Clinical Study Protocol

NCT Number: NCT04842643

Title: A Phase 3, Open-label, Non-controlled, Multi-dose, Extension Study to Evaluate the Long-term Safety and Tolerability of IGSC, 20% in Japanese Subjects with Primary Immunodeficiency Disease (PID)

Study Number: TAK-664-3002

Document Version and Date: Amendment 3.0 / 28-Nov-2022

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

TAKEDA PHARMACEUTICALS

PROTOCOL: TAK-664-3002

Title:	A Phase 3, Open-label, Non-controlled, Multi-dose, Extension Study to Evaluate the Long-term Safety and Tolerability of IGSC, 20% in Japanese Subjects with Primary Immunodeficiency Disease (PID)
Short Title:	Long-term Safety and Tolerability of IGSC, 20% in Japanese Subjects with PID
Study Phase:	Phase 3
Acronym:	TAK-664-3002
Drug:	TAK-664, Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%)
IND Number:	Not Applicable
EUDRACT Number:	Not Applicable
Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, Japan
Principal / Coordinating Investigator:	Multicenter
Protocol History:	Protocol Amendment 3.0: 28 Nov 2022 Protocol Amendment 2.0: 19 Jul 2022 Protocol Amendment 1.0: 02 Nov 2021 Original Protocol 1.0: 18 Jan 2021

1. ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

A separate contact information list will be provided to each site.

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

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

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

After obtaining the marketing authorization of this drug in Japan, this clinical trial will continue as a post-marketing clinical trial, and will comply with the GCP Ministerial Ordinance and the Ministerial Ordinance on the criteria for conducting post-marketing surveillance and testing of pharmaceuticals. After the transition to post-marketing clinical trials, the term “clinical trial” in the “clinical trial protocol” will be replaced with “post-marketing clinical trial”.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Summary of Changes from Previous Protocol Version

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Protocol Amendment 3.0	**Amendment Date 28 Nov 2022**	**Japan**
Description of Change	***Rationale for Change***	***Section Affected by Change***
Interim analysis will be conducted during the study.	The interim analysis data will be submitted during Japanese New Drug Application process as requested by Pharmaceuticals and Medical Devices Agency (PMDA).	Synopsis and Section 13.2

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2. STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-664, Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%)	
Title of Protocol: A Phase 3, Open-label, Non-controlled, Multi-dose, Extension Study to Evaluate the Long-term Safety and Tolerability of IGSC, 20% in Japanese Subjects with Primary Immunodeficiency Disease (PID).	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: TAK-664-3002	**Phase:** 3	

Rationale:

This is an open-label extension study, following completion of Study TAK-664-3001. It will provide data on the long-term safety and tolerability of IGSC, 20% in Japanese subjects with PID who successfully complete study TAK-664-3001 and wish to continue treatment with IGSC, 20%. The results from these 2 studies will extend/support the data obtained from 2 global (United States and European Union) pivotal studies for IGSC, 20% in PID, to Japanese patients with PID.

Study Design:

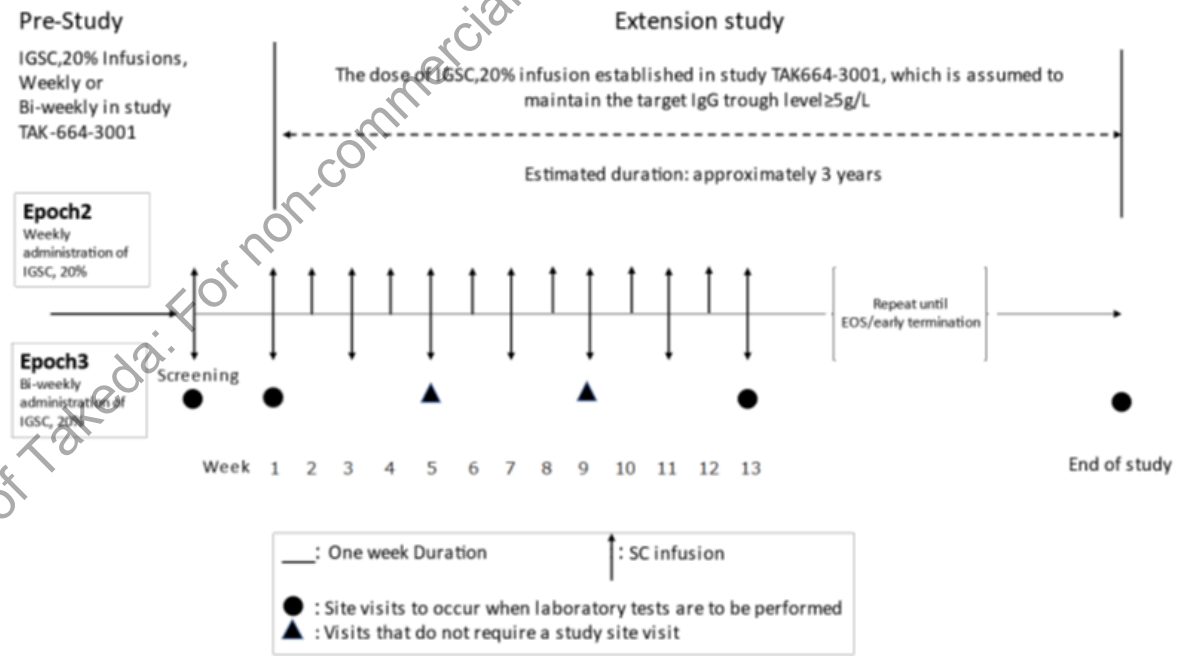
This is a Phase 3, prospective, multicenter, open-label, non-controlled, single-arm extension study.

This study will enroll Japanese subjects with PID who complete Study TAK-664-3001 successfully.

Subjects are considered to have completed Study TAK-664-3001 successfully if they fulfill the following criterion:

- Completed Epoch 2, in which IGSC, 20% is administered weekly (completion of Epoch 3, in which IGSC, 20% is administered biweekly, is not mandatory for participation in TAK-664-3002 study).

Schematic of study design:



Abbreviations: EOS=End of Study, IgG= immunoglobulin G, IGSC= subcutaneous immunoglobulin, SC=subcutaneous.

Screening/Baseline Period

Informed consent is expected to be obtained at last visit or prior to last visit of Study TAK-664-3001.

The subjects will undergo screening/baseline procedures for determination of eligibility before infusion of IGSC, 20%.

IGSC, 20% Treatment Period

Eligible subjects will receive IGSC, 20% until the commercial IGSC, 20% is available at each study site or study termination (estimated duration: approximately 3 years).

Visit Schedule

The number of infusion visits and study site visits during the subcutaneous (SC) treatment period will depend on where the SC injection is administered. Infusions may be performed at home or at the study site, at the investigator's discretion. The decision where the SC injection is administered is made during Study TAK-664-3001, however the location of injection administration can be changed based on the investigator's and subject's agreement.

Subjects should come to the study site for visits when laboratory test samples are to be collected every 12 weeks. Subjects are not required to come to the study site if all procedures/assessments can be performed at home.

Primary Objectives:

To evaluate the long-term safety and tolerability of IGSC, 20% in Japanese subjects with PID.

Secondary Objectives:

- To assess serum trough immunoglobulin G (IgG) and subclasses concentrations following weekly or biweekly administration of IGSC, 20% in Japanese subjects with PID.
- To evaluate the efficacy of IGSC, 20% in Japanese subjects with PID.
- To assess treatment preference of Japanese subjects with PID.

Subject Population: Japanese subjects aged 2 years or older with PID.

Number of Subjects: Approximately 10 subjects. A total of 16 subjects will be enrolled in Study TAK-664-3001, of whom 12 subjects are expected to complete Epoch 2. The subjects who successfully complete Epoch 2 are eligible to enter this extension study.	**Number of Sites:** Approximately 10 to 15 study sites planned, located in Japan.
Dosage Form: The dose of IGSC, 20% infusion was established in Study TAK-664-3001, and is assumed to maintain the target IgG trough level ≥5 g/L (Epoch 2: approximately between 50 and 200 mg/kg of IGSC, 20% weekly, Epoch 3: approximately between 100 and 400 mg/kg of IGSC, 20% biweekly). When the IgG trough level is found not to be maintained at ≥5 g/L during the study, adjustment of the dose is allowed at the discretion of the investigator.	**Route of Administration:** Subcutaneous infusion, weekly or biweekly.
Duration of Treatment: Eligible subjects will receive IGSC, 20% until the commercial IGSC, 20% is available at each study site or study termination (estimated duration: approximately 3 years).	**Period of Evaluation:** Subjects should come to the study site for visits when laboratory test samples are to be collected every 12 weeks. Subjects are not required to come to the study site if all the procedures/assessments can be performed at home (estimated duration: approximately 3 years).

Criteria for Inclusion:

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

1. Subject has completed or is about to complete Takeda Clinical Study TAK-664-3001.

   A subject is considered to have completed Study TAK-664-3001 successfully if they fulfill the following criterion:

   - Completed Epoch 2, in which IGSC, 20% is administered weekly (completion of Epoch 3, in which IGSC, 20% is administered biweekly, is not mandatory for participation in TAK-664-3002 study).
2. 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.
3. Subject is willing and able to comply with the requirements of the protocol.

Criteria for Exclusion:

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

1. Subject has developed a new serious medical condition during participation in Study TAK-664-3001 such that the subject's safety or medical care would be impacted by participation in the extension study TAK-664-3002.
2. Subject is scheduled to participate in another non-Takeda clinical study involving an Investigational Product or device-used-in-clinical-trial in the course of this study.
3. If a female of childbearing potential, subject is pregnant or has a negative pregnancy test but does not agree to employ adequate birth control measures for the duration of the study.

