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BLA Clinical Review Memorandum

Application Type	Efficacy Supplement - BLA
STN	125105/2184
CBER Received Date	8/29/2024
PDUFA Goal Date	6/29/2025
Division / Office	DCEGM/OCE
Priority Review (Yes/No)	No
Reviewer Name(s)	Aimee Magnarelli, DO (Clinical Reviewer, GMB1)
Review Completion Date / Stamped Date	June 27, 2025
Supervisory Concurrence Team Lead/Branch Chief (Acting), GMB1 Division Director (Acting), DCEGM/ Office Director (Acting), OCE	 Shelby Elenburg, MD Asha Das, MD
Applicant	Takeda Development Center Americas, Inc.
Established Name	Immune Globulin Infusion (Human) 10% solution
(Proposed) Trade Name	Gammagard Liquid ERC
Pharmacologic Class	Biologic: Immune Globulin

Formulation(s), including Adjuvants, etc.	Immune Globulin Infusion (Human), 10% Solution
Dosage Form(s) and Route(s) of Administration	Intravenous and Subcutaneous
Dosing Regimen	Intravenous • 300 to 600 mg/kg every 3 to 4 weeks based on clinical responses Subcutaneous • Initial dose: 1.37 x previous intravenous (IV) dose divided by # of weeks between IV doses • Maintenance dose: based on clinical response and target IgG trough level
Indication(s) and Intended Population(s)	Replacement therapy for primary humoral immunodeficiency (PI) in patients two years of age and older.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AR	adverse reaction
BLA	biologics license application
CMC	Chemistry, Manufacturing, and Controls
CVID	common variable immunodeficiency
ERC	enhanced removal capability
FDA	Food and Drug Administration
GGL	Gammagard Liquid
GG S/D	Gammagard S/D
IG	immune globulin
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgG4	immunoglobulin G subclass 4
IGIV	immune globulin intravenous
IGSC	immune globulin subcutaneous
IV	intravenous
PI	primary humoral immunodeficiency
PID	primary immunodeficiency
PK	pharmacokinetics
SAE	serious adverse event
SBI	severe bacterial infection
sBLA	supplemental biologics license application
SC	subcutaneous
TVR	triple virally reduced

1. EXECUTIVE SUMMARY

On August 29, 2024, Takeda Development Center Americas, Inc. submitted an efficacy supplement under BLA 125105/2184 for Gammagard Liquid ERC (TAK-880), a new immune globulin (IG) product for replacement therapy for primary humoral immunodeficiency (PI) in patients 2 years of age and older. TAK-880 is intended to restore serum immunoglobulin G (IgG) to protective levels to prevent or lessen the severity of infections in patients with PI.

No clinical studies were conducted with TAK-880. Instead, the Applicant leveraged efficacy and safety data from the original BLA approvals for Gammagard Liquid (GGL) and Gammagard S/D (GG S/D), along with Chemistry, Manufacturing, and Controls (CMC) comparability data demonstrating similarity between TAK-880 and these approved products. Substantial evidence of effectiveness of GGL and GG S/D were established in the original approvals based on rates of serious bacterial infections (GGL) and pharmacokinetic (PK) equivalence with another approved IG product (GG S/D). In clinical studies that supported approval of GGL (BLA 125105) for intravenous (IV, Study 160101) and subcutaneous (SC, Study 160601) administration in patients with PI, the primary efficacy endpoint was rate of acute serious bacterial infections (SBIs) as defined in accordance with FDA's Guidance for industry, "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency,"[1] which will be referred to as the FDA IGIV Guidance throughout the clinical review memo. The rates of acute SBI were 0 and 0.07 per person-year, respectively, which is consistent with effectiveness as defined by < 1 per person-year in the FDA IGIV Guidance. Approval of GG S/D (BLA 103133) was based on pharmacokinetic equivalence between GG S/D and another commercially available IG product, Gammagard (no longer on the market). The Applicant submitted a new study to this efficacy supplement (Study 160001, conducted outside the United States) to support similarities in infectious outcomes and PK parameters in patients who received both GGL and GG S/D, which provides greater assurance of the clinical comparability and similar effectiveness of both products.

Based on CMC findings that TAK-880, GGL, and GG S/D are sufficiently similar (with product comparability on major attributes), effectiveness of GGL and GG S/D can be leveraged to support approval of TAK-880 for the proposed indication of PI. Additionally, the review team assessed that there was sufficient data in pediatric patients with PI from the original GGL and GG S/D approvals to support leveraging of data to pediatric patients 2 years of age and older with PI for the TAK-880 product.

The safety profiles of GGL and GG S/D are similar to each other and to other IG products. Therefore, for the purposes of this review, safety findings primarily from GGL were used to support safety of TAK-880, given the greater similarity of product manufacturing and overall product comparability for attributes that would impact safety

[1] Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency: Guidance for Industry (June 2008), available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human

between TAK-880 and GGL. The most common adverse reactions (ARs) reported in ≥10% of patients who received GGL IV were headache, fatigue, pyrexia, chills, nausea, diarrhea, vomiting, dizziness, cough, pain in extremity, urticaria and asthma; and in those who received GGL SC were infusion site event, headache, pyrexia, fatigue, abdominal pain, and vomiting. Overall, the majority of ARs were mild, self-limited, and required minimal or no intervention for resolution.

The clinical review additionally focused on evaluating whether the data supported the proposed contraindication statement, which differs from other IG products by only contraindicating TAK-880 in patients with prior anaphylaxis to the product itself. This contraindication statement mirrors that of GG S/D, another product with reduced immunoglobulin A (IgA) content that is intended for patients with IgA deficiency and anti-IgA antibodies or anaphylaxis with other IG products. Although sample sizes were small, limited patient-level data from newly submitted studies and postmarketing experience with GGL and GG S/D support that patients with anaphylaxis or hypersensitivity to other IG products tolerated GG S/D. Therefore, it is reasonable to leverage this finding to support the proposed contraindication for TAK-880 to mirror that of GG S/D.

Based on the demonstration of substantial evidence of effectiveness and reasonable assurance of safety in the approvals of GGL and GG S/D, the newly submitted clinical data, and CMC comparability between TAK-880, GGL and GG S/D on key product attributes, the review team supports leveraging of clinical data from the approved products to TAK-880. The Clinical review team concludes that TAK-880 has a favorable benefit-risk profile for replacement therapy in PI patients 2 years and older, especially for those patients with IgA deficiency resulting in anaphylaxis to other IG products. The review team recommends approval of this efficacy supplement, with ongoing evaluation of the safety profile through routine postmarketing pharmacovigilance.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The review for this efficacy supplemental BLA primarily relied on the prior BLA approval for the products GGL and GG S/D. The study data from the original BLAs for GGL (BLA 125105) and GG S/D (BLA 103133) were reviewed in the context of the initial approvals for each product, and for GGL, the supplement that added SC administration as an option in addition to the already-approved IV route.

Previously reviewed BLAs for GGL and GG S/D study population demographics are as follows (Studies 160101, 160601, and 940163-CLN1):

BLA 125105 (GGL)

Study #1 160101

There were a total of 61 patients with PI, including 15 pediatric patients. Ages ranged from 6 years to 72 years (median age at enrollment was 34 years). Fifty-four percent were female, 93% were White, 5% were Black, and 2% were Asian.

Study #2 160601

There were a total of 49 patients with PI, including 18 pediatric patients. Ages ranged from 3 years to 77 years (median age at enrollment was 20 years). Fifty-five percent were male. Among those treated, 94% were White, 4.1% were Black, and 2% were Hispanic.

BLA 103133 (GG S/D)

Study #3 940163-CLN1

A total of 15 patients with PI were treated, including 9 pediatric patients. Ages ranged from 2 years to 41 years (median age at first infusion was 10 years. The mean age for patients previously treated was 15.7 years (range 2.5 to 41 years) and the mean age was 16.6 years (range 2.96 to 30.7 years) for previously untreated patients. Fifty-three percent were female. Race and ethnicity information were not available.

New to this sBLA Submission: Study 160001 (GGL and GG S/D):

New study summaries were provided for Study 160001 in which patients received both products, GGL and GG S/D. Efficacy and safety were compared in the study and the reports are described in Section 6. The study population included 22 patients, all of whom were adults. Ages ranged from 26 years to 70 years. Sixty-four percent were male. All patients were White.

1.2 Patient Experience Data

No patients received the new product.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiencies (PIDs) are a large heterogenous group of disorders resulting from inborn errors of immunity. They are characterized by absent or poor function in one or more components of the immune system. Consequently, affected patients are unable to mount an immune response to microorganisms and may experience recurrent protozoal, bacterial, fungal, and viral infections. The estimated overall prevalence of PIDs in the United States is approximately 1 in 1,200 live births; an exception is IgA deficiency, which occurs in approximately 1 in 200 to 1 in 500 persons.

PIDs are broadly classified based on the component of the immune system that is primarily disrupted. Disorders of the adaptive immune system include B-cell (humoral) immune deficiencies (also referred to as antibody deficiencies), T-cell (cellular) immune deficiencies, and combined (B-cell and T-cell) immunodeficiencies. PI is a humoral form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked agammaglobulinemia, common variable immunodeficiency (CVID), Wiskott-Aldrich syndrome, severe combined immunodeficiency, and congenital agammaglobulinemia. Patients with PI present with recurrent, often severe bacterial and viral infections affecting the respiratory tract, gastrointestinal system, skin, and other organs.

2.2 Currently Available Treatment(s)/Intervention(s) for the Proposed Indication(s)

Replacement therapy, comprised of polyclonal human normal IG infusions, is standard treatment for PI. IG is manufactured through fractionation of plasma pooled from many plasmapheresis donors and contains immune antibodies. IG restores serum IgG to protective levels and provides patients specific antibodies to prevent or minimize the

frequency or severity of severe bacterial and viral infections. For many patients, therapy is expected to be lifelong and increase life expectancy.

