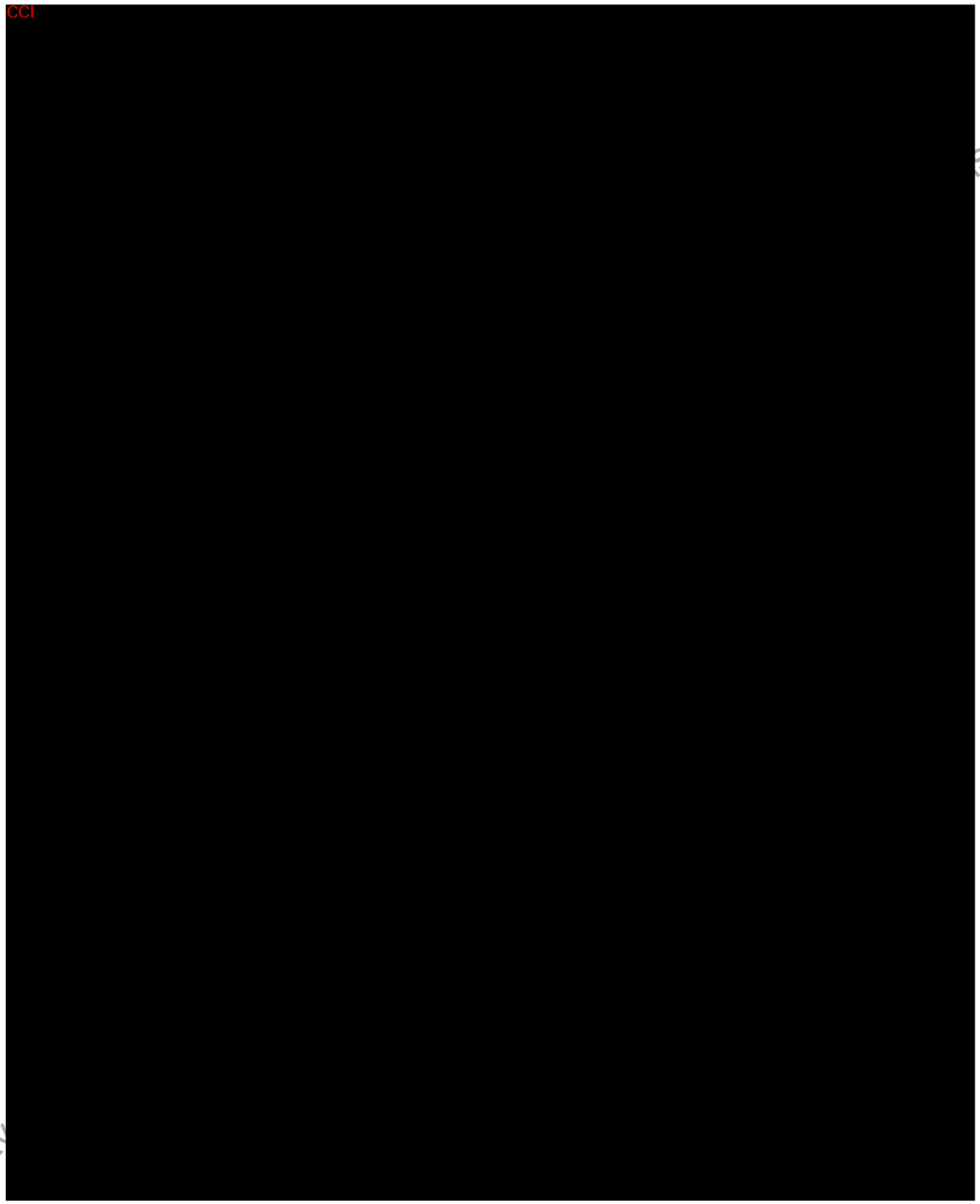

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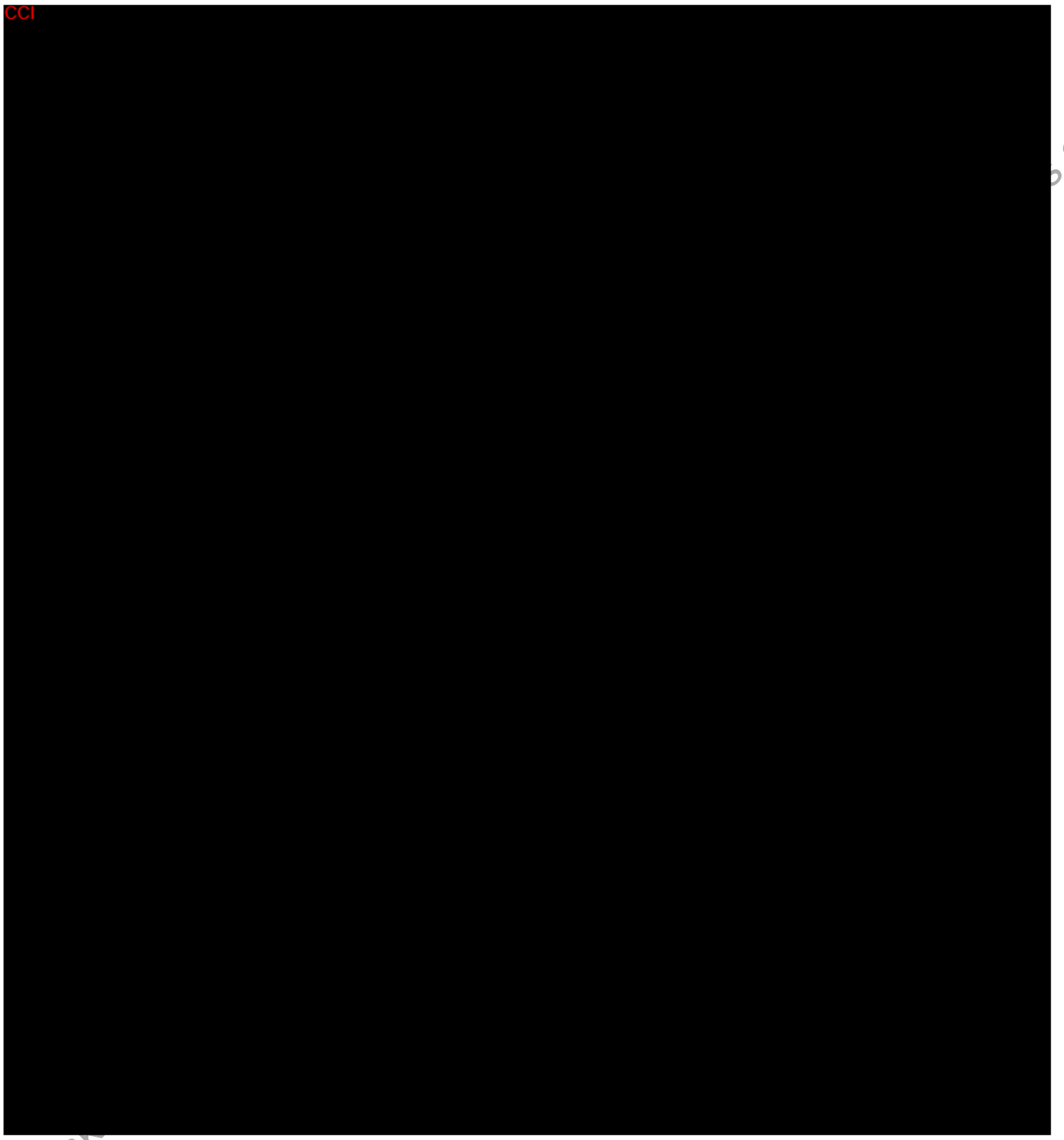

