

BLA Clinical Review Memorandum

Application Type	Original BLA
STN	125810/0
CBER Received Date	June 30, 2023
PDUFA Goal Date	June 28, 2024
Division / Office	DCEGM/OCE
Priority Review (Yes/No)	No
Reviewer Name(s)	Afsah Amin
Review Completion Date / Stamped Date	June 11, 2024
Supervisory Concurrence Team Lead GMB1	Shelby Elenburg
Branch Chief GMB1	Elizabeth Hart
Division Director	Lola Fashoyin-Aje
Applicant	Biotest AG
Established Name	Immune Globulin Intravenous (human), 10% Liquid
(Proposed) Trade Name	YIMMUGO
Pharmacologic Class	Immune Globulin
Formulation(s), including Adjuvants, etc.	10% liquid formulation in water with 100±10 mg/mL protein (96% IgG). It also contains 0.27 to 0.33 mmol/mL glycine, 2 to 20 mcg/mL polysorbate 80, has pH 4.4 to 5.2, osmolality of 280 to 380 mOsmol/kg, and (b) (4) of IgA. It does not contain carbohydrate stabilizers (e.g., sucrose, maltose) or preservatives.
Dosage Form(s) and Route(s) of Administration	Intravenous administration (5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL)
Dosing Regimen	(b) (4) to 800 mg/kg every 3 to 4 weeks
Indication(s) and Intended Population(s)	Treatment of Primary Humoral Immunodeficiency in patients 2 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
bw	body weight
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CVID	common variable immunodeficiency
EQ-5D	EuroQoL Five Dimension Health Questionnaire
FAS	full analysis set
FDA	Food and Drug Administration
IgG	immunoglobulin G
PSP	Pediatric Study Plan
IND	Investigational New Drug application
ITP	immune thrombocytopenic purpura
IVIG	Intravenous Immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
PedsQL	Pediatric Quality of Life Inventory
PeRC	Pediatric Review Committee
PI	primary humoral immunodeficiency
PK	pharmacokinetics
PMR	postmarketing requirement
PPS	per protocol set
PREA	Pediatric Research Equity Act
Q3W	3 weeks
Q4W	4 weeks
SAE	serious adverse event
SAF	safety population set
SBI	serious bacterial infection
SCID	severe combined immunodeficiencies
STN	submission tracking number
TEAE	treatment-emergent adverse event
XLA	X-linked agammaglobulinemia

1. EXECUTIVE SUMMARY

Biotest AG submitted a Biologic License Application (BLA) STN125810/0 on June 30, 2024, for its Human Immune Globulin product YIMMUGO for the treatment of patients with primary humoral immunodeficiency (PI) 2 years of age and older.

YIMMUGO is a 10% liquid formulation manufactured from purified human plasma. It is manufactured by using a modified (b) (4) cold ethanol fractionation process with caprylic acid preparation. It was noted that YIMMUGO IVIG lots used in clinical trials (Study 991 and Study 992) were manufactured by using Process (b) (4) and the full-scale manufacturing will be done by using Process (b) (4) which includes several changes in manufacturing parameters. Importantly, it was noted that the (b) (4) IVIG lots had (b) (4) (b) (4) compared to the (b) (4) IVIG lots (b) (4). This observation was supported by internal testing conducted by PDB1/DPD/OPPT/OTP/CBER. Published studies have reported that higher hemagglutinin titers are associated with hemolytic adverse events especially in immunoglobulin products purified via caprylate/chromatography steps compared to products made without caprylate¹. While the IVIG lots produced by (b) (4) and (b) (4) are both below the FDA maximum allowable limit of (b) (4) the manufacturing process of YIMMUGO may be associated with an increased risk of hemolytic events.

The indication sought by the applicant is for the treatment of patients with PI in patients 2 years of age and older. This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. These disorders are marked by hypogammaglobulinemia, which increases susceptibility to infections. Specifically, patients with PI are at increased risk for recurrent, severe bacterial infections, especially respiratory tract infections. The mainstay of treatment is lifelong, maintenance administration of immunoglobulins (either intravenous or subcutaneous), to provide antibodies and prevent serious bacterial diseases.