Additional infection prevention includes infection avoidance measures, vaccination, and prophylactic antibiotics. Treatment of infections often requires broad antimicrobial coverage and prolonged treatment courses. Bone marrow transplantation is a treatment option for some forms of PI (such as severe combined immunodeficiency) but is limited by availability of appropriate donors and is associated with multiple risks, including graft versus host disease, rejection of the graft, complications of conditioning agents, and death.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are numerous marketed IG products, which can be administered intravenously or subcutaneously, with similar efficacy but different safety profiles between the two routes of administration. There are currently eight licensed immune globulin subcutaneous (IGSC) (Human) products approved for adults and children 2 years of age and older with PI in the United States: Cuvitru (Baxalta US, Inc.), Hizentra (CSL Behring), Xembify (Grifols Therapeutics), Cutaquig (Octapharma), GGL (Baxter Healthcare Corporation), Gamunex-C, (Grifols Therapeutics), Gammaked (Kedrion Biopharma), and Hyqvia (Baxter Healthcare Corporation, Baxter Bioscience).

There are currently 14 licensed (Human) immune globulin intravenous (IGIV) products in the United States: Alyglo (GC Biopharma), Asceniv (ADMA Biologics, Inc.), Bivigam (Biotest Pharmaceuticals Corporation), Carimune (CSL Behring AG), Flebogamma DIF 5% and 10% (Instituto Grifols), GGL and GG S/D (Baxter HealthCare Corp), Gammaked (Kedrion Biopharma), Gammaplex 5% & 10% (Bio Products Laboratory), Octagam and Panzyga (Octapharma Pharmazeutika Produktionsges), Privigen (CSL Behring AG), and Yimmugo (Biotest AG). All are indicated as replacement therapy in patients with PI.

The safety profile for IGs as a class is well-established. The incidence of adverse reactions (ARs) reported in clinical studies supporting licensure varies according to the product, route of administration, and maximum infusion rate. Severe hypersensitivity reactions may occur with IGIV products. Common ARs for IGs (including those administered subcutaneously) include local infusion site reactions, headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. Most patients experience infusion site reactions with IGSC infusions, but few are severe. Systemic ARs are more likely with IGIV products but can occur with IGSC products. IGIV as a drug class carries an obligatory boxed warning for thrombosis, renal dysfunction, and acute renal failure. IGSC products carry an obligatory boxed warning for thrombosis. Other rare risks associated with the use of IGIV include hypersensitivity/anaphylaxis, transmission of infectious agents (e.g., viruses), hemolysis, aseptic meningitis, transfusion-associated lung injury, hyperproteinemia, and increased serum viscosity.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

There is no previous human experience with this product.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Initially an original BLA was submitted for TAK-880 which was later withdrawn and resubmitted as a CMC Prior Approval Supplement under the GGL BLA 125105 following FDA feedback. Following the Complete Response Letter received for the CMC Prior Approval Supplement, and based on FDA recommendations, TAK-880 was resubmitted as GGL Low IgA via an efficacy supplement to the GGL BLA 125105. There were initial promotional concerns regarding the intended commercial name of the new product, which was adjusted to GGL ERC during the course of interactive review.

Table 1. Regulatory History Correspondence

Regulatory History Correspondence
Type C meeting request: July 31, 2020
WRO to Type C meeting provided January 12, 2021
WRO clarification March 31, 2021
Comparability protocol submitted July 29, 2021
Biologics License Application (BLA) submitted September 28, 2022
Resubmitted as CMC PAS to Gammagard Liquid BLA on November 21, 2022
Complete Response Letter from FDA related to CMC PAS
Type A meeting September 14, 2023
TAK-880 presubmission Type B meeting request January 26, 2024
Type C meeting April 10, 2024 canceled (FDA found proposal acceptable)

Source: Reviewer table
Abbreviations: CMC, Chemistry, Manufacturing, and Controls; PAS, prior approval supplement; WRO, written response only

2.6 Other Relevant Background Information

This supplemental efficacy BLA is for TAK-880, a new IG product for the indication of replacement therapy for PI. No clinical data were obtained for the product under review, and it was agreed in presubmission meetings with Takeda that clinical data from similar approved products, GGL and GG S/D, could be leveraged in lieu of conducting clinical studies with TAK-880 because:

1. TAK-880 utilizes the same drug substance as GGL but undergoes (b) (4) anion exchange chromatography step that lowers the IgA (b) (4) content as compared to GGL;
2. IgA content is expected to be similar between TAK-880 and GG S/D; and
3. TAK-880 is intended to replace GG S/D commercially, and the target population is patients with PI and low IgA and anti-IgA antibodies and/or those with history of anaphylaxis to other IG products.

As the target population is expected to be very rare, it was previously agreed that studies in this population would be impracticable.

GG S/D has a broad indication for PI but clinically is primarily reserved for the target population noted (low IgA with anti-IgA antibodies and/or anaphylaxis with other products) because of how the contraindication statement is framed (anaphylaxis with GG S/D) as compared to other IG products (anaphylaxis with prior IG or low IgA with anti-IgA antibodies). Therefore, it is understood that clinical data with GG S/D in the target population is very limited, because:

1. GG S/D was initially studied in the broader PI population (for pharmacokinetics [PK] and safety only, with efficacy inferred from crossover from another with IGIV product), and
2. Postmarketing data in the target population is limited due to infrequent use and expected missing data in real-world evidence settings.

The Applicant requested labeling for TAK-880 with a similar contraindication statement to GG S/D (i.e., the only contraindication is prior anaphylaxis to TAK-880), so that the product would be available for this target population that may have no other available IG replacement options once GG S/D is discontinued.

During presubmission interactions with Takeda, it was acknowledged that relevant GGL and GG S/D clinical data in this rare population to support similar labeling for TAK-880 would be limited. However, the Applicant agreed to submit any available clinical data (in addition to data originally submitted for the GGL and GG S/D BLAs).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate a complete clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document according to the FDA Guidance for Electronic Submissions. Submission modules were in the common technical document structure.

3.2 Compliance With Good Clinical Practices and Submission Integrity

The Applicant affirms that the studies were conducted in compliance with Good Clinical Practices and conforms with appropriate local laws and regulations and the Declaration of Helsinki.

3.3 Financial Disclosures

This sBLA includes GGL and GG S/D studies that were completed between 1992 and 2009, submitted previously to the FDA and met all financial disclosure requirements at that time. There have been no updates to the financial disclosure since these studies were completed. An FDA Form 3454 was submitted to support this submission.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The clinical review of the supplemental BLA relied heavily on CMC comparability data. For full details, please refer to the CMC review memorandum. For completeness, we have included the CMC review memorandum summary here.

> "Takeda seeks approval of GAMMAGARD LIQUID ERC (TAK-880) for primary immunodeficiency. TAK-880 is a version of GAMMAGARD LIQUID (GGL) with a low level of IgA (≤2 µg/mL), which makes this product important for a rare subgroup of IgA-deficient patients who are IgA-sensitive. The manufacturing process of TAK-880 is the same as the GGL manufacturing process except for the (b) (4) purification step, anion exchange chromatography, the parameters of which were modified to increase IgA removal. Approval of TAK-880 required demonstrating CMC comparability of TAK-880 and GGL (except for the levels of IgA). The review of an earlier CMC supplement, supplement 125105/1998, concluded that comparability of GGL and TAK-880 was acceptable from the CMC perspective except for the lower levels of IgG4 in TAK-880. In the current supplement, the sponsor provided all the CMC information that has already been submitted in supplement 125105/2184 and additional comparison of IgG4 and IgA data for GG S/D (which has low levels of IgA) and TAK-880 to back using GG S/D clinical data in support of the TAK-880 approval. The data show that IgG4 and IgA levels in TAK-880 are within the ranges observed for GG S/D, possibly within the lower part of these ranges."

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical information was provided in this supplement.

4.4 Clinical Pharmacology

Please refer to Clinical Pharmacology memos for original BLAs 125105 and 103133 for GGL and GG S/D respectively. There is no separate Clinical Pharmacology review for this submission.

4.4.1 Mechanism of Action

TAK-880 contains a broad spectrum of IgG antibodies, some of which are directed toward infectious agents. TAK-880 is intended to restore serum IgG to protective levels and provide patients with specific antibodies to prevent or minimize the occurrence or severity of severe bacterial and viral infections.

4.4.2 Human Pharmacodynamics

Due to similar product attributes, pharmacodynamics are expected to be similar to GG S/D and GGL. Please refer to Clinical Pharmacology memos for original BLAs 103133 and 125105, respectively.

4.4.3 Human Pharmacokinetics

Due to similar product attributes, PK is expected to be similar to GG S/D and GGL. Please refer to Clinical Pharmacology memos for original BLAs 103133 and 125105, respectively.

The Applicant submitted study data from Study 160001 (see Section 6.1) that is newly submitted with this application, in which patients received both GGL and GG S/D to allow PK comparison for IgG parameters between the two similar products. The Applicant also performed retrospective PK modeling using data from this study and utilized product information for TAK-880 to support (b) (4) in relation to IgG4 content between the three products.

Summary of Study 160001 PK Analyses

From Clinical Study Report 160001, Immune Globulin Intravenous (Human), 10% Triple Virally Reduced Solution (2004) [IGIV, 10% TVR is another name for GGL], per the Applicant:

> "The primary pharmacokinetic endpoints in this clinical study with IGIV, 10% TVR Solution were the in vivo recovery, half-life and trough levels of total IgG of infusions of IGIV, 10% TVR Solution. The median in vivo recovery rate of total IgG was 89% (95% CI: 84%; 101%) with a median incremental recovery of 1.85 (mg/dL)/(mg/kg). The slightly lower recovery than expected can be explained by the inaccuracy of the immunonephelometric method to determine the plasma volume in individual subjects. The median terminal half-life of IGIV, 10% TVR Solution observed for total IgG was 30.1 days (95% CI: 27.1; 43.3 days). The median terminal half-lives for IgG subclasses were 28.3, 31.3, 20.9 and 24.2 days for subclasses IgG1, IgG2, IgG3 and IgG4, respectively.
>
> The median steady state trough level of total IgG after the treatment phase was 817 mg/dL (95% CI: 756; 905) with Gammagard S/D and 851 mg/dL (95% CI: 756; 1006) after treatment with IGIV, 10% TVR Solution which confirmed the similarity of the two products. The median percentage of total IgG trough levels of IGIV, 10% TVR Solution relative to Gammagard S/D was 105% (IQR: 100% to 109%) and 105% (IQR: 100% to 108%) for the Rochester and Vienna sites, respectively. This shows that, after previous treatment with a licensed product, comparable trough levels can be maintained with IGIV, 10% TVR Solution when comparable doses are given."