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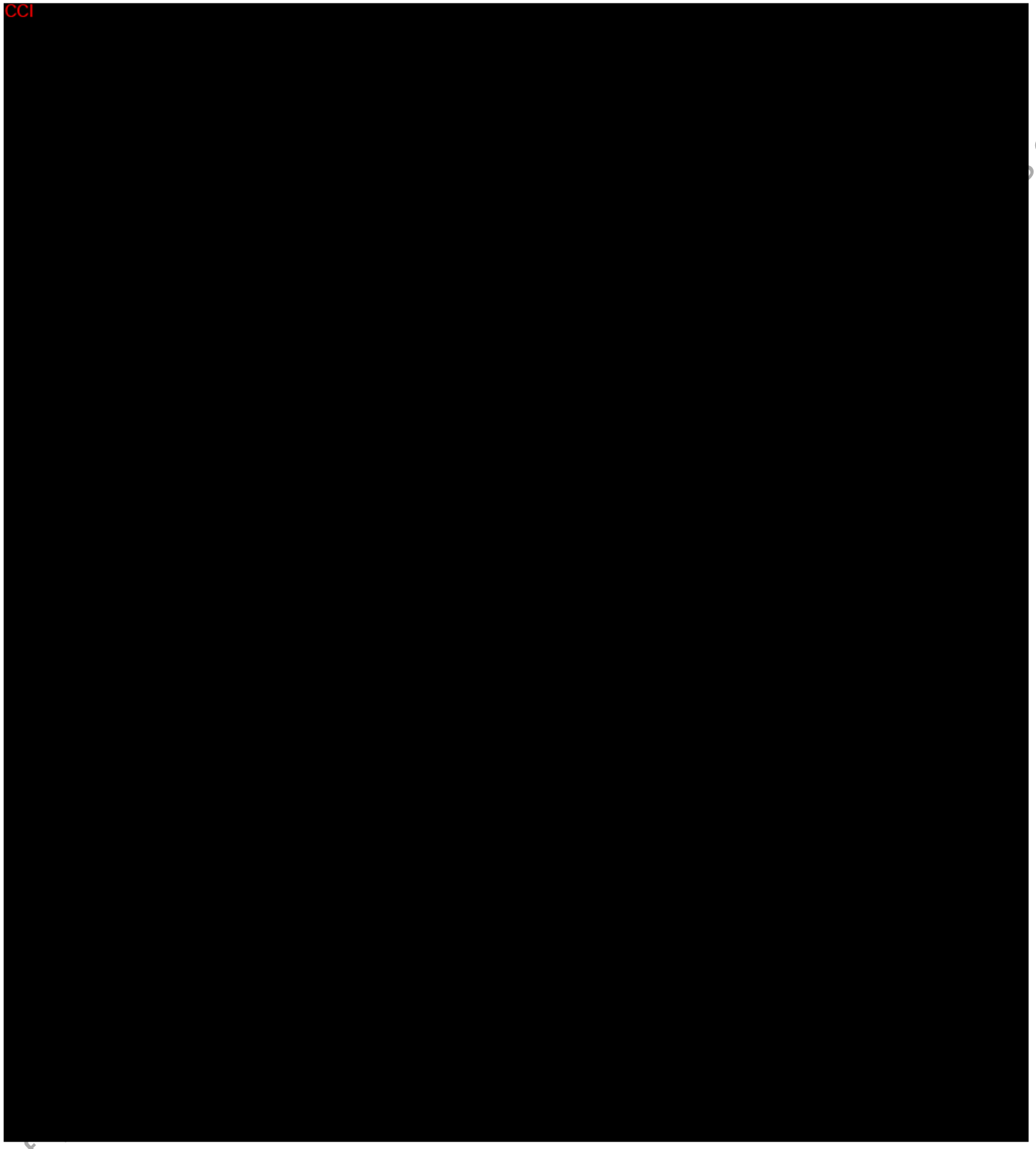