Criteria for Evaluation and Analyses:

The primary endpoint for this study is safety and tolerability.

Safety and tolerability endpoints/outcome measures:

- Occurrence of treatment-emergent adverse events (TEAEs), including but not limited to: investigation product-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 "probably related" or "possibly related" to study drug will be considered as IGSC, 20%-related adverse event (AE), and any AE recorded as "unlikely related" or "not related" will be considered as unrelated AE.

Secondary endpoints for this study are safety, tolerability, pharmacokinetic (PK), and efficacy.

Pharmacokinetic endpoint/outcome measure:

- Measurement of serum trough IgG and subclasses concentrations following weekly or biweekly administration of IGSC, 20% in Japanese subjects with PID.

Efficacy endpoints/outcome measures:

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

Safety endpoints/outcome measures:

- 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 time of participation in TAK-664-3001 study.

Tolerability endpoints/outcome measures:

- Occurrence of tolerability events related to the infusion of study drug.

  *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 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.

Statistical Considerations:

Analysis Sets

- **All-Treated Set**: All enrolled subjects who received IGSC, 20% administration at least once in this study, this will be the efficacy analysis set.
- **Safety analysis set (SAS)**: All enrolled subjects who received at least 1 dose of study drug (IGIV) in TAK-664-3001 study, this will be SAS.

Safety analysis will be performed using the SAS.

The number and percentage of subjects with TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term overall, by severity, and by relationship to study drug. Separate summaries will also be generated for TEAEs overall and by severity. Change from baseline in clinical laboratory tests, and vital signs will be summarized.

Efficacy and treatment preference endpoints will be summarized descriptively using the All-Treated Set.

Continuous endpoints/outcome measures (eg, change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation, minimum value, maximum value. Categorical endpoints/outcome measures (eg, AEs) will be summarized in terms of number and percent of subjects and number of occurrences in each category.

For serum IgG concentrations, descriptive statistics will also include geometric mean and the corresponding 2-sided 95% confidence interval. Confidence intervals are for descriptive purposes. Caution should be exhibited in their interpretation as this study is not designed for hypothesis testing.

An interim analysis of study data will be undertaken to support the Japanese New Drug Application submission. It will summarize PK (Serum IgG trough levels), safety, efficacy, and tolerability of treatment with IGSC, 20% in all subjects with PID in this study. The snapshot date will be stated in the statistical analysis plan. The target data will be all subject data obtained at snapshot date in this study.

Sample Size Justification: No formal sample size calculation has been performed in this extension study. A sample size of approximately 16 subjects is the estimated maximal number of subjects who can enroll from the previous TAK-664-3001 study.

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASBI	acute serious bacterial infection
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BUN	blood urea nitrogen
B19V	Parvovirus B19
CRO	contract research organization
CSF	cerebrospinal fluid
CT	computed tomography
eCRF	electronic case report form
EOS	End of Study
ERCSI	Emergency Reception Center for Safety Information
EU	European Union
EudraCT	European Union clinical trials database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IgG	immunoglobulin G
IGIV	intravenous immunoglobulin
IGSC	subcutaneous immunoglobulin
IGSC, 20%	Immune Globulin Subcutaneous (Human), 20% Solution
IP	investigational product
IRB	institutional review board

Abbreviation	Definition
IRT	interactive response technology
IV	intravenous
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
PID	primary immunodeficiency disease
PK	Pharmacokinetic
PT	preferred term
QoL	quality of life
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SC	subcutaneous
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SY	subject-year
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
US	United States
WBC	white blood cell
WHO	World Health Organization

4. INTRODUCTION

4.1 Background

4.1.1 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 406 distinct disorders (with >430 gene defects) (Bousfiha et al., 2020). The most recent classification of molecularly defined PIDs issued by the Expert Committee of the International Union of Immunological Societies (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 immunoglobulin G (IgG) as a replacement therapy. Antibody replacement can be administered either intravenously or subcutaneously (Melamed et al., 2012). Therapeutic options for treatment of PID itself to correct the defect are transplantation of bone marrow-derived stem cells, and recently, gene therapy (de la Morena and Nelson, 2014, Hernandez-Trujillo, 2014, Kuo, 2018, Picard et al., 2018, Sauer et al., 2014).

Currently, the majority of IgG products are licensed for intravenous (IV) administration, though in the past several years, subcutaneous (SC) administration has gained popularity. When given weekly or every other week, subcutaneous immunoglobulin (IGSC) leads to higher trough serum IgG concentrations than monthly IV infusions (Berger, 2011, Gardulf et al., 1995, Gardulf et al., 1991).

Immunoglobulin (Ig) replacement therapy administered by the SC route (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 (AEs) compared to intravenous immunoglobulin (IGIV) (Berger, 2013, Suez et al., 2016). The Ig preparations currently approved for SC use in the United States (US), Canada, and the European Union (EU) are formulated at 10% to 20% (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 (QoL) (Wasserman, 2012).

4.1.2 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 body weight 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 (PK) of SC administration are different from that of IV infusions, and bioavailability of Ig 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).

Subcutaneous immunoglobulin, 20%, a new Ig preparation for SC use, is formulated as a 20% solution. The manufacturing process for Immune Globulin Subcutaneous (Human), 20% Solution (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 European Medicines agency Guidelines for human normal Ig 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 2 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.

4.2 Rationale for the Proposed Study

Approximately 2,900 to 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 IV. The Study TAK-664-3001 evaluates serum trough IgG levels, safety and tolerability, and efficacy of IGSC, 20% (SC administration), and assesses disease activity and health-related QoL 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). TAK-664-3002 is an open-label extension study, following completion of Study TAK-664-3001. It will provide data on the long-term safety and tolerability of IGSC, 20% in Japanese subjects with PID who successfully complete Study TAK-664-3001 and wish to continue treatment with IGSC, 20%. The results from these 2 studies will extend/support the data obtained from 2 global (US and EU) pivotal studies for IGSC, 20% in PID, to Japanese patients with PID.

4.3 Benefit/Risk Profile

Subcutaneous immunoglobulin, 20% is a new Ig 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. Subcutaneous immunoglobulin, 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 IGIV, 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/hour 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, PK, efficacy, and safety of IGSC, 20%.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To evaluate the long-term safety and tolerability of IGSC, 20% in Japanese subjects with PID.

5.1.2 Secondary Objectives

- To assess serum trough IgG and subclasses concentrations following weekly or biweekly administration of IGSC, 20% in Japanese subjects with PID.
- To evaluate the efficacy of IGSC, 20% in Japanese subjects with PID.
- To assess treatment preference of Japanese subjects with PID.

5.2 Endpoints

5.2.1 Primary Endpoint: Safety and Tolerability

- Occurrence of treatment-emergent adverse events (TEAEs), including but not limited to: study drug-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 "probably related" or "possibly related" to study drug will be considered as IGSC, 20%-related AE, and any AE recorded as "unlikely related" or "not related" will be considered as unrelated AE.

5.2.2 Secondary Endpoints: Safety, Tolerability, PK, and Efficacy

Pharmacokinetic endpoint/outcome measure:

- Measurement of serum trough IgG and subclasses concentrations following weekly or biweekly administration of IGSC, 20% in Japanese subjects with PID.

Efficacy endpoints/outcome measures:

- Annual rate of validated ASBI per subject.
- Annual rate of all infections per subject.
- Health Resource Utilization:
  - Days not able to attend school/work or to perform normal daily activities due to illness/infection
  - Days on antibiotics
  - Number of hospitalizations due to illness/infection and length of stay (in days)

  - Number of acute (urgent or unscheduled) physician visits due to illness/infection.

- Treatment preference.

Safety endpoints/outcome measures:

- 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 time of participation in the TAK-664-3001 study.

Tolerability endpoints/outcome measures:

- Occurrence of tolerability events related to the infusion of study drug.

*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 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.

6. STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a Phase 3, prospective, multicenter, open-label, non-controlled, single-arm extension study.

Approximately 10 to 15 study sites planned, located in Japan. Number of subjects are approximately 10. A total of 16 subjects will be enrolled in Study TAK-664-3001, of whom 12 subjects are expected to complete Epoch 2. The subjects who successfully complete Epoch 2 are eligible to enter this extension study.

This study will enroll Japanese subjects with PID who complete Study TAK-664-3001 successfully.

Subjects are considered to have completed Study TAK-664-3001 successfully if they fulfill the following criterion:

- Completed Epoch 2, in which IGSC, 20% is administered weekly (completion of Epoch 3, in which IGSC, 20% is administered biweekly, is not mandatory for participation in TAK-664-3002 study).

Screening/Baseline Period

Informed consent is expected to be obtained at last visit or prior to last visit of Study TAK-664-3001.

The subjects will undergo screening/baseline procedures for determination of eligibility before infusion of IGSC, 20% (see Appendix-Table 1 for Schedule of Study Procedures).