Summary of PK Modeling

The Applicant conducted PK modeling using retrospective study data from Study 160001 related to predictive modeling for IgG4 and drug product information from TAK-880 to estimate IgG4 levels.

Per the Applicant in the Abbreviated Report: Retrospective Analysis on IgG4 Using 160001 Study Data TAK-880,

> "This analysis report illustrates that, following GG S/D treatment, the expected steady-state serum IgG4 trough levels and maximum IgG4 concentrations (C_{max}) are projected to align within the normal range for healthy individuals. Given the (b) (4) IgG4 content compared to GG S/D and an almost identical manufacturing process

compared to GGL, TAK-880 is anticipated to demonstrate a comparable PK pattern to GG S/D."

> ***Reviewer Comment**: This reviewer agrees these PK data and modeling support similarities between products to leverage data from GGL and GG S/D for safety and efficacy of TAK-880.*

4.5 Statistical

There were no new statistical analyses for this efficacy supplement that significantly impacted this clinical review. Please refer to the original BLA Statistics reviewers' memos for GGL and GG S/D.

4.6 Pharmacovigilance

The Division of Pharmacovigilance recommended routine pharmacovigilance. Please refer to Division of Pharmacovigilance memorandum for complete details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

For the review of this sBLA for TAK-880, no new clinical data were provided. Instead, this review relied on leveraging data from previously approved products, GGL and GG S/D, based on data already reviewed in their respective original BLA submissions, to provide substantial evidence of effectiveness and reasonable assurance of safety for the purposes of approval of the new product, TAK-880. The results from the original studies that served as the basis of approval for GGL and GG S/D are summarized in the sections related to integrated safety and efficacy, Section 7 and Section 8, respectively. Study 160001 was newly submitted to the sBLA (i.e., not previously reviewed by the Agency) and is summarized in Section 6; however, datasets were not reviewed and the summary represents the Applicant's interpretation of the study results. This study was considered supportive for this efficacy sBLA; the patients in the study received both of the prior approved products, GGL and GG S/D, which allowed for comparison of clinical outcomes between the two products.

Postmarketing data were also provided to support this sBLA and were largely not applicable to the review. However, postmarketing data to support the labeling for TAK-880 are presented in Section 9.2.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Documents within STN 125105/2184 (including original sBLA submission and additional submissions during interactive review) that served as the basis for the Clinical review are within the following electronic Common Technical Document modules and locations:

- Module 1
  - 1.1 Forms
  - 1.2 Cover Letters
  - 1.4 References
  - 1.6 Meetings
  - 1.9 Pediatric Administrative Information
  - 1.11 Information not Covered Under Module 2 to 5
  - 1.12 Other Correspondence
  - 1.14 Labeling
  - 1.16 Risk Management Plan
- Module 2
  - 2.2 Introduction
  - 2.3 Quality Overall Summary
  - 2.5 Clinical Overview
  - 2.7 Clinical Summary
- Module 5
  - 5.2 Tabular Listing of all Clinical Studies
  - 5.3 Clinical Study Reports
  - 5.4 Literature References

5.3 Table of Studies/Clinical Trials

No clinical studies were performed with the new product TAK-880. The data provided in Table 2 and Table 3 are related to the studies for currently approved products GGL and GG S/D.

Table 2. Gammagard Liquid Studies Supporting TAK-880 in Subjects With Primary Immunodeficiency

Study ID	Number of Study Centers (Locations)	Study Start/ Year Completed	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered/ Completed	Duration	Gender M/F Age Range	Primary Endpoints
160101	11 (USA)	25 Jun 2002 16 Dec 2003	Phase 3, uncontrolled, randomized, double-blind, multi-center study	IGIV, 10% TVR (triple virally reduced solution)	To assess the safety and efficacy of GGL in subjects with PID	61 subjects enrolled and treated	Minimum 12 months	28 M / 33 F 6-72 years (median 34 years)	The primary efficacy endpoint for this study was the rate of acute serious bacterial infections i.e., the mean number of acute serious bacterial infections per subject per year.
160001	6 (4 in Sweden; 2 in Finland)	13 Jun 2002- 24 Sep 2003	Phase II, prospective, open label, uncontrolled, multi-center study	Immune Globulin Intravenous (Human), 10% TVR Solution (IGIV, 10% TVR Solution[b]) and GAMMAGARD S/D	To investigate the pharmacokinetic parameters, efficacy and safety of IGIV, 10% TVR Solution in subjects with PID disorders.	24 enrolled, 22 treated and evaluated	Approx. 9 months	14 M / 8 F 26-70 years	Pharmacokinetic parameters for the primary endpoint included in vivo recovery, half-life, and trough levels of total immunoglobulin G (IgG) after treatment with IGIV, 10% TVR Solution.
160601	9 (USA)	03 Oct 2007- 08 Jul 2009	Prospective, open-label, non-controlled, multi-center Phase II/III study	IGIV 10% administrated intravenously or subcutaneously	To evaluate the tolerability of IGIV, 10% given subcutaneously and the pharmacokinetics of immunoglobulin G (IgG) following subcutaneous (SC) treatment with IGIV, 10% in subjects with primary immunodeficiency (PID) disorders. A further aim was to evaluate efficacy in terms of acute serious bacterial infections.	49 subjects enrolled and treated	Minimum 10 months	22 F/ 27 M 3-77 years (median 20 years)	Pharmacokinetics: In subjects aged ≥12 years, bioavailability of IgG after administration of IGIV, 10% given IV, SC, and SC at an adjusted/individually adapted dose, as measured by area under the IgG concentration versus time curve per week. In subjects aged 2 to <12 years, bioavailability of IgG after administration of IGI, 10% given IV, SC and SC at an adjusted/ individually adapted dose, measured by IgG trough levels Primary safety endpoint: Ability to tolerate IGIV, 10% administered intravenously or subcutaneously

Study ID	Number of Study Centers (Locations)	Study Start/ Year Completed	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered/ Completed	Duration	Gender M/F Age Range	Primary Endpoints
KIOVIG-PASS-EU-005 Post-Authorization Safety Surveillance of KIOVIG (Human Normal Immuno-globulin 10% liquid, Baxter) An open, uncontrolled, non-interventional observational cohort study in immuno-deficiencies and autoimmune diseases	20 (Austria, Czech Republic, Denmark, France, Germany, Great Britain, Spain and Sweden)	2010	A prospective, multi-center, uncontrolled, open-label, non-interventional, post-authorization safety surveillance study	KIOVIG The dose and dosage regimen were dependent on the indication as approved in the local SPC. In replacement therapy the dosage was individualized for each subject depending on the pharmacokinetic and clinical response. Mode of Administration: Intravenous administration	The objective of this surveillance study was to corroborate the therapeutic profile of KIOVIG under clinical routine conditions. Assessments included safety, tolerance and current clinical practice: - Incidence of non-serious and serious adverse events (SAEs) in general, and KIOVIG-related adverse events (AEs) (i.e. suspected adverse drug reactions) - Frequency and severity of infections (for subjects with immunodeficiency only) - Total dose, maximum infusion speed and duration of infusion - Treatment outcome	Planned: approx. 150 Analyzed: 88	2 years and 3 months	53 M/ 35 F 0 to 84 years	The endpoints of this study are to assess general safety and tolerance under clinical routine conditions: - Incidence of non-serious AEs and SAEs in general, and KIOVIG/related AEs (i.e. suspected adverse drug reactions). Adverse events will be categorized (e.g. relation to underlying disorder, hypersensitivity type, other). - Dosage of KIOVIG (total dose, maximum infusion speed, duration of infusion) - Overall assessment by Investigator of the therapeutic response to KIOVIG.

Source: Reproduced from Supplemental BLA 125105 submission, Table 5.2 Tabular Listing of All Clinical Studies
Abbreviations: AE, adverse event; F, female; GGL, Gammagard Liquid; IgG, immunoglobulin G; IGIV, immune globulin intravenous; IV, intravenous; M, male; PID, primary immunodeficiency; SAE, serious adverse event; SC, subcutaneous; SPC, Summary of Product Characteristics; TVR, triple virally reduced; USA, United States

Table 3. Summary of Gammagard S/D Studies Supporting TAK-880 in Subjects With Primary Immunodeficiency

Study Title / Study ID	Number of Study Centers (Locations)	Year Completed	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective(s) Endpoint(s)	# Subjects by Arm	Duration	Gender M/F Age Range	Primary Endpoints
A Clinical Investigation to Assess the Safety and PK of IGIV (Human) Solvent/ Detergent Treated in Patients with PID 940163-CLN1	1 (USA)	1992	PK and acute safety were evaluated in two populations of immunodeficiency patients. Ten previously treated patients underwent a randomized, double-blind, cross-over study. Five previously untreated patients received infusions of IGIV S/D, open label, for half-life determination.	GG S/D Gammagard (non S/D-treated predecessor) 400 mg/kg for all infusions	The study had two objectives: (a) to evaluate the acute safety of solvent/detergent treated immune globulin intravenous (human) (IGIV S/D) in patients with primary immunodeficiency disease; and (b) to establish the half-life of IGIV S/D and compare it to the half-life of commercially available Gammagard, immune globulin intravenous (human) (IGIV).	15 subjects with PID Subjects with a history of IGIV treatment: n=10 Subjects with no prior IGIV treatment: n=5	16 Jan 1992 - 26 May 1992 (4 months)	7 M/8 F 2 to 41 years	Acute safety and half-life