The primary evidence of safety and efficacy for this BLA comes from study 991, an open-label, prospective, single-arm study conducted at US, European and Russian sites comparing outcomes to historical standards. The study enrolled 67 patients, including 49 adults and 18 children. To be eligible for the study, participants had to be between 2 and 75 years of age with a diagnosis of PI with impaired antibody production, on established IVIG therapy at a constant dose for at least 3 months, and at least one IgG trough level of ≥ 5 g/L during the previous 3 months. During the trial, patients could receive YIMMUGO at doses between 0.2 and 0.8 g/kg body weight (bw) either every 3-weeks (Q3W) or every 4-weeks (Q4W). The initial dose and dosage interval for YIMMUGO had to be consistent

1 Romberg, V., Hoefflerer, L., El Menyawi I. Effects of the manufacturing process on the anti-A isoagglutinin titers in intravenous immunoglobulin products. *Transfusion* 2015 Jul; 55 Suppl 2: S105-9. Doi: 10.1111/trf.13115.

with the patient's pre-study IVIG treatment and was only to be adjusted due changes in weight or if medically indicated. Each study participant was to be followed for approximately 12 months.

The primary study outcome was the rate of serious bacterial infections (SBIs, e.g., bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) over a period of 12 months. The secondary efficacy endpoints evaluated the IgG trough levels before each infusion; rate of any infection; rate of non-serious infections; time to resolution of infection; antibiotic treatment; the number of days missed from work or school; hospitalizations; and fever episodes. The safety objectives of the study included assessment of number, severity, causality, and seriousness of infusional adverse events (AEs) occurring during infusion or within 1, 24, or 72 hours after the end of infusion and the number of positive intravascular hemolysis test results. The primary pharmacokinetic (PK) endpoints (assessed in the PK subpopulation) included PK parameters at steady state for total IgG, antigen-specific IgG trough levels, and trough serum total IgG levels before each infusion of YIMMUGO in all patients.

The study enrolled 67 patients, 12 patients were in the Q3W schedule group and 55 were in the Q4W schedule group, for evaluation of safety and efficacy of YIMMUGO. The age range of patients was between 2 and 74 years of age, with a mean age of 35 years. Forty-nine were adult patients (≥ 17 years of age), six were adolescents (12 to < 17 years of age), nine were children (6 to < 12 years of age), and three were young children (2 to < 6 years of age). The study population was predominantly White ($n=66$; 98.5%), with males representing 55.2% of the population. Forty-one patients were from European sites, 21 from U.S. sites, and 5 from Asian sites. The most common underlying cause of PI was CVID ($n=53$; 79.1%). The other etiologies included XLA ($n=10$; 14.9%); congenital agammaglobulinaemia ($n=2$; 3%); congenital hypogammaglobulinaemia ($n=1$; 1.5%); and specific antibody defect ($n=1$; 1.5%). A total of seven patients discontinued early from the study including two patients who discontinued due to product-related SAE.

The applicant reported a single event of SBI during the trial and an unadjusted SBI rate of 0.01 patient-year based on total person-years of 67.6. During the BLA review, an additional four infections were adjudicated as SBIs. All SBIs were bacterial pneumonias. The updated annualized SBI rate was 0.074, with an upper one-sided 99% confidence limit (CI) of 0.21. The study met its primary endpoint of less than 1 SBI per patient-year, which conforms to the FDA guidance referenced hereafter in the review as *FDA IVIG guidance* and precedence for establishing efficacy of immunoglobulins for PI². The secondary efficacy endpoints reported the following: 1) a total of 189 treatment-emergent infections in 48 patients (annualized rate of infection = 2.8 per patient-year); 2) a

2. Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. U.S. Food and Drug Administration. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human>

total of 39 patients who reported antibiotic use including both prophylactic and therapeutic (annualized rate of antibiotic use =33 days); 3) a total of 26 patients who lost at least 1 day of work/school due to infection (annualized rate =4.3); and 4) a total of four hospitalizations in three patients due to infection (annualized rate of hospitalization =0.06). Overall, the secondary outcomes were supportive of the primary efficacy assessment for the study. However, in review of sub-population analysis, it was noted there was lack of adequate efficacy data in the young children cohort (2 to <6 years of age), which included only two evaluable patients. One of those patients had 18 infections (including one SBI) and was hospitalized due to an infection. With the possible lack of efficacy signals, the efficacy in young children 2 to <6 years of age cannot be determined.

The mean total IgG trough levels at steady state were above the targeted minimal trough level of 5 g/L and remained constant after reaching steady state. The PK profiles of patients aged 6 to <76 years were characterized by non-compartmental analyses (NCA). The applicant conducted population PK analysis to predict PK parameters for three young children (age 2 to < 6 years) and assess potential effect of the intrinsic and extrinsic factors on total IgG PK. It was noted that the PK sampling for pediatric patients aged <6 years of age was limited and there was uncertainty regarding the PK results from the modeling simulation.