IGSC, 20% Treatment Period

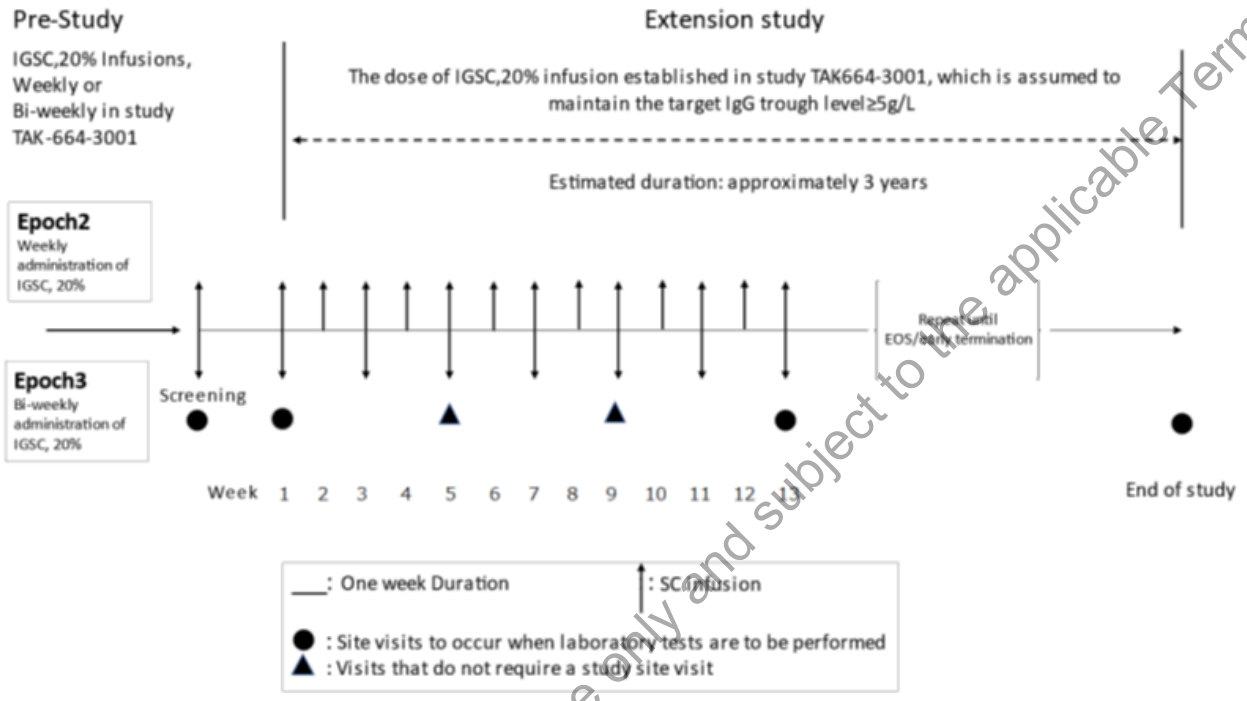
Eligible subjects will receive IGSC, 20% until the commercial IGSC, 20% is available at each study site or study termination (estimated duration: approximately 3 years).

Visit Schedule

The number of infusion visits and study site visits during the SC treatment period will depend on where the SC injection is administered. Infusions may be performed at home or at the study site, at the investigator's discretion. The decision where the SC injection is administered is made during the Study TAK-664-3001, however the location of injection administration can be changed based on the investigator's and subject's agreement. Subjects should come to the study site for visits when laboratory test samples are to be collected every 12 weeks. Subjects are not required to come to the study site if all procedures/assessments can be performed at home.

A schematic of the study design is included as In-Text Figure 6-1. A schedule of assessments is listed in Appendix A.

In-Text Figure 6-1. Schematic of Study Design



Abbreviations: EOS=End of study, IgG= immunoglobulin G, IGSC= subcutaneous immunoglobulin, SC=subcutaneous.

6.2 Justification for Study Design, Dose, and Endpoints

For all study subjects, the Ig dose during the pre-study period (equivalent to approximately 200 mg/kg to 600 mg/kg body weight at 3- or 4-week intervals, as according to the product package insert) was maintained upon study entry into Study TAK-664-3001. In replacement therapy, the dose may need to be individualized for each subject 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.

This is an extension study for Study TAK-664-3001 and has been designed to primarily evaluate long-term safety and tolerability. Serum trough IgG concentrations, rate of bacterial infections, Health Resource Utilization, QoL, treatment preference, and treatment satisfaction questionnaires were all endpoints in TAK-664-3001 and these data (except the QoL and treatment satisfaction) will continue to be collected in this extension study.

In principle, the dose regimen as established in Study TAK-664-3001 should be maintained during the extension study. Subjects who complete Epoch 2 will start weekly dosing, and subjects who complete Epoch 3 will start biweekly dosing. The dose interval may be switched to weekly or biweekly on a case-by-case basis for the subjects if needed. For subjects who discontinue Epoch 3 and enter Study TAK-664-3002, the dose regimen will be determined on a case-by-case basis.

The dose of IGSC, 20% infusion was established in Study TAK-664-3001 and is assumed to maintain the target IgG trough level ≥5 g/L (Epoch 2: approximately between 50 and 200 mg/kg of IGSC, 20% weekly, Epoch 3: approximately between 100 and 400 mg/kg of IGSC, 20% biweekly).

When the IgG trough level is found not to be maintained at ≥5 g/L during the study, adjustment of the dose is allowed at the discretion of the investigator.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied, which will require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-664, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the study site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7. SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

Japanese subjects aged 2 years or older with PID are enrolled in this study. All entry criteria, including test results, need to be confirmed prior to first dose.

7.1 Inclusion Criteria

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

1. Subject has completed or is about to complete Takeda Clinical Study TAK-664-3001.

   A subject is considered to have completed Study TAK-664-3001 successfully if they fulfill the following criterion:

   - Completed Epoch 2, in which IGSC, 20% is administered weekly (completion of Epoch 3, in which IGSC, 20% is administered biweekly, is not mandatory for participation in TAK-664-3002 study).
2. 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.
3. Subject is willing and able to comply with the requirements of the protocol.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Subject has developed a new serious medical condition during participation in Study TAK-664-3001 such that the subject’s safety or medical care would be impacted by participation in the extension study TAK-664-3002.
2. Subject is scheduled to participate in another non-Takeda clinical study involving an Investigational Product or device-used-in-clinical-trial in the course of this study.
3. If a female of childbearing potential, subject is pregnant or has a negative pregnancy test but does not agree to employ adequate birth control measures for the duration of the study.

7.3 Excluded Medications

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

- Other IgG products after first exposure to study drug.
- Hyper immune serum.
- Immunosuppressive drugs following transplantation.

Pre-medication on the Day of 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.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, see Section 9.1.12.

1. AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
2. Lack of efficacy: The investigator has determined that the subject is not benefiting from study treatment; and continued participation would pose an unacceptable risk to the subject.
3. Non-compliance with study drug.
4. Non-compliance with study procedures.
5. Physician decision.
6. Pregnancy: The subject is found to be pregnant.
   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.9.
7. Progressive disease.
8. Significant protocol deviation: The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
9. Withdrawal by parent/guardian.
10. Withdrawal by subject: The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

11. Lost to follow-up: The subject did not return to the clinic and 3 attempts to contact the subject were unsuccessful. The 3 attempts should be documented. At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgment of receipt request) asking that the subject return to the study site for final safety evaluations and return any unused study drug.
12. Death.
13. Study site terminated by the sponsor.
14. Study termination: The sponsor, IRB or regulatory agency terminates the study.
15. Other.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8. CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study Drug

The study drug 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 to 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 IB.

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

8.1.1.2 Packaging

Immune Globulin Subcutaneous (Human), 20% Solution 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.

8.1.1.3 Labeling

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

8.1.2 Storage

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

Study drug must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug 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 study site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the study drug and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

All study drug 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 study drugs must be maintained, as well as chain of custody, for all study drug movement.

8.1.3 Dose and Regimen

In principle, the dose regimen established in TAK-664-3001 should be maintained during the extension study. Subjects who complete Epoch 2 will start weekly dosing, and subjects who complete Epoch 3 will start biweekly dosing. The dose interval may be switched to weekly or biweekly on a case-by-case basis for the subjects if needed. For subjects who discontinue Epoch 3 and enter Study TAK-664-3002, the dose regimen will be determined on a case-by-case basis.

The dose of IGSC, 20% infusion was established in Study TAK-664-3001 and is assumed to maintain the target IgG trough level ≥5 g/L (Epoch 2: approximately between 50 and 200 mg/kg of IGSC, 20% weekly, Epoch 3: approximately between 100 and 400 mg/kg of IGSC, 20% biweekly). The dose can be modified based on subject's IgG level/condition/body weight.

Infusion Volumes and Rates

The infusion rate and volume that was tolerated in the TAK-664-3001 study and as recommended by the investigator will be followed in this study. Multiple infusion sites can be used for infusion simultaneously as determined by the subject and investigator. Infusions will be conducted with a pump. It is suggested to complete the administration within 2 hours due to the potential formation of particles caused by siliconized syringes.

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. In-Text Table 8-1 presents the volume and rate of infusion, (when tolerated well by the subject).

In-Text Table 8-1. Infusion Volume and Rate

Infusion Parameters	Subsequent Infusions	
	Subjects <40 kg	Subjects ≥40 kg
Volume (mL/site)	≤60	
Rate (mL/h/site)	≤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 2 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% average 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.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database.

An overdose should be reported to the sponsor according to the serious adverse event (SAE) reporting procedure whether or not they result in an AE/SAE according to the procedure outlined in Section 10.2.2.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of overdose unless it results in an SAE.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

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 interactive response technology (IRT) as they consent to take part in the study. Within each study site (numbered uniquely within a protocol), the subject number is assigned according to the sequence of subject presentation for study participation.

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

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

8.3 Device-Used-in-Clinical-Trial/Device-related Defects

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

Device name	FREEDOM60® Integrated Syringe Infusion System
Type	Infusion Pump Syringe Driver
Manufacturer	KORU Medical Systems
Version	Not Applicable

8.3.1 Marketing Approval

The FREEDOM60 Syringe Driver® is US FDA 510(k) Class 2 device under K200176. Further, the device is CE marked as a Class 2a, in accordance with EU Medical Device Directive 93/42/EEC.

The FREEDOM60 Integrated Syringe Infusion System consists of the following components:

- FREEDOM60 Syringe Driver
- Precision Flow Rate Tubing™
- HIgH-Flo SC Safety Needle Sets™.