Study Title / Study ID	Number of Study Centers (Locations)	Year Completed	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective(s) Endpoint(s)	# Subjects by Arm	Duration	Gender M/F Age Range	Primary Endpoints
A Clinical Investigation to Assess the Acute Safety and Viral Safety of Immune Globulin Intravenous (Human) Solvent/ Detergent Treated in Patients with PID 9401630	6 (USA)	1996	See above; Subjects with no history of treatment with IGIV (from study 940163-CLIN1) received 2 consecutive infusions of GG S/D in an open-label fashion	GG S/D 400 mg/kg for all infusions	The primary objectives of this study were to evaluate the acute safety (adverse reaction pattern) and pharmacokinetics of Immune Globulin Intravenous (Human) treated with organic solvent and detergent (IGIV S/D)	38 subjects with PID, SID, and autoimmune disorders: 5 subjects thereof from the PK/acute safety segment of the study (Study 940163-CLN1)	Jan 1992 to Jan 1996 (4 years)	17 M, 21 F; 0.7 to 57 years	The primary objectives of this study were to evaluate the acute safety (adverse reaction pattern) and pharmacokinetics of Immune Globulin Intravenous (Human) treated with organic solvent and detergent (IGIV S/D). The primary endpoint for assessing the safety of the solvent/detergent-treated IGIV was the percentage of patients who experienced treatment-related adverse reactions

Study Title / Study ID	Number of Study Centers (Locations)	Year Completed	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective(s) Endpoint(s)	# Subjects by Arm	Duration	Gender M/F Age Range	Primary Endpoints
A Phase 4 Study to Assess the Acute and Medium-term Safety of Gammagard S/D in Patients with PID No study number available: in this document the Study is refered to as 'Phase 4 Safety Study'	5 (USA)	1997	Randomized, double-blind, active-controlled cross-over study	GG S/D Gamimune-N 300 to 600 mg/kg bw IV The dose for previously treated patients was based on their prestudy IGIV infusion regimen. Dose for previously untreated patients was determined by investigator at enrollment.	To compare the short- and medium-term adverse clinical and laboratory effects of Gammagard S/D and Gamimune-N in patients with PID.	36 subjects with PID	12 Sep 1995 to 22 Dec 1997 (2.25 years)	22 M/14 F 1 to 55 years	The primary endpoint was the number of infusions of each IGIV product associated with at least 1 adverse event sign and/or symptom coincident with the infusion and up to 48 hours after completion of the infusion.

Source: Reproduced from Supplemental BLA 125105 submission, Table 5.2 Tabular Listing of All Clinical Studies
Abbreviations: F, female; GG S/D, Gammagard S/D; IGIV, immune globulin intravenous; M, male; PID, primary immunodeficiency; PK, pharmacokinetics; USA, United States

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was held.

5.4.2 External Consults/Collaborations

No external consults were obtained during the review process.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study #1

Study 160001: Prospective Open-Label Study of Pharmacokinetics, Efficacy and Safety of Immune Globulin Intravenous (Human), 10% TVR Solution in Patients with Hypo- or Agammaglobulinemia.

The Applicant provided summaries of this study, which are included in this section (6.1) with tables, listings, and figures. As data from this study was considered supportive to the efficacy and safety of GGL and GG S/D demonstrated in their respective original BLAs, the review team did not review datasets or patient specific data for this study (except where as noted). These sections reflect the Applicant's interpretation of the study and study results not previously submitted to the FDA for review. This study provided information for patients who received both GG S/D and GGL (also known as Immune Globulin Intravenous (Human), 10% Triple Virally Reduced [TVR] Solution) to allow for a direct comparison of the two products in relation to spontaneous bacterial infections and adverse reactions (ARs) within one study.

6.1.1 Objectives

The purpose of this study was to investigate the PK parameters, efficacy, and safety of IGIV (Human), 10% TVR Solution in patients with PI disorders. Initially, patients were

treated with GG S/D (first three infusions), to standardize the IgG replacement therapy of all patients to the same product and to acquire data with a licensed product. Patients were then treated with IGIV (Human), 10% TVR Solution.

6.1.2 Design Overview

The study was a prospective, open-label, noncontrolled, multicenter international study to determine the in-vivo recovery and half-life of IGIV (Human), 10% TVR Solution in patients with PI. Efficacy was determined by infection rate and frequency of antibiotics use, as well as safety (changes in vital signs and other adverse events [AEs]). IgG troughs were collected throughout the study.

To ensure steady state, the study started with a lead-in phase, during which three infusions of GG S/D (reconstituted to a 10% solution) were administered. After this lead-in phase, a total of nine infusions of IGIV (Human), 10% TVR Solution were administered. The dose for both IG replacement products was 100 to 150 mg/kg/week administered every 21 days (+/- 2 days).

Trough levels of total IgG were analyzed throughout the study. PK studies were performed after the third, fourth, or fifth infusion of IGIV (Human), 10% TVR Solution, according to the preference of the patient and investigator. Additional serum samples for the determination of in vivo recovery and half-life of IgG were collected at 15 minutes (+/- 5 minutes) after completion of the infusion, and on Days 1, 3, 7, 14 (+/-2 days) and 21 (+2 days, before the next infusion) after infusion of IGIV (Human), 10% TVR Solution.

> ***Reviewer Comment:*** *This study design allowed for direct comparison of GG S/D and GGL related to infection rates and IgG troughs to show comparability between the two products within the same study.*

6.1.3 Population

The study population included 22 adult patients 18 years and older with PI requiring IG replacement therapy. Patients had regular treatment for at least 3 months with either intravenous (IV) or intramuscular (given subcutaneously) IG preparations and had a serum IgG level ≥5 g/L at the start of the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

GG S/D and IGIV, 10% TVR Solution were only administered intravenously.

6.1.5 Directions for Use

Not applicable

6.1.6 Sites and Centers

The study was conducted outside the United States. A total of six study sites were recruited for the study, four in Sweden and two in Finland. Dr. Janne Björkander of Sahlgrenska University, Allergisektionen in Gothenburg was the lead investigator in Sweden. Professor Jukka Nikoskelainen of the Turku University Central Hospital, Department of Internal Medicine in Turku was the lead investigator in Finland.

6.1.7 Surveillance/Monitoring

A study monitor was used throughout the study to visit the clinical sites to ensure investigator understanding; compliance with the protocol; and verify accuracy and completeness of the data reported. The study monitor was also available for consultations with the investigator as a liaison between the clinical study site and the Study Sponsor.

6.1.8 Endpoints and Criteria for Study Success

Primary Pharmacokinetic Endpoints

The primary pharmacokinetic endpoints were the in vivo recovery, half-life, and trough levels of IGIV (Human), 10% TVR Solution

Secondary Pharmacokinetic and Efficacy Endpoints

1. Pharmacokinetic parameters: area under the curve, maximum concentration, time to maximum concentration
2. Rate of infections
3. Number of courses of antibiotics required by study patients for infection management

6.1.9 Statistical Considerations & Statistical Analysis Plan

The study used descriptive statistics for the primary endpoints of in vivo recovery, half-life and trough levels of IGIV (Human), 10% TVR Solution. Pharmacokinetic parameters were summarized using medians, quartiles, and their nonparametric 95% confidence intervals. Descriptive statistics were used for analysis of secondary endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Twenty-four patients were screened, and 22 patients were included for treatment in the study. The majority of patients included in the study had hypogammaglobulinemia/CVID (18 of 22). Two had X-linked agammaglobulinemia and one patient each had hypogammaglobulinemia-Good syndrome and hypogammaglobulinemia with high IgM.

Twenty-one patients completed the study. Patient (b) (6) was withdrawn due to diffuse large B-cell lymphoma on April 7, 2003.

The full analysis data set included all patients in Study 160001 who received IGIV, 10% TVR Solution and were monitored for infections after administration for any period of time (N=22). The pharmacokinetic analysis set included all patients who received IGIV, 10% TVR Solution and provided IgG level data suitable for pharmacokinetic analysis (N=22). The safety analysis data set included all patients in Study 160001 who received IGIV, 10% TVR Solution (N=22).

6.1.10.1.1 Demographics

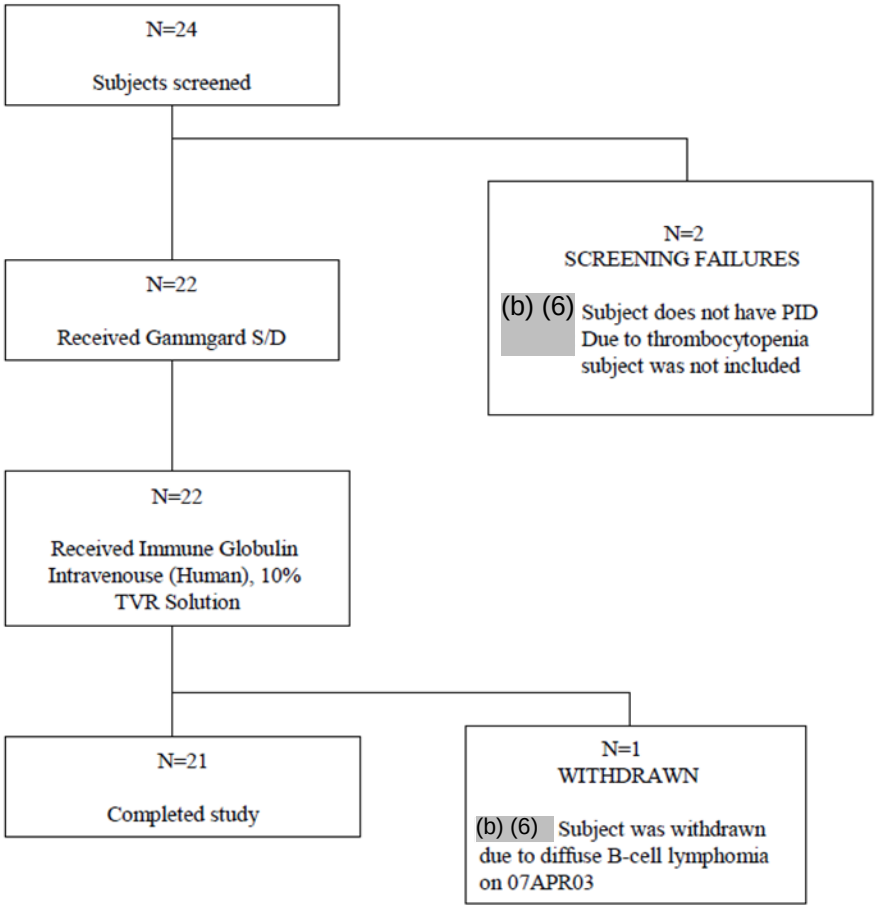
Fourteen male patients ages 26 to 61 years and eight female patients ages 36 to 70 years were treated in this study. All patients were White.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of patients included in the study had hypogammaglobulinemia/CVID (18/22). Two had X-linked agammaglobulinemia and one patient each had hypogammaglobulinemia-Good syndrome and hypogammaglobulinemia with high IgM.