The safety population set (SAF) consisted of all patients who received ≥ 1 dose of YIMMUGO (n=67). A total of 923 YIMMUGO infusions were administered during the trial. No deaths were reported. A total of two serious adverse events (SAEs) related to the product administration was reported in two patients (anaphylactic reaction, severe neutropenia). Mild hemolysis and positive Coombs test were reported in one patient. Overall, 63 out of 67 patients experienced a total of 458 TEAEs. Of these, 93 events in 39 patients were FDA-specified adverse reactions (ARs). The most common ARs observed in >5% of patients included headache, upper respiratory infections, fatigue, nausea, and increased blood pressure.

Additionally, the applicant submitted the results from Trial 992 to support the safety of YIMMUGO. Trial 992 was an open-label, prospective, randomized, multicenter study investigating higher doses of YIMMUGO on clinical efficacy and safety in adults with chronic primary immune thrombocytopenia (ITP). The trial enrolled 34 adult patients who received Yimmugo either 1 g/kg bw per day for 2 consecutive days (n=18) or 0.4 g/kg bw per day for 5 consecutive days (n=16) (i.e., a total dose of 2 g/kg bw per treatment course) and were followed for 36 days after the first infusions. A total of 115 infusions were administered and all 34 patients were included in the safety analysis. No deaths were reported. One SAE was reported in a patient (anemia). Additionally, six patients were reported to have hemolytic events and 12 patients tested positive for Coombs test during the study. Because of the significant differences in the study population, higher dose administration, and limited follow-up duration, it was difficult to generalize the results from Trial 992 to patients with PI. However, the high number of hemolytic events noted during the study may indicate that YIMMUGO is at a higher risk for causing hemolytic events especially at higher dose levels.

In summary, the Trial 991 is consistent with the FDA IVIG guidance for studies supporting marketing applications for IVIG therapies for the treatment of PI and provides the primary evidence of safety and efficacy of YIMMUGO. However, the reviewer is concerned about the lack of adequate efficacy data in the young children cohort (2 to <6 years of age). Further, there are uncertainty in the PK results from the modeling simulation and the PK is not adequately characterized in this age group. Therefore, the reviewer recommends approval of YIMMUGO for the treatment of patients PI in patients 6 years of age and older and requests a clinical study under Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) to gain additional data on safety and efficacy in young children 2 to <6 years of age.

Division Director Note: I concur with the clinical reviewer’s summary assessment of the safety and efficacy of YIMMUGO. While I acknowledge the limited available PK data in patients 2 to <6 years of age, my overall assessment is that approval is this younger age group is supported (see clinical pharmacology reviewer memo).

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1. Trial 991 Demographics

Criteria	Adults (n=49)	Pediatric Patients 2 to <6 Years of Age (n=3)	Pediatric Patients 6 to <12 Years of Age (n=9)	Pediatric Patients 12 to <17 Years of Age (n=6)	Overall (N=67)
Age at screening, years					
Mean (SD)	43.8 (14.9)	2.7 (0.6)	9.2 (2.0)	13.7 (1.6)	34.6 (20)
Median	42.0	3.0	10.0	13.5	37.0
Min – Max	20 –74	2 – 3	6 – 11	12 – 16	2 – 74
Gender, n (%)					
Male	22 (44.9)	3 (100)	8 (88.9)	4 (66.7)	37 (55.2)
Female	27 (55.1)	0	1 (11.1)	2 (33.3)	30 (44.8)
Region, n (%)					
United States	16 (32.7)	0	2 (22.2)	3 (50.0)	21 (31.3)
Europe	28 (57.1)	3 (100)	7 (77.8)	3 (50.0)	41 (61.2)
Asia (1 site in Russia)	5 (10.2)	0	0	0	5 (7.5)
Race, n (%)					
White	49 (100)	3 (100)	8 (88.9)	6 (100)	66 (98.5)
Asian	0	0	1 (11.1)	0	1 (1.5)

Source: Reproduced from Trial 991 CSR-Table 11-2 (with modification to 1 decimal place)

Abbreviations: max, maximum; min, minimum; n, number of patients in a specified category; N, number of patients; SD, standard deviation.

Reviewer Comment: *There were mostly White patients enrolled in the study. Further, it was noted that there was lack of information regarding the ethnicity (Hispanic, non-Hispanic) and blood groups of patients enrolled in the study. While it is advisable that applicants collect these variables in*

their pivotal trials, the lack of ethnicity and blood group data were not thought to significantly influence the outcomes in patients with PI, and therefore, this was not considered a major review issue.