The FREEDOM60 Integrated Syringe Infusion System has not yet been approved for marketing in Japan.

8.3.2 Indications for Use

The FREEDOM60 Syringe Driver is indicated for use with Becton Dickinson & Co. BD® Plastipak™ Luer-Lok® 50 mL (EU Reference #300865, US Reference #309653).

The FREEDOM60 Syringe Driver is an ambulatory device designed to accommodate a BD Plastipak Luer-Lok 60 mL Syringe (Catalog No.: 8881-560125, BD 309653), and fluid volumes ranging from 10 to 60 cc. The pump uses a constant force spring mechanism to apply pressure to the plunger-end syringe.

The FREEDOM60 Integrated Syringe Infusion System is assembled by loading the prefilled syringe with tubing into the FREEDOM60 Syringe Driver.

The infusion system is indicated for continuous delivery at controlled infusion rates via IV and SC route. The infusion system is indicated to deliver SC infusion of immune globulin human plasma derived Igs, electrolyte solutions, iron chelating agents, and infusible selective immunosuppressants; and IV infusion of beta lactamase resistant penicillin's, other aminoglycosides, and carbapenems.

The infusion system is indicated for continuous delivery of SC infusion of TAK-664 at controlled rate.

8.3.3 Usage Instructions and Warnings

For the usage instructions and warnings, please refer to Site Infusion Manual and Subject Infusion Manual.

8.3.4 Device-related Defects

Investigators are required to report device-related defects to sponsor within 24 hours. Please report the device-related defects using the "Clinical Trial Material Complaint Form" via the email address: [redacted]

The Reference Safety Information (RSI) for the Devise-Used-in-the-Clinical-Trial is the Instructions For Use, which the sponsor has provided under separate cover to all investigators in Japan.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

Investigators will be provided with sufficient amounts of the study drug to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the study drug, documenting shipment content and condition. Accurate records of all study drug 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 (eg, 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 study drug only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the study drug carrying his/her treatment assignment. All administered/dispensed medication will be documented in the subject's source and/or other study drug record. The investigator is responsible for ensuring the retrieval of all study supplies from subjects. Due to the health/safety concerns with returning the study drug container, the investigator must request that subjects keep the empty study drug packaging after use and return it to the study site for drug accountability purposes.

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

No study drug stock or returned inventory from a Takeda-sponsored study may be removed from the study 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 study drug, and empty/used study drug packaging are to be sent to a nominated contractor on behalf of the sponsor. Study drug being returned to the sponsor's designated contractors must be counted and verified by study site personnel and the sponsor (or designated contract research organization [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 (ie, IRT) do not require a shipment form. Returned study drug must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any study drug prior to shipment. Shipment of all returned study drug must comply with local, state, and national laws.

Based on entries in the study 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.

9. STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or study site personnel whenever possible. The Schedule of Study Procedures is located in Appendix-Table 1.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed. In this study, informed consent is expected to be obtained at the last visit or prior to the last visit of Study TAK-664-3001.

A subject identification number (subject number) will be assigned to each subject via the IRT at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Subject demographic information including gender, age, and race will be collected in the main study (TAK-664-3001).

Medical and medication history will be collected and recorded in the subject's source documents. When the evaluation is performed in the Study TAK-664-3001, the medical and medication history will not be collected in this study at the Baseline Visit.

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 eCRFs.

9.1.3 Physical Examination Procedure

At baseline and subsequent scheduled study visits at the site (see Appendix-Table 1), 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 baseline, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease, not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

9.1.4 Vital Sign Procedure

Vital signs will include height (in or cm), weight (lb or kg), body temperature (°C or °F), respiratory rate (breaths/minute), pulse rate (beats/minute), and systolic and diastolic blood pressure (mmHg). Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least 1 minute. Vital signs can be measured at subject's home as described in Section 9.3.2.

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. Vital signs at home will be recorded in subject diary and will be reviewed by investigators.

9.1.5 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. This information can be taken from subjects at home by the procedure determined by each study site (eg, telephone, telemedicine to subject's home) as described in Section 9.3.2.

Requirement for all antibiotic therapy must be documented as an AE. Prophylactic treatment with systemic antibacterial antibiotics is allowed during the study. The use of antibiotics should be recorded as concomitant medication.

9.1.6 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, or physical examination abnormalities noted at baseline examination, according to the judgment of the investigator. As subjects are from the preceding study (TAK-664-3001), concurrent medical conditions will be those recorded in TAK-664-3001.

9.1.7 Procedures for Clinical Laboratory Samples

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.

Laboratory tests including assessment of IgG trough levels will be performed every 12 weeks from Visit 1.

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

The Common Toxicity Criteria of the (Eastern Cooperative Oncology Group, 2006) will be used to grade the following laboratory values: alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), hemoglobin, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and white blood cell (WBC) count. Grading for lactate dehydrogenase (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).

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 Section 10.1). 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 laboratory error, was due to a pre-existing disease (see Section 10.1.3), 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 shall be re-tested and confirmed.

9.1.7.1 Hematology and Clinical Chemistry

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

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, ALT, serum total bilirubin, AST, ALP, LDH, BUN, serum creatinine, creatinine phosphokinase, glucose, haptoglobin, and lipase.

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

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

9.1.7.2 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-Table 2. These assessments will be performed at the central laboratory. Local laboratory can be used if deemed necessary.

A urine pregnancy test will be performed at the study site for females of childbearing potential which is indicated in Appendix-Table 2 (see also Section 9.1.9).

9.1.7.3 Specialty Tests

Specialty tests include: hepatitis B surface antigen, polymerase chain reaction (PCR) for hepatitis C virus (HCV) and PCR for human immunodeficiency virus (HIV)-1/2. For a schedule of laboratory test blood drawings, see Appendix-Table 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, hepatitis A virus (HAV), hepatitis B virus (HBV), HCV, hepatitis E virus (HEV), or Parvovirus B19 (B19V).

9.1.7.4 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:

- direct antiglobin test (Coombs-test or antiglobin test)
- urine hemosiderin

In addition, these assessments 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).

Hemolysis test will be done every 24 weeks from Visit 1. For a schedule of laboratory test blood drawings, see Appendix-Table 2.

9.1.7.5 Specific Antibodies

Specific antibody tests (quantitative method) to clinically relevant pathogens (*Clostridium tetani* toxoid, *Haemophilus influenzae* Type B [HIB] and HBV) will be performed.

For a schedule of specific antibody testing see Appendix-Table 2.

9.1.8 Contraception and Pregnancy Avoidance Procedure

9.1.8.1 Definitions and Procedures for Contraception and Pregnancy Avoidance

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 the study drug. 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 the study drug.

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 1 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 Baseline Visit. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, or vaginal ring), stabilized for at least 30 days prior to the Baseline Visit, plus condoms. Note: If the subject becomes sexually active during the study, she should use 1 of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

9.1.8.2 Contraceptive Guidance

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

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] ➢ Oral
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] ➢ Intrauterine device ➢ Intrauterine hormone-releasing system Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment

9.1.9 Pregnancy

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

All pregnancies are reported from the time informed consent is signed until the End of Study (EOS)/Early Termination Visit.

Any report of pregnancy for any female study participant must be reported within 24 hours of the investigator's awareness, using a pregnancy notification form (see Appendix F).

A copy of the Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO medical monitor using the details specified in the Appendix F. The pregnant female subject must be withdrawn from the study.

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

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

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported in the Safety Report Form as well in the Pregnancy Report Form. The test date of the first positive urine hCG or serum β-hCG test or ultrasound result will determine the pregnancy onset date.

9.1.10 Pharmacokinetic

9.1.10.1 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-Table 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.

9.1.11 Efficacy

9.1.11.1 Acute Serious Bacterial Infection Rate

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

The diagnostic criteria for ASBIs are included in Appendix E.

The ASBI rate will be calculated as the mean number of ASBI per subject per year in the All-Treated Set.

9.1.11.2 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.
   This information will be collected using diaries or other source data options throughout the study and will be transcribed to eCRFs.
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 eCRFs.
4. Number of hospitalizations due to illness/infection and length of stay (in days)
   Admissions to a hospital as an inpatient 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 eCRFs.
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 eCRFs.

9.1.11.3 Treatment Preference

Treatment preference will be assessed at the Baseline Visit and the EOS/Early Termination Visit in this study.

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

9.1.11.4 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 9.1.11.2.

9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

The primary reason for screen failure should be recorded in the eCRF using the following categories:

- AE
- Did not meet eligibility criteria
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal
- Study termination
- Other.

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

9.1.13 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the treatment phase.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

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

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Study Entrance

Informed consent is expected to be obtained at last visit or prior to last visit of Study TAK-664-3001. The subjects will undergo screening/baseline procedures for determination of eligibility. Baseline can correspond to the EOS Visit of Study TAK-664-3001. In such case, the Screening/Baseline Visit and Visit 1 can be on the same day. The following procedures will be performed and documented:

- Informed consent
- Eligibility criteria
- Physical examination
- Vital signs
- Laboratory assessments as per Appendix-Table 2
- Assessment of non-drug therapies
- Assessment of concomitant medication
- Assessment of AEs
- Collection/Review of Diary (Diary of Study-TAK-664-3001)
- Treatment Preference
- Healthcare Resource Utilization.

9.3.2 Treatment Phase

Eligible subjects will receive IGSC, 20% until the commercial IGSC, 20% is available at each study site or study termination (estimated duration: approximately 3 years).

The number of infusion visits and study site visits during the SC treatment period will depend on where the SC injection is administered. Infusions may be performed at home or at the study site, at the investigator's discretion. The decision where the SC injection is administered is made during Study TAK-664-3001, however the location of injection administration can be changed based on the investigator's and subject's agreement.