6.1.10.1.3 Subject Disposition

Figure 1. Disposition of Subjects



Source:
Abbreviations: N, population size; PID, primary immunodeficiency; TVR, triple virally reduced

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary pharmacokinetic endpoints were the in vivo recovery, half-life, and trough levels of IGIV (Human), 10% TVR Solution. For the purposes of this review, in vivo

recovery and half-life were not considered relevant and are not discussed. Comparison of IgG trough levels between the two products is discussed in Section 4.4.3.

6.1.11.2 Analyses of Secondary Endpoints

Pharmacokinetics

Secondary PK endpoints were evaluated by the Applicant; they are not discussed because they are not relevant to this review.

Infections

A total of 89 episodes of infection occurred in 22 patients during the study. A total of 59 infections started at or after the first infusion with IGIV, 10% TVR Solution and all 59 were considered nonserious. The severity was mild for 39 infections and moderate for 20 infections. Thirty infections started while patients were receiving treatment with GG S/D, which was administered to all patients for the first three infusions.

> ***Reviewer Comment:*** *Though this study did not specifically document serious bacterial infections (SBIs), infections overall appeared similar between the two products, further supporting the similar efficacy of GGL and GG S/D that can be leveraged to support TAK-880.*

Antibiotics

Antibiotic use was evaluated by the Study Sponsor but was not considered relevant to the review for TAK-880.

6.1.11.3 Subpopulation Analyses

No subpopulation analysis from this study was used to support the sBLA.

6.1.11.4 Dropouts and/or Discontinuations

The handling of missing stop dates for periods of infections and treatment with antibiotics was specified during the statistical analysis.

6.1.11.5 Exploratory and Post Hoc Analyses

The Applicant performed post hoc analyses, but these analyses were not used to support the review of the sBLA.

6.1.12 Safety Analyses

6.1.12.1 Methods

Although the study evaluated safety of GGL and GG S/D, safety of these products was already demonstrated in the original BLA review for each product. No new safety signals were identified in this study. For the purposes of the sBLA review, the safety review focused on events of hypersensitivity or anaphylaxis compared between the two products to support product labeling.

***Reviewer Comment**: The safety review provided is based on the Applicant's interpretation of the data and results for GGL and GG S/D. Aside from review of hypersensitivity/anaphylaxis data as noted, no safety data were reviewed from this study during the sBLA review.*

6.1.12.2 Overview of Adverse Events

AEs were mostly mild and unrelated to the study drugs. A low rate (4%) of infusions of IGIV 10%, TVR Solution were followed by one or more ARs. No severe nonserious AEs were reported with either GG S/D or IGIV, 10% TVR Solution. Urticaria was the most frequently reported nonserious AR for both study drugs. However, all events of urticaria occurred in one patient (b) (6) .

***Reviewer Comment**: ARs reported in the study are consistent with those in the studies that supported original approval of GG S/D and GGL and with those observed with other IGIV products.*

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of five serious adverse events (SAEs) were reported, all of which were judged by the investigator to be unrelated to the study drugs.

Three SAEs were reported during the treatment phase with IGIV, 10% TVR Solution. Patient (b) (6) experienced autoimmune hepatitis, Patient (b) (6) experienced diffuse large B-cell lymphoma, and Patient (b) (6) experienced a febrile respiratory tract infection.

Patient (b) (6) experienced two SAEs (angiography of coronary vessels and planned coronary stent operation) while undergoing treatment with GG S/D.

***Reviewer Comment**: This reviewer agrees with the investigator's assessment that the SAEs are likely not related to study drugs or procedures.*

6.1.12.5 Adverse Events of Special Interest

Adverse events of special interest were not defined by the Study Sponsor, but the review focused on events of hypersensitivity/anaphylaxis reported in the study. Urticaria was the most frequentlyreported nonserious AR for both study drugs, however, all cases of study drug-related urticaria occurred in one patient (b) (6) .

***Reviewer Comment**: Though post hoc analyses were performed by the Applicant, they were not used for the review as they were not considered relevant to establishing the safety of TAK-880. Multiple patient-level data showed coded events of anaphylaxis that upon review were not consistent with the clinical definition of anaphylaxis, or were considered not related to the product, either based on the symptoms or timing of the event relative to receiving the*

product. Therefore, study data was not able to demonstrate differences between GG S/D and GGL in events of anaphylaxis for the purposes of TAK-880 product labeling.

6.1.12.6 Clinical Test Results

The Study Sponsor reported laboratory abnormalities, but FDA did not consider them relevant to the review, as abnormalities, such as positive Coombs' test without clinical hemolysis, have already been reported with the products in their original BLA applications.

6.1.12.7 Dropouts and/or Discontinuations

Please refer to Section 6.1.11.4.

6.1.13 Study Summary and Conclusions

This study supports the safety and efficacy conclusions from the original BLAs for GGL and GG S/D while also supporting similar safety and efficacy between the two products for leveraging to TAK-880.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Primary Humoral Immunodeficiency

7.1.1 Methods of Integration

There is no efficacy data submitted in this application for the new product, TAK-880. The Applicant is leveraging data from prior BLA approvals for GGL (BLA 125105) and GG S/D (BLA 103133) for which TAK-880 is comparable on most attributes as described in the CMC Review Memorandum. The Applicant submitted additional supportive data on infectious outcomes from postmarketing surveillance and clinical claims data for GGL and GG S/D; however, these were challenging to interpret due to differences in real-world clinical documentation of diagnosis codes and infections, as well as missing information that would typically be available in trial data (e.g., laboratory data, defining characteristics for SBIs). As a result, these additional data sources were not considered relevant to efficacy of TAK-880 and are not discussed in the efficacy review.

The studies that were the basis of approval of GGL (for IV and SC administration) and GG S/D summarized in this section are described below.

BLA 125105 (GGL)

Study #1 160101

A Phase 3, randomized, double-blind, uncontrolled, multicenter study to evaluate the safety and efficacy of GGL IGIV in subjects with PI. Efficacy was determined by the number of acute severe bacterial infections (SBIs) per subject per year and safety was determined by the percentage of infusions with one or more temporally associated AEs.

Study #2 160601

A prospective, open-label, noncontrolled study in subjects with PI to determine tolerability and PK of GGL IGIV given subcutaneously. Patients received GGL IGIV every 3 or 4 weeks for 12 weeks and then received weekly doses of GGL SC for a minimum of 12 weeks.

BLA 103133 (GG S/D)

Study #3 940163-CLN1

This study evaluated the safety of GG S/D IGIV in patients with PI and established the half-life of GG S/D compared to the half-life of commercially available IGIV. The study enrolled patients who were previously untreated or previously treated with another commercially available IGIV (Gammagard).

7.1.2 Demographics and Baseline Characteristics

BLA 125105 (GGL)

Study #1 160101

There were a total of 61 patients with PI, including 15 pediatric patients. Ages ranged from 6 years to 72 years (median age at enrollment was 34 years). Fifty-four percent were female, 93% were White, 5% were Black, and 2% were Asian.

Study #2 160601

There were a total of 49 patients with PI, including 18 pediatric patients. Ages ranged from 3 years to 77 years (median age at enrollment was 20 years). Fifty-five percent were male. Among those treated, 94% were White, 4.1% were Black, and 2% were Hispanic.

BLA 103133 (GG S/D)

Study #3 940163-CLN1

A total of 15 patients with PI were treated, including 9 pediatric patients. Ages ranged from 2 years to 41 years (median age at first infusion was 10 years. The mean age for patients previously treated was 15.7 years (range 2.5 to 41 years) and the mean age was 16.6 years (range 2.96 to 30.7 years) for previously untreated patients. Fifty-three percent were female. Race and ethnicity information were not available.

7.1.3 Subject Disposition

Study #1 160101

A total of 61 patients were enrolled. Eleven discontinued, of which three discontinued prior to 12 months. Two patients withdrew consent, and one patient was withdrawn by the investigator for a non product-related reason. There were no deaths during the study.