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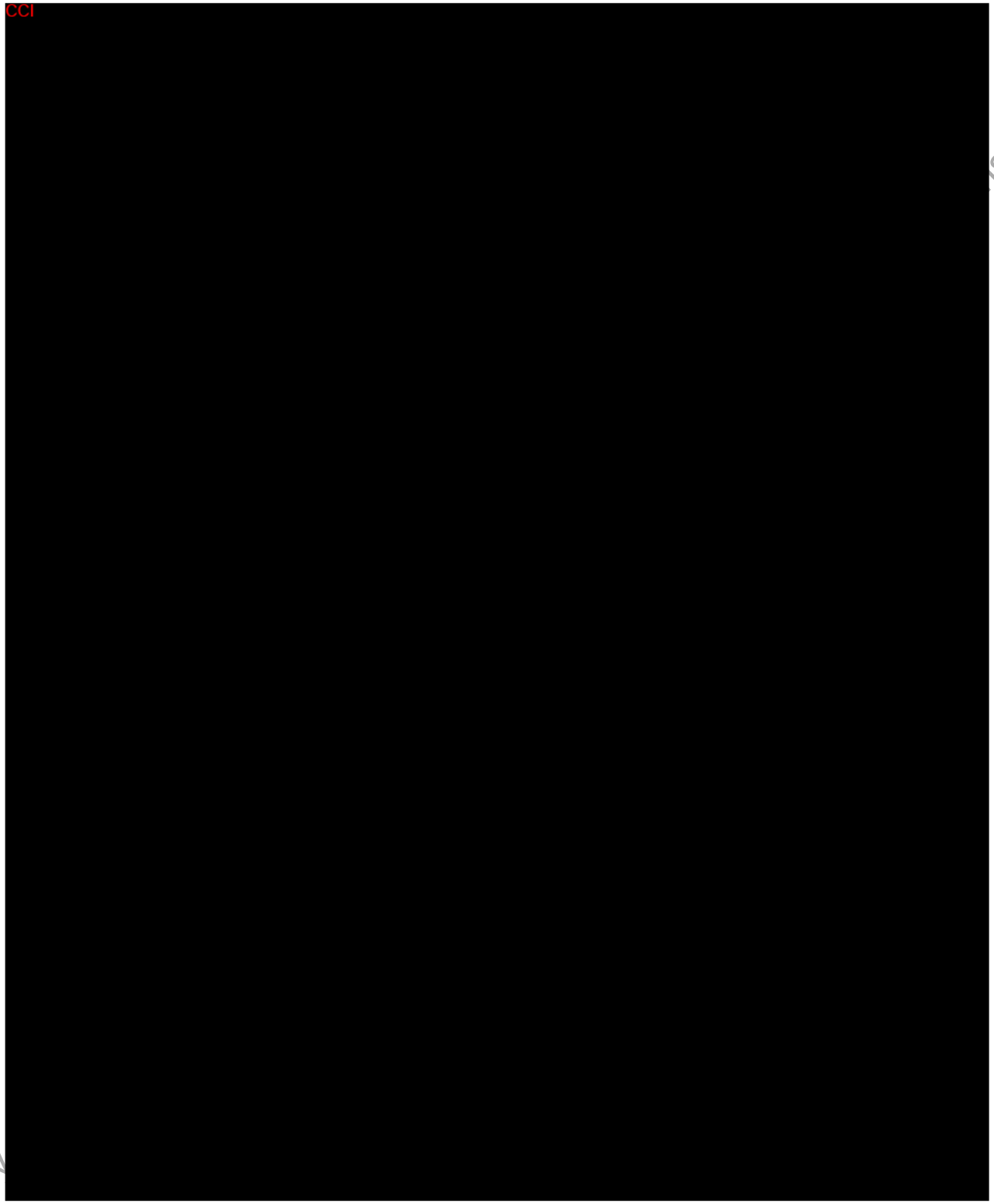