Subjects should come to the study site for visits when laboratory test samples are to be collected every 12 weeks. Subjects are not required to come to the study site if all procedures/assessments can be performed at home. The following procedures will be performed and documented:

- Physical examination
  Physical examination will be performed only on subject's study site visits.
- Vital signs
  Height will be measured at every 24-week visit starting from Visit 1 and it will not be required at other visits. Respiratory rate will be measured when the subjects come to study site, and it will not be required at visits from home. Weight, body temperature, pulse rate, systolic and diastolic blood pressure will be measured at all visits. At home, these will be measured with equipment provided by the sponsor and the measurement results should be recorded in subject diaries.
- Laboratory assessments as per Appendix-Table 2
- Assessment of non-drug therapies
  At Visit 2 or Visit 3, this information will be taken with procedure determined by each study site (eg, telephone, telemedicine) from subjects at home. At the time of weekly or biweekly treatment other than site visits, subjects will record this information in subject's diary.
- Assessment of concomitant medication
  At Visit 2 or Visit 3, this information will be taken with procedure determined by each study site (eg, telephone, telemedicine) from subjects at home. At the time of weekly or biweekly treatment other than site visits, subjects will record this information in subject's diary.
- Assessment of AEs
  At Visit 2 or Visit 3, this information will be taken with procedure determined by each study site (eg, telephone, telemedicine) from subjects at home. At the time of weekly or biweekly treatment other than site visits, subjects will record this information in subject's diary.
- Collection/Review of diary
  During the study site visit and home visit, the investigator or designee will inquire about subject diaries for pages of changes in subject's condition, administration status (including healthcare resource utilization) and vital sign results. Subject diaries will be collected when the subjects visit the study sites.
- Administration of study drug
  Infusions may be performed at home or at the study site, at the investigator's discretion

- Healthcare Resource Utilization.
  At Visit 2 or Visit 3, this information will be taken with procedure determined by each study site (eg, telephone, telemedicine) from subjects at home. At the time of weekly or biweekly treatment other than site visits, subjects will record this information in subject's diary.

9.3.3 End of Study Visit or Early Termination

The following procedures will be performed and documented:

- Physical examination
- Vital signs
- Laboratory assessments
- Assessment of non-drug therapies
- Assessment of concomitant medication
- Assessment of AEs
- Collection/Review of diary
- Treatment Preference
- Healthcare Resource Utilization.

For all subjects receiving study drug, the investigator must complete the EOS eCRF page.

9.3.4 Post Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10. PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

Not applicable.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values:

- Changes in laboratory values are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

10.1.4 SAEs

An SAE is defined as any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to study treatment or not at any dose):

1. Results in DEATH.
2. Is LIFE-THREATENING.
   Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
   Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.
   For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT.
   Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:

- Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.
- Reviewed and confirmed seroconversion for HIV, HAV, HBV, HCV, HEV, or B19V.

Adverse events that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Unexpected Adverse Event

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the RSI. "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IGSC, 20% IB and/or prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

10.1.6 Suspected Unexpected Serious Adverse Reaction

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

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

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

Symptoms of the Disease under study

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

Pre-existing conditions prior to randomization or initiation of study medication are described in the medical history, and those that manifest with the same severity, frequency, or duration after drug exposure, are not be recorded as AEs. However, when there is an increase in the severity, duration or frequency of a pre-existing condition, the event must be described on the AE CRF.

10.1.7 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

- Mild: The event is transient and easily tolerated by the subject.
- Moderate: The event causes the subject discomfort and interrupts the subject's usual activities
- Severe: The event causes considerable interference with the subject's usual activities.

10.1.8 Causality of AEs

An investigator must make the assessment of relationship to study drug for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study drug.

If there is no valid reason for suggesting a relationship, then the AE should be classified as "unlikely related" or "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE, then the AE should be considered "probably related" or "possibly related". The causality assessment must be documented in the source.

The relationship of each AE to study drug will be assessed using the following categories:

In-Text Table 10-1. Relationship of AE to Study Drug

Probably related	The temporal relationship between the event and the administration of the study drug is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Possibly related	Suggests that a reasonable temporal sequence of the event with the study drug administration exists and the likely causal association of the event with the study drug. This will be based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the investigator's clinical experience.
Unlikely related	Suggests that the clinical picture is highly consistent with a cause other than the study drug, but attribution cannot be made with absolute certainty and a relationship between the study drug and adverse event cannot be excluded with complete confidence.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the study drug and the event.

10.1.9 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.10 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

The start date of AEs will be determined using the following criteria:

In-Text Table 10-2. Criteria for Start Date of Adverse events

Adverse events	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.1.11 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.12 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.13 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.14 Outcome

- Recovered/Resolved – subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.
  - Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

- For any SAE that results in the subject's death or any ongoing events at the time of death, unless another study drug (IGSC, 20%) action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the study drug (IGSC, 20%) should be recorded as "dose not changed" or "not applicable" (if the subject never received study drug [IGSC, 20%]). The study drug action of withdrawn should not be selected solely as a result of the subject's death.

- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time that the subject is first administered study drug. Routine collection of AEs will continue until EOS/Early Termination Visit. All AEs 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. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter or vital sign measure, can represent an AE if the change is clinically relevant or if, during administration of study drug, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration of the study drug, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, which were not present at the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, or vital sign parameter is clinically significant and represents an AE.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until 30 days after EOS/Early Termination Visit. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date.
- Frequency.
- Intensity.
- Investigator's opinion of the causal relationship between the event and administration of study drug(s) (probably related, possibly related, unlikely related, or not related).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study drug.
- Outcome of event.
- Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

An SAE should be reported by the investigator to the sponsor/the Emergency Reception Center for Safety Information (ERCSI) (see Appendix F) within 24 hours/1 business day of the SAE occurrence, along with any relevant information. The investigator should submit the detailed Safety Report Form to the sponsor/the ERCSI appropriate personnel within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.

- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The investigator should submit the original copy of the Safety Report Form to the sponsor (Note: Source documents are not to be sent unless requested).

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up Safety Report Form (copy) or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all SUSARs and any other applicable SAEs to regulatory authorities, investigators, and IRBs, as applicable.

Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11. STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12. DATA HANDLING AND RECORD KEEPING

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

12.1 CRFs

Completed eCRFs are required for each subject who signs an informed consent.

A subject diary will be provided to each subject at enrollment to record the information. 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.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate study site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. Electronic CRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

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

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

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

Electronic CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated informed consent forms (ICFs), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

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

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

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

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

13. STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Specifications for the corresponding tables, figures, and listings (TFLs) will be provided separately, in the study TFL shells document.

Continuous endpoints/outcome measures (eg, change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation, minimum value, maximum value. Categorical endpoints/outcome measures (eg, AEs) will be summarized in terms of number and percent of subjects and number of occurrences in each category.

13.1.1 Analysis Sets

- All-Treated Set: All enrolled subjects who received IGSC, 20% administration at least once in this study, this will be efficacy analysis set.
- Safety Analysis Set (SAS): All enrolled subjects who received at least 1 dose of study drug (IGIV) in TAK-664-3001- study, this will be SAS.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized descriptively. As noted above, 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, and prior and concomitant medications.

13.1.3 Safety Analysis

Safety analysis will be performed using the SAS.

The primary objective of the study is to assess the long-term safety and tolerability. Safety and tolerability endpoints (defined in Sections 5.2.1 and 5.2.2) will be analyzed using descriptive statistics.

For laboratory and vital sign analyses, baseline will be defined as the last non-missing value before the time of participation in the TAK-664-3001 study.

13.1.3.1 Analysis of Adverse Events

13.1.3.1.1 Definitions

Treatment-emergent adverse events are defined as AEs with onset after date/time of first dose of study drug (IGIV) in Study TAK-664-3001, or medical conditions present prior to the start of study drug (IGIV) in Study TAK-664-3001 but increased in severity or relationship after date/time of first dose of study drug (IGIV) in Study TAK-664-3001.

Related TEAEs are defined as causally related TEAEs.

13.1.3.1.2 Handling of Recurrent AEs and Other AE situations

Multiple Severities and Relationships: For 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.

Related AEs: Any AE that is recorded as "probably related" or "possibly related" to study drug 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 the study drug. For example, if a subject experienced a mild headache not related to the study drug, and a moderate headache related to the study drug, then the subject will be counted once for headache using the moderate headache related to the study drug.

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

13.1.3.1.3 Occurrence and Numbers of Adverse Events

All AEs will be summarized by MedDRA System Organ Class (SOC) and PT. Only TEAEs will be analyzed.

Note: Hereafter, TEAE and AE are used interchangeably.

The following summaries will be provided:

- Number and percentage of subjects with TEAEs by SOC and PT, and overall
- Number of TEAEs by SOC and PT, and overall
- These summaries will be repeated by severity and relationship

The following approaches will be used, where applicable:

- Overall summary: Overall summary will include, but not limited to: Any TEAE, local TEAE, systemic TEAE, related TEAE, unrelated TEAE, severe TEAE, severe related TEAE, serious TEAE, serious related TEAE, TEAE leading to discontinuation from study, infusion-associated TEAE 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.
- Summaries by PT only: In the summaries, PT will be sorted in decreasing frequency.
- 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 1 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.

13.1.3.1.4 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 (SY), by SOC and PT

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

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

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

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

The following calculations apply, where applicable:

- AEs per infusion = number of AEs/total number of infusions administered to subjects in the analysis set.
- AE per subject = number of AEs/total number of subjects in the analysis set.

- AEs per SY = number of AEs/total number of days of exposure, ie., the sum of duration of treatment for all subjects in the analysis set, converted into years.
- AEs per 1000 SYs = 1000 × (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 in this study)/365.25. If the subject's last date is missing, then the date of last dose of study drug will be used if available.