Table 4. Overall Subject Disposition

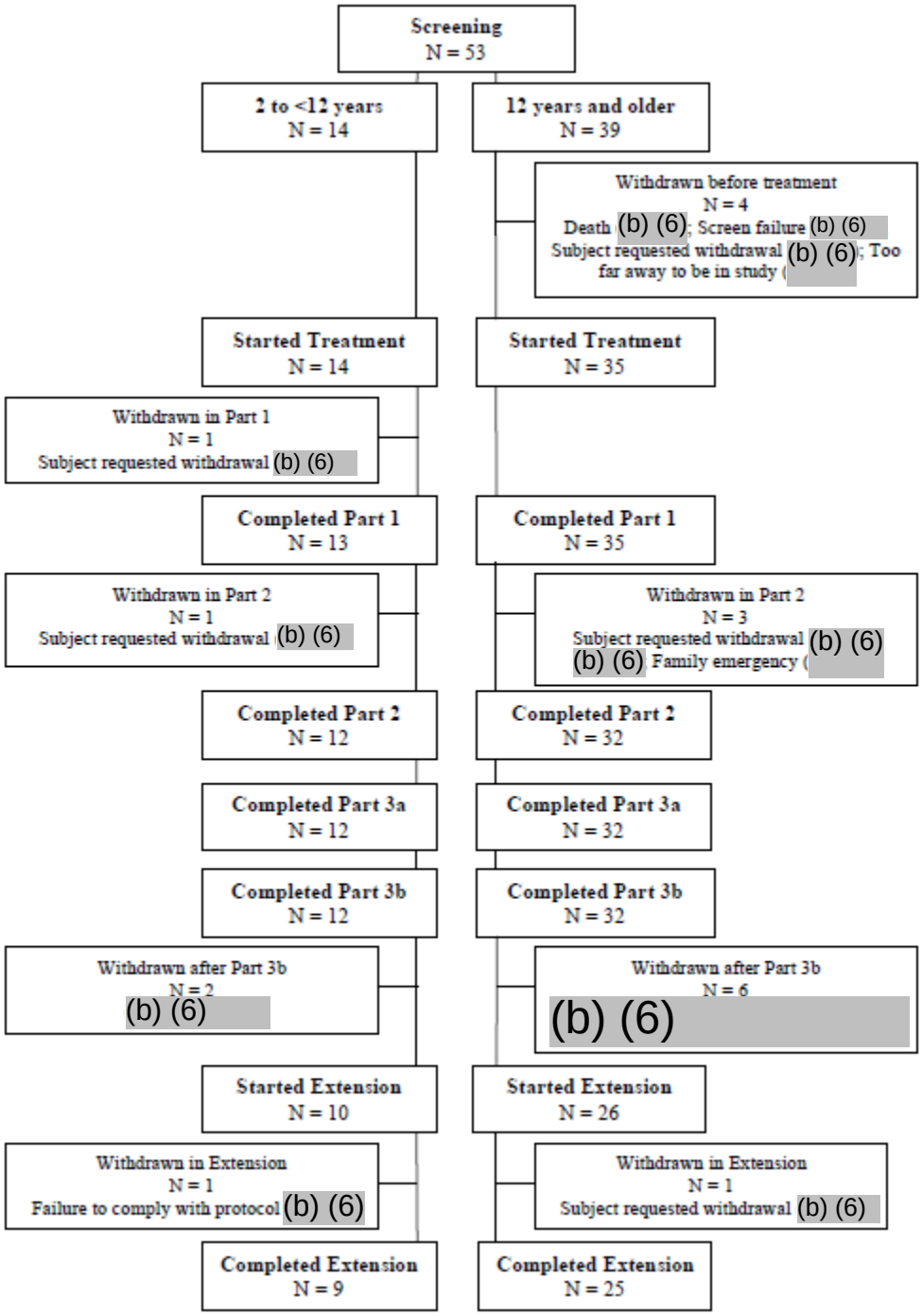
Categories		Subjects N	Subjects %
Total Enrolled		61	100.00
Total Discontinued		11	18.03
Discontinued before 12 Months		3	4.92
	Adverse Experience due to study product	0	0.00
	Withdrawal by investigator for non-product-related reasons	1 [a]	1.64
	Subject-initiated withdrawal	2 [b]	3.28
	Lost to follow-up	0	0.00
	Death	0	0.00
	Other	0	0.00
Discontinued after 12 Months		8	13.11
	Adverse Experience due to study product	1 [c]	1.64
	Withdrawal by investigator for non-product-related reasons	0	0.00
	Subject-initiated withdrawal	6 [d]	9.84
	Lost to follow-up	0	0.00
	Death	0	0.00
	Other	1 [e]	1.64
Continued post 12 Months		50	81.97

a. Subject (b) (6) was withdrawn for non-study product-related reasons.
b. Subject and Subject (b) (6) withdrew consent.
c. Subject withdrew due to an AE (see subject narrative in Section 12.3.2.2.1.1).
d. Six subjects elected to withdraw from the study in the post-efficacy period.
e. The investigator withdrew from the study (Subject (b) (6)

Source: Adapted from Table 14.1-2 Overall Subject Disposition in sBLA document, Interim Clinical Study Report 160101 IGIV, 10% TVR.
Abbreviations: AE, adverse event; N, population size

Study #2 160601

Figure 2. Disposition of Subjects, Study 160601



Source: Adapted from Figure 14.1.1-1: Disposition of Subjects from sBLA document IGIV 10% Full Clinical Study Report: 160601
Abbreviations: N, population size

Study #3 940163-CLN1

Patient disposition is not available for this review of the GG S/D study but does not affect the noted efficacy for GGL.

7.1.4 Analysis of Primary Endpoint(s)

Primary endpoints were defined differently within the individual studies. For the purposes of this sBLA review, the primary efficacy endpoint of interest was rate of acute SBIs.

Study #1 160101 (GGL administered IV)

The primary efficacy endpoint was acute SBI rate (i.e., the mean number of acute SBIs per patient year). There were no acute SBIs in the intention-to-treat or per-protocol groups.

Study #2 160601 (GGL administered IV and SC)

The protocol- defined primary efficacy endpoint was bioavailability of IGIV and IGSC, evaluated by the areas under the curve IgG concentration versus time curve per week, or PK equivalence. Per the study report provided by the Applicant, the PK equivalence after IV and SC IgG replacement was demonstrated within the predetermined margins of equivalence, which ultimately supported expansion of the GGL label to include SC administration.

Although acute SBIs were evaluated as a secondary endpoint, for the purposes of this review they were reviewed as the primary endpoint of interest for integrated efficacy to support efficacy of TAK-880. A total of three patients had acute SBIs while on SC treatment with IGIV, 10%. All three infections were bacterial pneumonias. The annual rate of acute SBIs while on SC treatment with GGL, determined in an additional analysis, was 0.067; the 99% upper confidence limit was 0.134.

Study #3 940163-CLN1 (GG S/D)

The study objectives were to evaluate the safety of GG S/D in PI and establish the half-life of IGIV GG S/D and compare it to the half-life of commercially available IGIV. Per the study report, the PK of IGIV and GG S/D did not differ. Approval of GG S/D was based on safety and PK while SBIs were not reported.

> **Reviewer Comment:** The rate of acute SBIs with GGL administered either IV or SC was well below the established rate of 1 per person-year in the FDA IGIV Guidance*, which supported approval for both routes of administration for PI. The GG S/D approval pre-dates the FDA* IGIV *Guidance, and SBI rates were not evaluated in the study to support approval. Rather, efficacy was extrapolated from similarities in PK between GG S/D and another commercially available IGIV. However, clinical efficacy from GGL can be leveraged for TAK-880, which is comparable on all product attributes aside from IgA and IgG4 levels. These differences are not expected to impact product efficacy, as described in Section 4. Although no data is available for GG S/D for acute SBI rates, similar efficacy between GGL and GG S/D in Study 160001 (as described in* Section 6*)*

additionally support leveraging of data from GG S/D (which is similar to TAK-880 in IgA content).

7.1.5 Analysis of Secondary Endpoint(s)

Study #1 160101

The secondary endpoints related to infections included mean rate of other bacterial infections in PI patients and number of hospitalizations secondary to infectious complications. There were no hospitalizations secondary to bacterial infections. Four other non-SBI bacterial infections commonly occurring in PI patients were reported.

The other studies evaluated additional secondary endpoints that were reviewed in the original BLA submissions but were not considered in this review.

7.1.6 Other Endpoints

Additional endpoints were not reviewed as supportive evidence for efficacy of TAK-880 as they were not considered relevant.

7.1.7 Subpopulations

The Applicant submitted information for subpopulations of IgA and IgG4 subclass deficient patients within the clinical studies. These were not considered in the supportive evidence for the efficacy of TAK-880 as:

- The specific PI diagnoses (and whether they would be expected to be associated with IgA and/or IgG4 deficiency) were difficult to define based on the PI diagnosis codes used in clinical practice at the time.
- Patient-level laboratory data for IgA and IgG4 were not available to assess whether the selected patients were truly IgA and/or IgG4-deficient. Even if data were available, there are no universally accepted levels to define IgA or IgG4 deficiency in clinical practice.

7.1.8 Persistence of Efficacy

Continued clinical use of GGL and GG S/D, as well as other IG products, to prevent infections in the PI populations remains a standard of care. Persistence of efficacy relies on repeat administration at regular intervals as defined in product labeling.

7.1.9 Product-Product Interactions

No product-product interactions were reviewed or considered as supportive evidence for TAK-880.

7.1.10 Efficacy Conclusions

Substantial evidence of effectiveness for GGL and GG S/D was already demonstrated in the original BLAs . The efficacy of GGL as demonstrated by rate of acute SBIs, and of GG S/D as demonstrated by PK analyses (Section 4.4.3) and similar infectious outcomes to GGL (Section 6), can be leveraged to efficacy of TAK-880 based on similar product attributes between the 3 products.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Integration and Assessment Methods

The safety of GGL and GG S/D is detailed in the original clinical review memorandums for GGL and GG S/D, respectively. This review focused on safety of GGL, administered IV and SC, due to greater product comparability between GGL and TAK-880 (with the exception of IgG4 and IgA content, which are not expected to negatively impact safety and may actually make safety of TAK-880 more favorable). As such, the integrated safety review focuses on summarizing studies of GGL that supported initial IV and SC approvals as described in product labeling. These studies were not separately reviewed for this sBLA, and full details of the safety reviews at time of approval are available in the respective BLA 125105 memorandums.

GG S/D has a similar safety profile to GGL and is not detailed in this integrated safety review, as it was not considered additive to the safety of GGL for the purposes of TAK-880 approval. However, differences in anaphylaxis/hypersensitivity between GG S/D and other IG products were of interest for product labeling (i.e., contraindications), and are discussed in Section 9.2, which integrates additional postmarketing safety data submitted by the Applicant not considered relevant to the overall safety review.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

No clinical studies have been conducted using TAK-880. The safety of TAK-880 in patients with PI is supported by two clinical studies conducted with GGL, Study 160101 and Study 160601, which supported approval for IV and SC administration of GGL, respectively. Additional relevant information about study design and patient dispositions are included in Section 7.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

No patients were exposed to the new product, TAK-880. Refer to Section 7.1.2 for demographics of individual studies; there was no pooled safety population.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The pooling of data is not applicable.

8.4 Safety Results

Study #1: 160101 (GGL administered IV)

A total of 61 patients received 1,812 IV infusions of GGL at a dose of 300 to 600 mg/kg every 21 to 28 days for 12 months.