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APPENDIX 8 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	25 SEP 2019	Japan
Amendment 1	06 DEC 2019	Japan
Amendment 2	27 OCT 2020	Japan

Summary of Change(s) from Original to Amendment 1 of the Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **06 Dec 2019**	**Japan**
Protocol Amendment Summary and Rationale: The protocol was amended to address wording change requests received from the PMDA in order to meet Japanese requirements.		
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Minor grammatical, editorial and/or administrative changes have been made.	To improve the readability and/or clarity of the protocol.	Throughout the document.
Updated name of sponsor signatory	Administrative.	Protocol Signature Page
Revised the text on dosing in Epochs 1, 2 and 3 to read as follows: Epoch 1: "In Epoch 1, IGIV will be administered via IV infusions every 3 or 4 weeks, as per local product label, at the same dose as during pre-study period (200 mg/kg – 600 mg/kg BW at 3- or 4- week intervals)." Epoch 2: "In Epoch 2 (24 weeks), between 50 and 200 mg/kg of IGSC, 20% will be administered subcutaneously once a week. The dose in Epoch 2 will be adjusted so that it is an equivalent weekly dose, of the dose administered in Epoch 1." Epoch 3: "In Epoch 3, between 100 and 400 mg/kg of IGSC, 20% will be administered subcutaneously once every 2 weeks in a sub-set of 7 subjects. The dose in Epoch 3 will be twice the dose in Epoch 2."	As per PMDA request, revision of the text for consistency with the IGIV dosage and administration in Japan.	Synopsis, Sections 4.1, 4.3, 6.4.3 and 6.4.5

Summary of Change(s) from Original to Amendment 1 of the Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **06 Dec 2019**	**Japan**
Protocol Amendment Summary and Rationale: The protocol was amended to address wording change requests received from the PMDA in order to meet Japanese requirements.		
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Changed inclusion criterion 5 from "Subject has been receiving a consistent dose of IG over a period of at least 3 months prior to screening at an average minimum dose over that interval equivalent to 200 mg/kg body weight (BW)/4 weeks and a maximum dose equivalent to 800 mg/kg BW/4 weeks at a dosing frequency as follows: intravenously (IV) at mean intervals of approximately 3 or 4 weeks" to "Subject has been receiving a consistent dose of IGIV over a period of at least 3 months prior to screening of 200 – 600 mg/kg BW at 3- or 4- week intervals"	As per PMDA request, revision of the text for consistency with the IGIV dosage and administration in Japan.	Synopsis, Section 5.1
Deleted the following sentence: "Healthcare providers/physicians should balance the potential risks and only prescribe IGSC, 20% if clearly needed."	As per PMDA request; as it is it is clearly stated in the exclusion criteria for this study that women subject with a test positive pregnancy test will be excluded	Section 5.4
Deleted use of the wording "Investigational Product" for the IGIV in Epoch 1 and redefined subsections to reflect this change; emphasized that the IGIV used in Epoch 1 will be the same IGIV preparation being administered to the patient prior to enrollment in the study; and added information that the lot number should be recorded in the eCRF by clinical site personnel.	As per PMDA request; to be consistent with the ICF and follow the "Ministerial Ordinance on Criteria for Conducting Clinical Studies of Drug Products." in Japan.	Section 6 and subsections

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