13.1.3.1.5 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.

13.1.3.2 Clinical Laboratory Data

Raw (actual) values and change from baseline in clinical laboratory tests and vital signs will be summarized at each post-baseline assessment time point as continuous variables.

Shift from baseline (shift table) to each post-baseline assessment time point will be provided for laboratory 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.

13.1.3.3 Vital Signs

Raw (actual) values and change from baseline in vital sign tests will be summarized at each post-baseline assessment time point as continuous variables.

13.1.4 Serum IgG Concentrations

Serum IgG concentrations will be summarized using descriptive statistics which will also include geometric mean and the corresponding 2-sided 95% confidence interval. Confidence intervals are for descriptive purposes. Caution should be exhibited in their interpretation as this study is not designed for hypothesis testing.

13.1.5 Efficacy Analysis

Efficacy analysis will be performed using the All-Treated Set. Assessment of efficacy is a secondary objective of the study. Efficacy endpoints are:

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

Efficacy endpoint data will be analyzed using descriptive statistics.

13.1.6 Other Analyses

13.1.6.1 Treatment Preference Analyses

Treatment preference data will be listed in the subject data listing(s). The following endpoint will be analyzed using descriptive statistics, as planned for the efficacy endpoints.

- Treatment Preference (EOS/Early Termination).

Endpoint details will be provided in the study SAP.

13.2 Interim Analysis

An interim analysis of study data will be undertaken to support the Japanese New Drug Application submission as described below.

It will summarize PK (Serum IgG trough levels), safety, efficacy, and tolerability of treatment with IGSC, 20% in all subjects with PID in this study. The snapshot date will be stated in the SAP. The target data will be all subject data obtained at snapshot date in this study. No adaptive design or data monitoring committee is planned for this study.

13.3 Determination of Sample Size

No formal sample size calculation has been performed in this extension study. A sample size of approximately 16 subjects is the estimated maximal number of subjects who can enroll from the previous TAK-664-3001 study.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, International Council for Harmonisation (ICH) GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

Alternative Approaches to Monitoring Due to Coronavirus Disease-2019 (COVID-19) or Other Unavoidable Circumstances

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

14.2 Protocol Deviations

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible IRB is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the IRB and applicable regulatory authorities of any investigator termination.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the Pharmaceuticals and Medical Devices Agency of Japan, other regulatory authorities, the sponsor or its representatives, and the IRB for each site.

15. ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or ethics committee for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity/signing a contract for the clinical study). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify the study site once the sponsor has confirmed the adequacy of study site regulatory documentation. Until the study site receives notification no protocol activities, including screening may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering into the study.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record.

Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the study site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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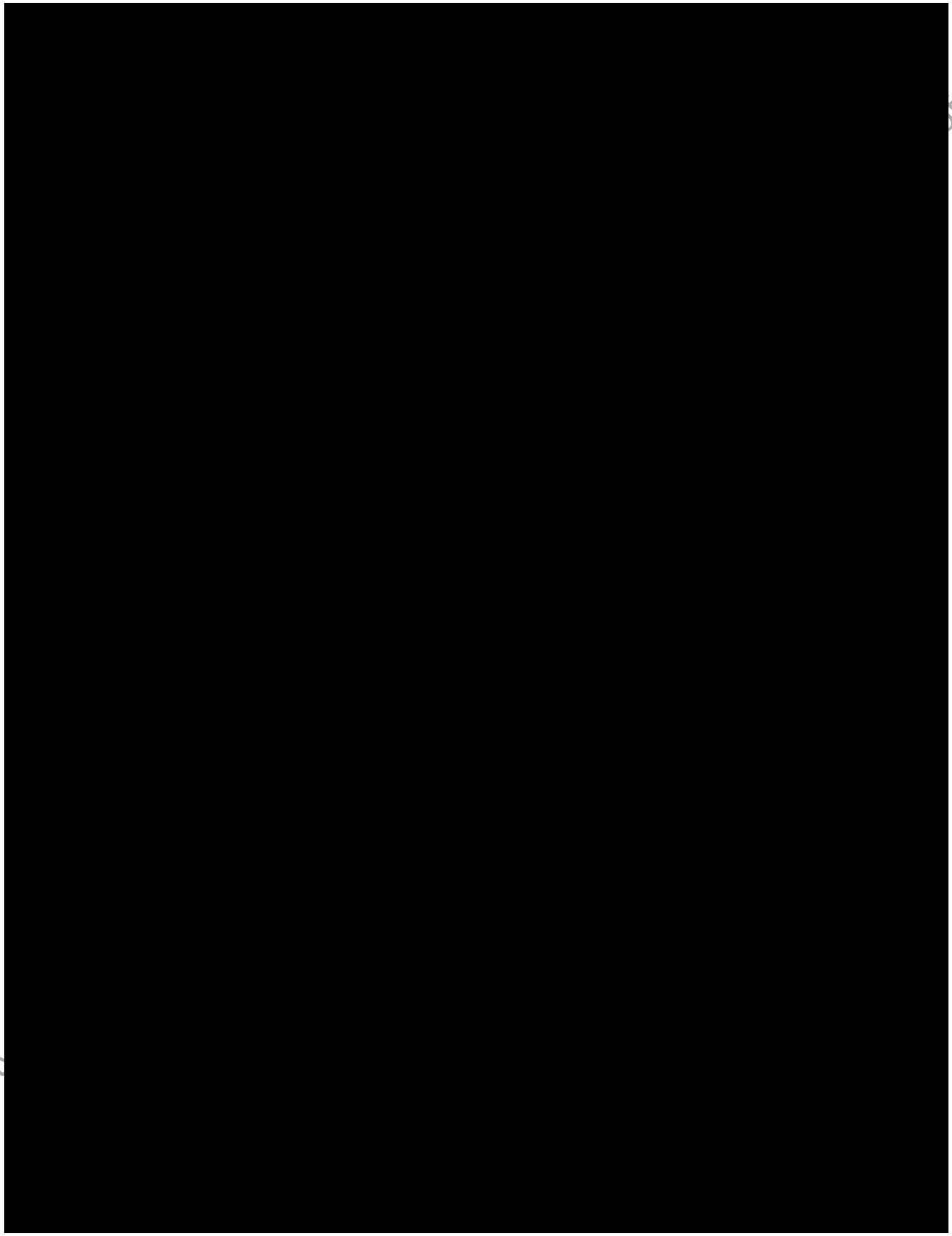