A total of five serious AEs were reported in four patients (28%), including two cases of aseptic meningitis in one subject, stent placement, gastrointestinal hemorrhage, and encephalopathy. Out of these five serious AEs, only one case of aseptic meningitis was deemed to be related by the investigator. Two patients were discontinued, likely due to ARs, which were pruritic papular rash and aseptic meningitis.

Table 5 summarizes the most common ARs occurring in ≥5% of patients in Study 1.

Table 5. Adverse Reactions Occurring in ≥5% of Patients in Study 1

Adverse Reactions[a] MedDRA[b]-Preferred Term	By Infusion N (%) (N=1811 Infusions)	By Subject N (%) (N=61 Subjects)
Headache	94 (5%)	29 (48%)
Fatigue	33 (2%)	14 (23%)
Pyrexia	28 (2%)	17 (28%)
Chills	28 (2%)	12 (20%)
Nausea	17 (0.9%)	11 (18%)
Pain in extremity	13 (0.7%)	7 (11%)
Diarrhea	12 (0.7%)	9 (15%)
Migraine	12 (0.7%)	4 (7%)
Vomiting	11 (0.6%)	9 (15%)
Dizziness	11 (0.6%)	8 (13%)
Urticaria	10 (0.6%)	6 (10%)
Cough	9 (0.5%)	8 (13%)
Asthma	7 (0.4%)	6 (10%)
Oropharyngeal pain	7 (0.4%)	5 (8%)
Infusion site extravasation	7 (0.4%)	4 (7%)
Arthralgia	6 (0.3%)	5 (8%)
Rash	6 (0.3%)	4 (7%)
Myalgia	5 (0.3%)	5 (8%)
Pruritus	5 (0.3%)	4 (7%)
Cardiac murmur	4 (0.2%)	4 (7%)

Source: TAK-880 product labeling
[a]Adverse reactions (excluding infections) were defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period.
[b]MedDRA: Medical Dictionary for Regulatory Activities, version 26.0.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, population size

Study #2: 160601 (GGL administered IV and SC)

The safety of GGL SC infusion was evaluated in Study 2. Patients were initially treated with GGL IV every 3 to 4 weeks for 12 weeks followed by GGL SC weekly for a minimum of 12 weeks. A total of 47 patients received 2,294 SC infusions of GGL. Mean weekly subcutaneous doses ranged from 182 mg/kg to 191 mg/kg (at 130% to 137% of the intravenous dose).

One serious AE of chest pain was reported in one patient (2%). One patient discontinued likely due to ARs of fatigue and malaise.

Table 6 summarizes the most common ARs occurring in ≥5% of patients in Study 2.

Table 6. Adverse Reactions Occurring in ≥5% of Patients in Study 2

Adverse Reactions[a] MedDRA[b]-Preferred Term	By Infusion N (%) (N=2294 Infusions)	By Subject N (%) (N=47 Subjects)
Infusion site (local) event[c]	55 (2%)	21 (45%)
Headache	31 (1%)	19 (40%)
Pyrexia	11 (0.5%)	9 (19%)

Adverse Reactions[a] MedDRA[b]-Preferred Term	**By Infusion N (%) (N=2294 Infusions)**	**By Subject N (%) (N=47 Subjects)**
Fatigue	11 (0.5%)	7 (15%)
Heart rate increased	11 (0.5%)	3 (6%)
Abdominal pain upper	9 (0.4%)	5 (11%)
Vomiting	7 (0.3%)	5 (11%)
Arthralgia	7 (0.3%)	3 (6%)
Nausea	7 (0.3%)	3 (6%)
Asthma	6 (0.3%)	4 (9%)
Blood pressure systolic increased	6 (0.3%)	3 (6%)
Diarrhea	5 (0.2%)	3 (6%)
Ear pain	4 (0.2%)	3 (6%)
Aphthous ulcer	3 (0.1%)	3 (6%)
Migraine	3 (0.1%)	3 (6%)
Oropharyngeal pain	3 (0.1%)	3 (6%)
Pain in extremity	3 (0.1%)	3 (6%)

Source: TAK-880 product labeling
[a] Adverse reactions (excluding infections) were defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period.
[b] MedDRA: Medical Dictionary for Regulatory Activities, version 26.0.
[c] Included rash, erythema, edema, hemorrhage, pain, hematoma, pruritis, and swelling.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, population size

8.4.8 Adverse Events of Special Interest

Adverse events of special interest were not defined for the studies summarized in this review. For the purposes of this review, anaphylaxis/hypersensitivity were adverse events of special interest for the purposes of labeling. Please refer to Section 9.2 for additional details.

8.5 Additional Safety Evaluations

Although no data for TAK-880 were provided, the following additional safety evaluations/considerations are not expected to be different for TAK-880 as compared to other IG products.

8.5.1 Dose Dependency for Adverse Events

No data for TAK-880 were submitted in this efficacy supplement.

8.5.2 Time Dependency for Adverse Events

No data for TAK-880 were submitted in this efficacy supplement.

8.5.3 Product-Demographic Interactions

No product-demographic interactions for TAK-880 were submitted in this efficacy supplement.

8.5.4 Product-Disease Interactions

No data for product-disease interactions were submitted in this efficacy supplement.

8.5.5 Product-Product Interactions

No data for product-product interactions were submitted in this efficacy supplement.

8.5.6 Human Carcinogenicity

No human carcinogenicity data were submitted in this efficacy supplement.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This product does not have drug abuse potential.

8.5.8 Immunogenicity (Safety)

No immunogenicity data were submitted in this efficacy supplement.

8.5.9 Person-to-Person Transmission, Shedding

No data regarding person-to-person transmission or shedding were submitted in this efficacy supplement.

8.6 Safety Conclusions

The safety profile for TAK-880 is expected to be similar to other IG products, specifically GGL and GG S/D to which the new product is generally comparable. The safety profile of GGL administered IV or SC is favorable, with most ARs mild, transient, and manageable. Safety of GGL can be leveraged to safety of TAK-880 and is supported by similar safety of GG S/D. The overall safety conclusions do not differ from the safety conclusions in the original GGL and GG S/D BLA reviews.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No new human reproduction or pregnancy data were submitted in this efficacy supplement.

9.1.2 Use During Lactation

No new human lactation data were submitted in this efficacy supplement.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

No clinical studies were performed in adults or pediatric patients. The sBLA was submitted without an agreed initial pediatric study plan. The Applicant submitted an initial pediatric study plan with the sBLA. The Applicant requested a full waiver of required pediatric assessments in all pediatric age groups. However, the Applicant proposed to leverage data from the two similar products, GGL and GG S/D, which are approved for use in pediatric patients with PI ages 2 years and older.

FDA agreed to grant a partial waiver for patients less than 2 years of age because studies are impossible or highly impracticable. PI is rarely diagnosed prior to 2 years of

age, and when it is, availability of approved products and early definitive treatment makes enrollment of children <2 years in IG clinical studies highly impractical.

FDA agreed with the pediatric assessment of patients 2 years to 16 years of age based on the data from the approved similar products.

No additional pediatric studies are required.

9.1.4 Immunocompromised Patients

Both GGL and GG S/D are indicated for PI, which is the same intended indication for TAK-880. Patients with PI are immunocompromised by virtue of their underlying condition, and IG products are intended as replacement therapy.

9.1.5 Geriatric Use

No data regarding specific safety concerns in the geriatric population were submitted in this efficacy supplement

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Although the requested indication was replacement therapy for PI, with no limitations in the indication related to IgA deficiency, IgA antibodies, or anaphylaxis with other IG products, TAK-880 is intended to replace GG S/D once it is discontinued, and GG S/D is primarily reserved for such patients in clinical practice. GG S/D is similarly labeled for PI without a narrowed population, but the product labeling includes a contraindication only for patients who have had a previous anaphylactic or severe hypersensitivity event with GG S/D (as compared to other IG products for which the product is contraindicated in patients who have had anaphylaxis/hypersensitivity to any IG product, or who have low IgA and anti-IgA antibodies).

To support the proposed contraindication statement in this sBLA, the Applicant submitted new data (from additional clinical studies, postmarketing reports, and claims data) related to anaphylaxis events with GG S/D and GGL, as well as subgroup analyses of events in patients presumed to have IgA deficiency from the original studies that supported the approval of GG S/D and GGL. Data for review was narrowed to patients who received at least one dose of GG S/D to focus on differences in events between GG S/D (reduced IgA content product) and other IG products in order to support the proposed contraindication for TAK-880.

After reviewing additional data provided by the Applicant during the interactive review process, based on Study 160001 (new study submitted with this sBLA, Section 6) and Phase 4 Safety Study (previously submitted and reviewed under BLA 103133), multiple patient level data showed coded events of anaphylaxis that on review are not consistent with the definition of anaphylaxis related to the product, either based on the symptoms reported or timing of the event related to receiving the product. However, the following specific patient level data support the proposed contraindications noted in the label for TAK-880, based on hypersensitivity reactions with other IG products that resolved upon switch to GG S/D:

1. Phase 4 Safety Study, Patient IV(b) (6): 3-year-old male with PI developed urticaria, described as hives, at IV site during infusion number 5 with Gamimune N, coded under Standardized Medical Dictionary for Regulatory Activities

Queries term “hypersensitivity.” The rate of infusion was decreased and the “subject recovered after symptomatic treatment.” No AEs of hypersensitivity or anaphylaxis were reported with GG S/D.

2. Phase 4 Safety Study, Patient IV(b) (6): 13-year-old female with PI experienced urticaria (with no other symptoms and did not require treatment) during infusion number 1 with Gamimune N, coded as hypersensitivity and anaphylaxis. No AEs of hypersensitivity or anaphylaxis were reported with GG S/D.
3. Phase 4 Safety Study, Patient IV(b) (6): 11-year-old male with PI experienced wheezing, coded as hypersensitivity and anaphylaxis, on Day 1 of infusion numbers 1, 3, and 6 with Gamimune N. During infusion 1, the wheezing was associated with dyspnea and coded as anaphylaxis. During infusions 3 and 6 the events were coded as hypersensitivity. This same patient developed pruritis on Day 1 of infusion number 4 with Gamimune N and “recovered after symptomatic treatment.” This patient was noted to have an AE of asthma, recorded as an asthma flare, 6 days after infusion number 10 with GG S/D and localized edema (recorded as generalized truncal edema) 15 days after infusion number 12 with GG S/D; while the events reported following Gamimune N infusions are consistent with hypersensitivity reactions, neither of the two events following GG S/D infusions are consistent with hypersensitivity nor anaphylaxis related to the product based on timing of the events.