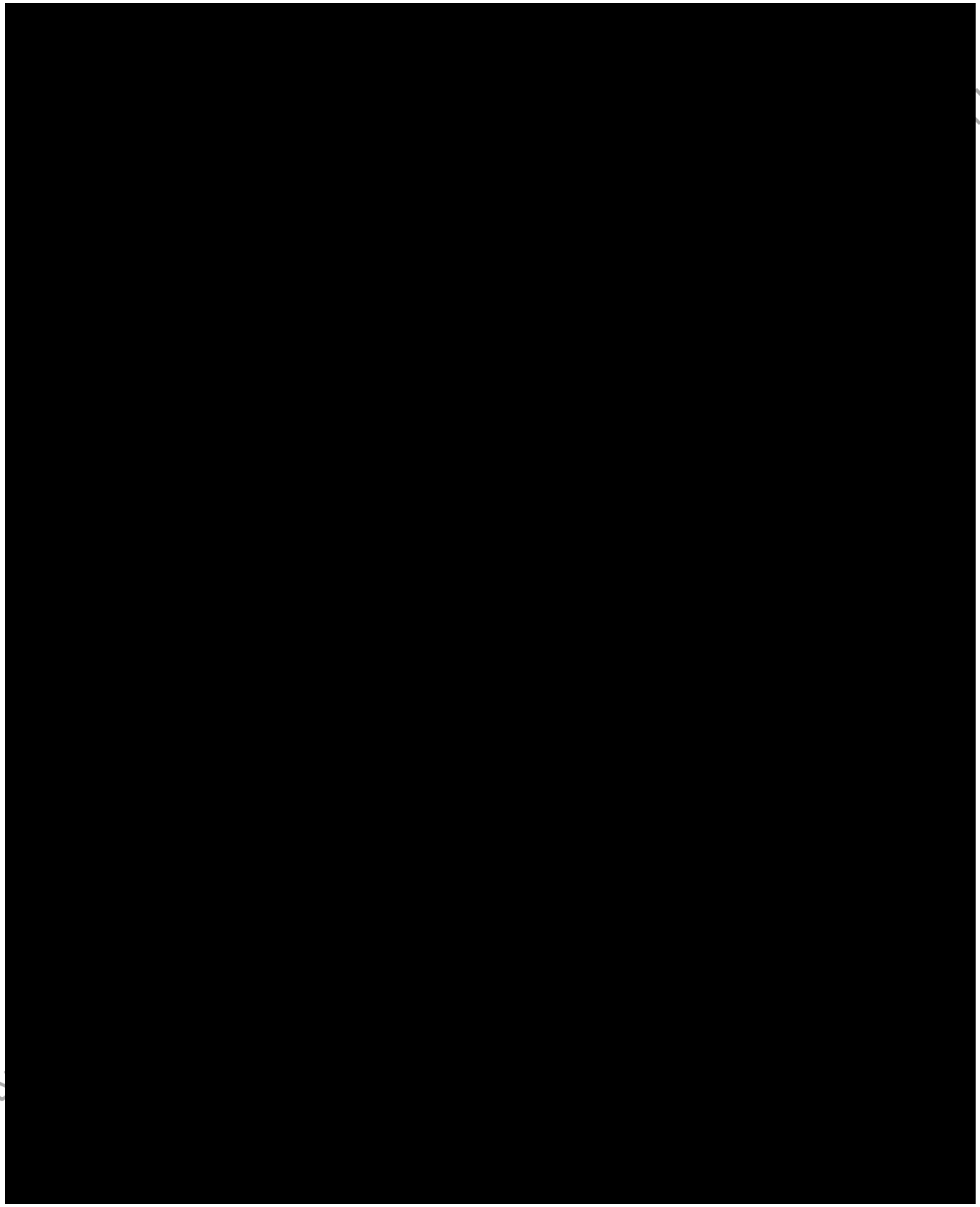

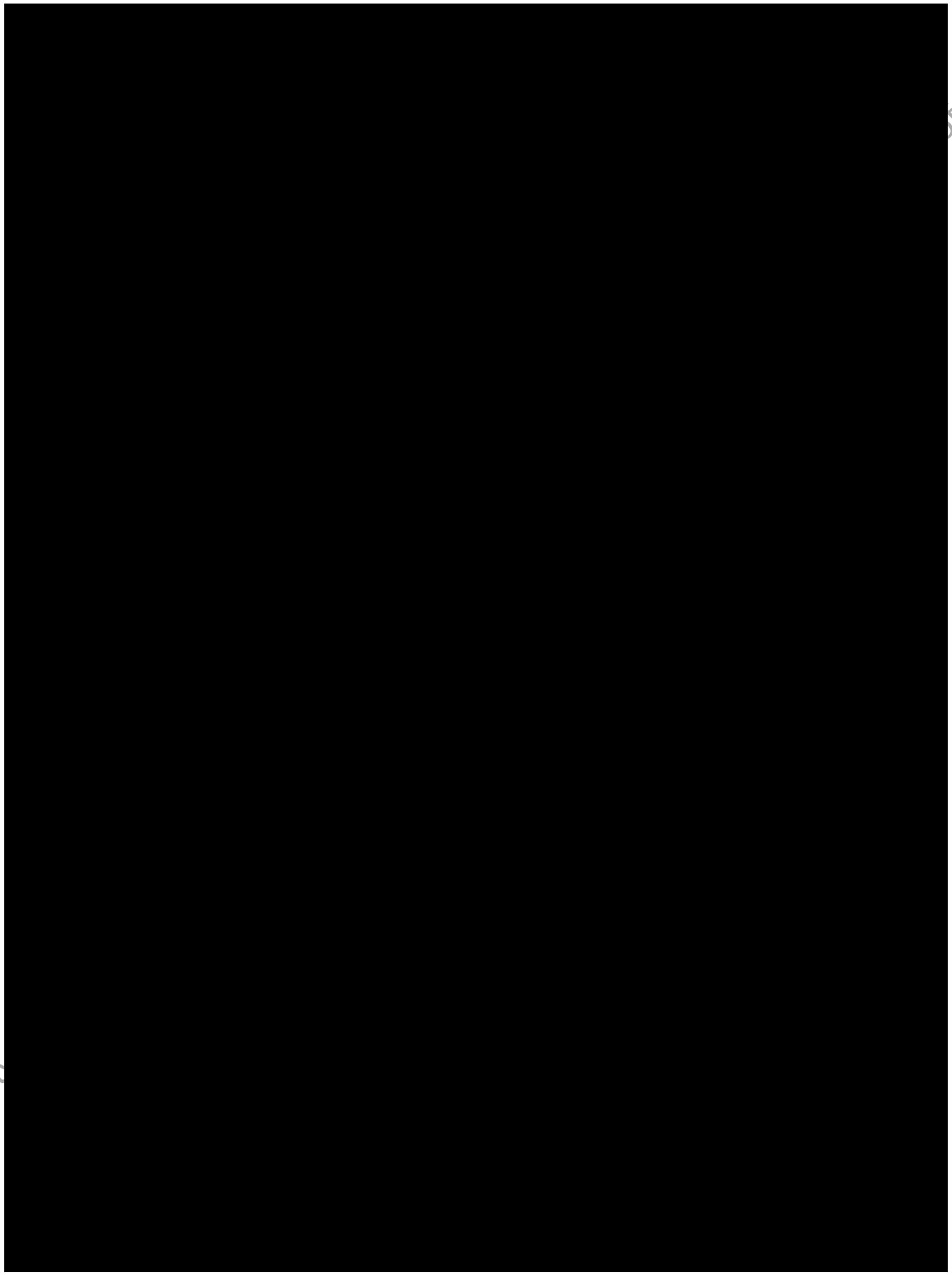

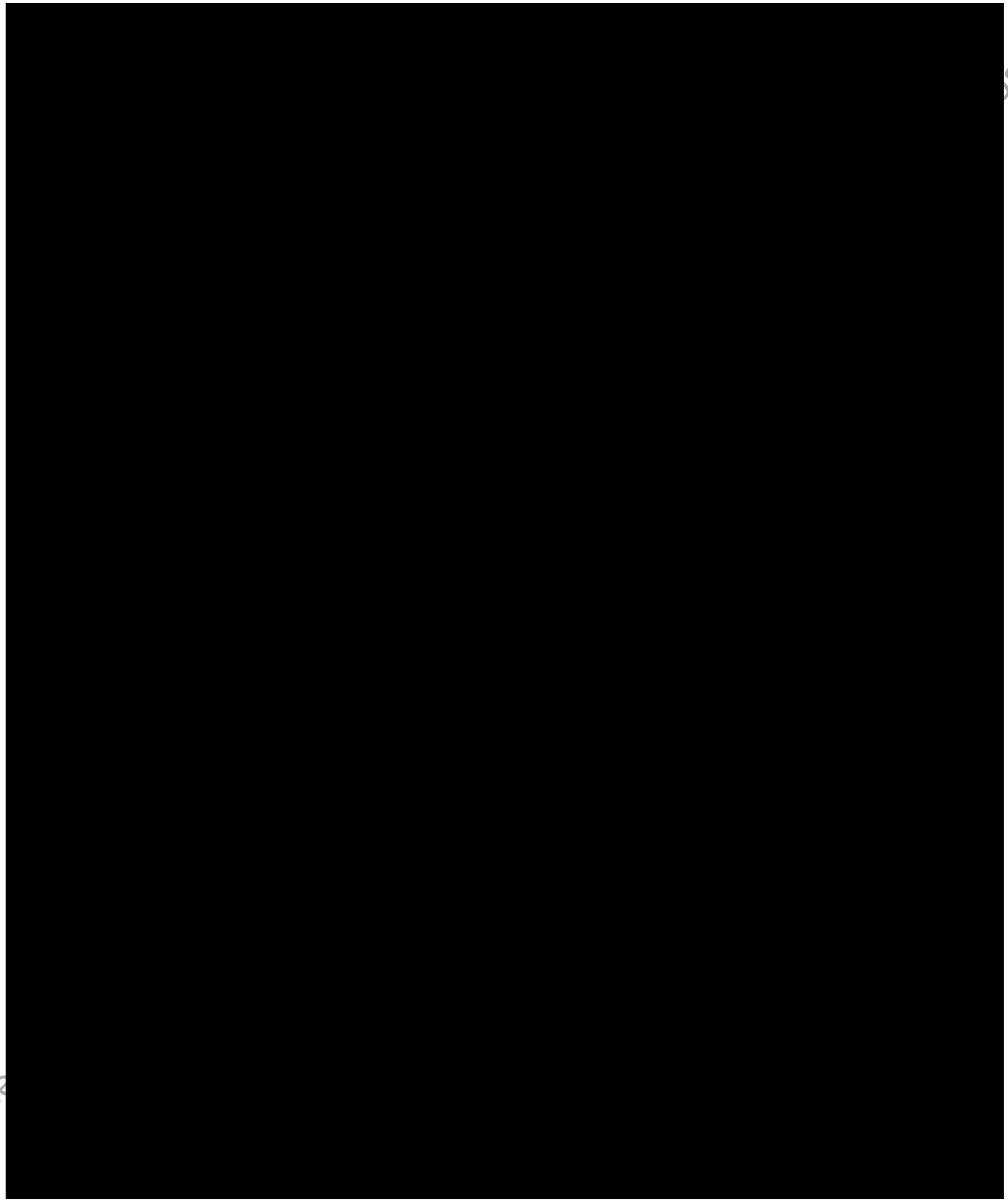

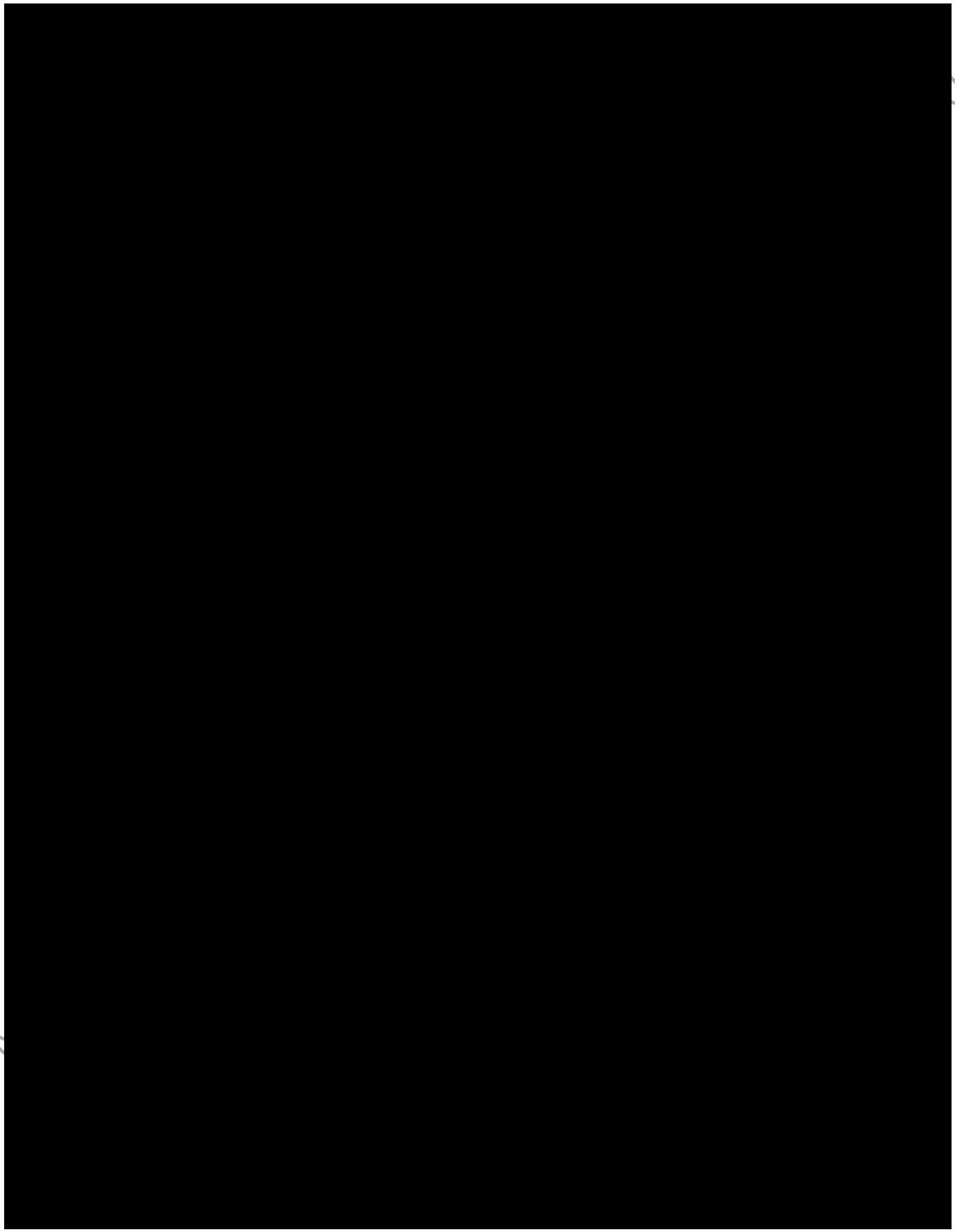

APPENDIX G. PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 3.0	28 Nov 2022	Japan
Protocol Amendment 2.0	19 Jul 2022	Japan
Protocol Amendment 1.0	02 Nov 2021	Japan
Original Protocol	18 Jan 2021	Japan

Summary of Changes Protocol Amendment 2.0

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Protocol Amendment 2.0	**Amendment Date 19 Jul 2022**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Relationship of adverse event to study drug.	The order and definitions for probably related and possibly related updated in order to clarify strength of relationship of adverse event to study drug.	Section 2 Section 5.2.1 Section 10.1.8 In-Text Table 10-1 Section 10.2.1.2 Section 13.1.3.1.2
Investigational device term was replaced with device-used-in-clinical-trial	To ensure consistency due to the modification of Japanese GCP	Section 2 Section 7.2
A new section for description of 'Device-used-in-clinical-trial' is added. The section also includes information regarding reporting of device related defects.	Due to the modification of Japanese GCP, information required for the 'Device-used-in-clinical-trial' is added.	Section 8.3
The study schema is updated	To indicate home visits	Section 2 Section 6.1
The following revision was done: Infusions may be performed at home or at the study site, at the investigator's discretion.	To allow administration of investigation product at home or study site.	Section 2 Section 6.1 Section 9.3.2 Appendix-Table 1 Schedule of Study Procedures

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
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The following revision was done: Subjects should come to the study sites for visits when laboratory test samples are to be collected every 12 weeks. Subjects are not required to come to the study site if all procedures/assessments can be performed at home.	Allow some visits to be done at subject's home without visiting the study site.	Section 2 Section 6.1 Section 9.3.2 Appendix-Table 1 Schedule of Study Procedures
The following sentence was amended to: The decision where the SC injection is administered is made during the Study TAK-664-3001, however the location of injection administration can be changed based on the Investigator's and subject's agreement	Statement added to provide flexibility to change the location of injection administration	Section 2 Section 6.1 Section 9.3.2 Appendix-Table 1 Schedule of Study Procedures
Added 'body weight' in the below sentence: "The dose can be modified based on subject's IgG level/condition/body weight"	To clarify 'body weight', is to be taken into consideration while calculating the dose.	Section 8.1.3
The following sentence is added: "The site may use an alternative method for dispensing. If permitted by country or local regulations and IRBs, the IP can be shipped from the site directly to the subject's home address. Subjects must be provided with instructions on how to receive, store, and ultimately return the IP/sponsor-supplied treatments."	Statement added for clarifying provision of IP to subject's home.	Section 8.4
The following sentences were added in Section 9.1.4 Vital signs can be measured at subject's home as described in Section 9.3.2. Vital signs at home will be recorded in subject diary and will be reviewed by investigators.	To specify what will be done during home visits.	Section 9.1.4

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The following statement was added in Section 9.1.5: This information can be taken from subjects at home by the procedure determined by each study site (eg, telephone, telemedicine to subject's home) as described in Section 9.3.2.	Statement added to clarify how information on intake of concomitant medication should be obtained during home visit.	Section 9.1.5
Visit 1 was added to the following statement Laboratory tests including assessment of IgG trough levels will be performed every 12 weeks from Visit 1	To clarify timing of laboratory testing	Section 9.1.7
Visit 1 was added to the following statement Hemolysis test will be done every 24 weeks from Visit 1.	To clarify timing of hemolysis testing	Section 9.1.7.4
Text added for physical examination, vital signs, assessment of non-drug therapies, assessment of concomitant medications, assessment of AEs, collection/review of diary, administration of study drug, and healthcare resource utilization	To specify what will be done during site and home visits.	Section 9.3.2