Within the Optum and MarketScan database review provided in this application, 179 patients initiated GG S/D between December 1, 2018 and December 31, 2022 (MarketScan) or June 30, 2023 (Optum). Three patients were noted to have the identified International Classification of Diseases code, “T78.2XXA: anaphylactic shock, unspecified, initial encounter.” Of these three patients, Patient #1’s narrative may support the proposed contraindication, though analysis of the event is limited by missing data inherent to data collection from such sources. As the other two events were not supportive of product labeling, only Patient #1’s event is summarized.

Patient #1

The first patient identified in the MarketScan database had evidence of anaphylactic shock 84 days prior to first evidence of GG S/D administration. On the date of the anaphylactic event, there were diagnosis codes for hypogammaglobulinemia, Type 2 diabetes, hypertension, and long-term use of aspirin; as well as evidence of systemic high-dose corticosteroids, likely for the treatment of the anaphylactic event. Documentation is missing for prior treatments of PI and details of the anaphylactic event, as show in Table 7. The patient went on to have five GG S/D infusions before the database lock, with no reported associated hypersensitivity or anaphylactic events.

Table 7. Patient-Level Information From the MarketScan Database

Variable	Date of Anaphylactic Event	Evidence of Intervention	Date of First Prescription for GG S/D	Evidence of Primary Immunodeficiency Treatment Prior to Event	Evidence of Subsequent Primary Immunodeficiency Treatment
Patient #1	(b) (6)	Systemic high-dose corticosteroids	(b) (6)	N/A	5 GG S/D

Source: Adapted from "response to clinical information request #4 dates February 4, 2025, regarding TAK-880 supplement biologics license application (sBLA)"
Abbreviations: GG S/D, Gammagard S/D

Within the global safety database review provided by the Applicant, multiple patients reported in the table provided experienced anaphylaxis events in relation to GG S/D. The following patients' safety events may provide support for the proposed contraindication, though it is unclear if enough information is available.

Table 8.Patient-Level Information From the Global Safety Database

Patient ID	Product	Recorded AE	Intervention for AE	Change in Product	Applicant Comment/Review
(b) (6)	GG S/D	Anaphylactic shock	Y: treated with epinephrine	Y	Patient was switched to GG S/D following anaphylactic reaction with GGL. Event was treated and resolved
(b) (6)	GG S/D	Anaphylactic reaction	Y: nor reported	Y	Patient was stable on GG S/D and experienced anaphylactic reaction when he received GGL, was treated, however outcome was not reported.
(b) (6)	GG S/D	Anaphylactic reaction	Y: Benadryl and steroids	Y	Patient experienced anaphylactic reaction following inadvertent GGL therapy instead of GG S/D

Source: Adapted from "Response to Clinical Information Request #4 dates February 04, 2025, regarding TAK-880 Supplement Biologics License Application (sBLA)"
Abbreviations: AE, adverse event; GGL, Gammagard Liquid; GG S/D, Gammagard S/D; Y, yes

Reviewer Comment: *This reviewer's interpretation of the Phase 4 Study and Database information provided by the Applicant is some patients with hypersensitivity or anaphylactic reactions to other IG products were able to tolerate GG S/D without reactions. While patients' IgA levels were not available to confirm, it is reasonable to infer that patients who were able to tolerate GG S/D were sensitive to the higher IgA content in other products. This supports the current labeling for GG S/D for which the product is only contraindicated in patients with anaphylaxis or severe hypersensitivity reactions to GG S/D. This label differs from other IG replacement contraindication statements which typically include anaphylactic or severe hypersensitivity reactions to IG (Human) AND IgA deficient patients with antibodies against IgA and a history of hypersensitivity. Currently, GG S/D provides an option for patients who have had reactions with other IG products. Given the similar IgA content in GG S/D and TAK-880, it is reasonable for TAK-880 to be contraindicated only in patients who have had anaphylaxis or severe hypersensitivity to TAK-880. It should be noted that as there is no clinical data with TAK-880, the contraindication statement in product labeling may need to be revised in the future should new evidence*

emerge from postmarketing surveillance that suggests the risk of hypersensitivity with TAK-880 is greater than that observed with GG S/D.

10. CONCLUSIONS

The safety and efficacy of GGL and GG S/D in patients 2 years and older with PI has already been established through their respective original approvals and is supported by additional clinical trial and postmarketing data submitted in this application. Product comparability data submitted to the efficacy supplement is sufficient to establish the general comparability between TAK-880 and the approved products. It is therefore reasonable to extend safety and efficacy of the approved products, GGL and GG S/D, to TAK-880, given the described comparability of key product attributes.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The risk-benefit considerations for TAK-880 were based on the prior favorable risk-benefit considerations for the previously approved GGL and GG S/D products. IG replacement therapy is standard of care for PI to help restore serum IgG levels and prevent or reduce the severity of serious infections, as demonstrated by low rates of acute SBI in GGL and similar products. Risks of IG are well-characterized and adverse reactions are generally mild, self-limited and require no to minimal intervention. The risk-benefit profile of TAK-880 is expected to be similarly favorable, particularly for patients with PI and previous hypersensitivity/anaphylactic reactions to other IG products or with IgA deficiency and anti-IgA antibodies.

Table 9. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary humoral immunodeficiency (PI) is a form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked agammaglobulinemia, Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, Severe Combined Immunodeficiency, and congenital agammaglobulinemia. • Patients with PI present with recurrent, often severe bacterial and viral infections affecting the respiratory tract, gastrointestinal system, skin, as well as other organs.	• PI and associated antibody deficiencies are serious, chronic conditions associated with considerable morbidity and mortality. • Immunoglobulin replacement therapy administered via IV or SC route has been shown to reduce the incidence of serious infections through provisions of passive immunity.
Unmet Medical Need	• There are numerous approved immune globulin replacement products, and therefore there is not an unmet medical need for additional products except during periods of product shortages. • Patients with history of anaphylaxis or severe systemic hypersensitivity reaction to immune globulin products, as well as IgA deficient patients with antibodies to IgA, have limited options for immune globulin replacement products and depend on the use of the limited IgA reduced immune globulin products (GG S/D).	• There is not currently unmet medical need, per se, due to similar products on the market, but even with available products there remain treatment burdens that impact quality of life for patients. • Patients with anaphylaxis, hypersensitivity reactions, and IgA antibodies have limited options for immune globulin replacement.
Clinical Benefit	• The comparability of the product to the already approved immune globulin replacement products GGL and GG S/D, and their ability to prevent spontaneous bacterial infections in adults and children 2 years and older with PI, has been previously established and can be leveraged to the new product. • GG S/D is available for patients with known anaphylaxis or severe hypersensitivity reactions to other immune globulin products, or patients with IgA deficiency with IgA antibodies. Ability to target a similar population for TAK-880 through product labeling is reasonable based on lower IgA content in GG S/D and TAK-880 as compared to other immune globulin products.	• The ability to receive immune globulin replacement therapy for patients with PI who have experienced anaphylaxis or severe hypersensitivity reactions with other immune globulin products is a crucial part of treatment.
Risk	• The risks associated with TAK-880 are expected to be similar to those of other immune globulin replacement products, especially GGL and GG S/D. • There are no clinical studies with TAK-880 to determine additional risks.	• Safety in the clinical studies submitted in the efficacy supplement for GGL and GG S/D implies no new safety signals or apparent increase in risks associated with the new product as it is comparable on most product attributes to the currently approved products

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Serious risks of immune globulin products include hypersensitivity and anaphylaxis, decline in renal function, hemolysis, TRALI, aseptic meningitis, and transmission of infectious agents. • No new serious risks were identified related to the new product in this efficacy supplement, though no clinical data was provided for TAK-880.	• The package insert and pharmacovigilance plan are adequate to manage and identify new risks.

Source: Reviewer table

Abbreviations: IgA, immunoglobulin A; IV, intravenous; PI, primary humoral immunodeficiency; PID, primary immunodeficiency; SC, subcutaneous; TRALI, transfusion-associated lung injury

11.2 Risk-Benefit Summary and Assessment

Based on substantial evidence of effectiveness and reasonable assurance of safety as demonstrated in the original approvals for GGL and GG S/D, and submitted product data for TAK-880 demonstrating general comparability between the 3 products, TAK-880 is expected to be equally safe and effective. Additional clinical study and postmarketing data submitted in the sBLA are supportive with no change in the safety profiles for GGL and GG S/D since initial approvals. TAK-880 will likely be used most frequently in patients with IgA deficiency or who have a history of hypersensitivity or anaphylaxis with other IGIV products; the risk-benefit profile of the new product is favorable, especially for this subset of patients. The totality of data supports approval of the new product TAK-880 for the indication of replacement therapy for PI in patients 2 years and older.

11.3 Discussion of Regulatory Options

The regulatory options for this BLA efficacy supplement are approval or complete response.

When considering approval, additional options include modification of the indication (e.g., to only approve the new dosing regimens for adults) or the route of administration (e.g., IV only versus IV and SC) with considerations for postmarketing requirements in patients with PI given lack of clinical data with the product at time of approval, or for pediatric patients if only approved in adults.

11.4 Recommendations on Regulatory Actions

Based on a favorable risk-benefit assessment for the new product, TAK-880, the Clinical reviewer recommends approval of the efficacy supplement for replacement therapy in patients with PI 2 years and older, with options for IV or SC administration.

11.5 Labeling Review and Recommendations

At the time of this review signing, labeling negotiations have been completed and agreed upon with the Applicant.

11.6 Recommendations on Postmarketing Actions

No clinical postmarketing requirements or commitments are required for this sBLA.