Appendix-Table 1. Schedule of Study Procedures is updated	The table and footnotes are updated to reflect the provision of home visits.	Appendix-Table 1 Schedule of Study Procedures.
Appendix-Table 2. Clinical laboratory assessments is updated	The table and footnote is updated to reflect the provision of home visits as well as study site visits.	Appendix-Table 2 heading: Clinical Laboratory Assessments at Study Site and Home Visits.
Minor grammatical, editorial and/or administrative changes have been made.	To improve the readability and/or clarity of the protocol.	Throughout the document

Summary of Changes Protocol Amendment 1.0

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Protocol Amendment 1.0	**Amendment Date 02 Nov 2021**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Changed the inclusion criteria #1 to allow subjects who have completed Epoch 2 to participate in this study even if they have not completed Epoch 3 in TAK-664-3001 study.	To provide subjects who discontinued Epoch 3 with their opportunities to continue weekly TAK-664 injection in TAK-664-3002 study.	Section 2 Section 6.1 Section 7.1 Appendix A
Extended the visit window from 28 days (±1 day) to 28 days (±2 days).	For more convenience of the subjects.	Appendix A
Extend the estimated duration of this study from approximately 2 years to approximately 3 years.	Updated to the latest information	Section 2 Section 6.1 Section 9.3.2
Added statement, 'For subjects who discontinue Epoch 3 and enter Study TAK-664-3002, the dose regimen will be determined on a case-by-case basis.'	As a guidance, in case the subject enters TAK-664-3002 study in the middle of Epoch 3.	Section 6.2 Section 8.1.3
Added the following criteria for discontinuation or withdrawal of the subjects: • Non-compliance with study drug • Non-compliance with study procedures • Physician decision • Progressive disease • Withdrawal by parent/guardian • Withdrawal by subject • Death • Study site terminated by the sponsor	To align with categories in the electronic case report form.	Section 7.4

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Protocol Amendment 1.0	**Amendment Date 02 Nov 2021**	**Japan**
Description of Change	***Rationale for Change***	***Section(s) Affected by Change***
Amended text to mention that, Overdose should be reported as a SAE irrespective of not having safety issue. Replaced the following text: "Cases of overdose without manifested signs or symptoms are not considered AEs. Adverse events associated with an overdose will be documented on AE eCRF(s) according to Section 10. Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2." with "An overdose should be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE according to the procedure outlined in Section 10.2.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of overdose unless it results in an SAE." The following is deleted: "Overdose: Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF."	To keep consistent with pivotal Study TAK-664-3001.	Section 8.1.4 Section 10.1.3
'Full Analysis Set' updated to 'All-Treated Set'	To keep consistent with pivotal Study TAK-664-3001.	Section 2 Section 9.1.11.1 Section 13.1.1 Section 13.1.5
Changed the definition of: 1)'All-Treated Set', as, 'all enrolled subjects who received IGSC, 20% administration more than once in the study' to 'all enrolled subjects who received IGSC, 20% administration at least once in the study.'	1) 'More than once' was an incorrect description and is replaced with 'at least once'.	Section 2 Section 13.1.1

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2)'Safety Analysis Set', as, all enrolled subjects who received at least 1 dose of study drug (IGIV) in TAK-664-3001 study.'	2) The SAS definition is modified to maintain consistency with the definition of TEAE and definition of SAS in the SAP.	
Changed the definition of 'baseline' as, for laboratory and vital sign analyses, "baseline will be defined as the last non-missing value before the time of participation in this study" to "baseline will be defined as the last non-missing value before the time of participation in the TAK-664-3001 study."	Corrected definition of 'baseline'	Section 2 Section 5.2.2 Section 13.1.3
Minor grammatical, editorial and/or administrative changes have been made.	To improve the readability and/or clarity of the protocol.	Throughout the document