1.2 Patient Experience Data

The applicant collected clinician-reported outcomes including infections other than SBIs, duration of infections, duration of antibiotic use, unscheduled physician visits/hospitalizations as secondary endpoints. Additionally, Pediatric Quality of Life Inventory (PedsQL) and EuroQoL Five Dimension Health Questionnaire (EQ-5D) were assessed as exploratory endpoints in pediatric and adult patients, respectively.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input checked="" type="checkbox"/>	Patient-reported outcome	6.1
<input type="checkbox"/>	Observer-reported outcome	
<input checked="" type="checkbox"/>	Clinician-reported outcome	6.1
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Primary humoral immunodeficiency represents a heterogeneous group of disorders resulting from largely inherited defects of the immune system. It is estimated that 1 to 2% of the population worldwide is affected. These disorders are characterized by hypogammaglobulinemia, with increased susceptibility to infections. The major antibody deficiency syndromes of clinical significance include CVID, severe combined immunodeficiencies, XLA, Wiskott-Aldrich Syndrome, Hyper IgM Syndrome, Chronic Granulomatous Disease, and IgG subclass deficiency. Patients with PI are at increased risk for recurrent, severe respiratory tract and other infections (both viral and encapsulated bacterial in origin). Symptoms can be severe and can lead to substantial morbidity. Patients with PI have day-to-day personal life disruptions with unscheduled physician office visits and hospital admissions. At present, most primary immunodeficiencies are not curable. Hematopoietic cell transplantation may be curative for some patients with PI. There are ongoing clinical trials that are exploring safety and efficacy of gene therapy for different syndromes of PI. Replacement therapy with immunoglobulins provides antibodies to help prevent viral and bacterial diseases and remains the mainstay of treatment.

2.2 Currently Available, Pharmacologically Unrelated

Treatment(s)/Intervention(s) for the Proposed Indication(s)

The general management of PI involves preventing and treating infections. Prevention of infections consists of avoidance measures, age-appropriate vaccination, prophylactic antibiotics, and lifelong maintenance immunoglobulin therapy. Treatment of infections often involves prolonged treatment courses of broad-spectrum antimicrobials.

2.3 Safety and Efficacy of Pharmacologically Related Products

The FDA IVIG Guidance states that a statistical demonstration of an SBI rate per person-year of less than 1.0 is adequate to provide substantial evidence of effectiveness to support licensure.

Several immunoglobulin products (both intravenously and subcutaneously administered) have been licensed in the U.S. based on demonstration of an SBI rate of less than 1.0 per person-year. There are currently 14 licensed (Human) IVIG products in the United States: Aylglo (GC Biopharma), Asceniv (ADMA Biologics, Inc.), Bivigam (Biotest Pharmaceuticals Corporation), Carimune (CSL Behring AG), Flebogamma DIF 5% and 10% (Instituto Grifols), Gammagard and Gammagard S/D (Baxter HealthCare Corp), Gammaked (Kedrion Biopharma), Gammaplex 5% & 10% (Bio Products Laboratory), Octagam and Panzyga (Octapharma Pharmazeutika Produktionsges), Priviligen (CSL Behring AG). All are indicated as replacement therapy in patients with PI.

The safety profile for immunoglobulins as a class is well established. The incidence of 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 IVIG products. Common ARs for intravenously administered immunoglobulins typically include headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. IVIG (Human) as a drug class carries an obligatory boxed warning for thrombosis, renal dysfunction, and acute renal failure. Other rare risks associated with the use of IVIG include transmission of infectious agents (e.g., viruses), hemolysis, aseptic meningitis, transfusion-associated lung injury, hyperproteinemia, and increased viscosity.

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

The product was approved for marketing in Germany on November 11, 2022, and was later approved in Austria and United Kingdom on December 20, 2024. The product is authorized in the listed foreign market as replacement therapy for the treatment of PI and secondary immune deficiency, and as immunomodulation therapy for the treatment of ITP, Guillain-Barré Syndrome, Kawasaki Disease, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, and Multifocal Motor Neuropathy in adults, children, and adolescents (0 to 18 years of age).

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

Table 2. Regulatory History

Date	Item
January 26, 2016	The applicant had a pre-IND meeting with the agency. FDA provided feedback on the design elements of Trial 991.
June 16, 2016	The applicant submitted their original IND to conduct Trial 991 titled “An open-label, prospective, multicenter study investigating clinical efficacy, safety, and pharmacokinetic properties of human normal immunoglobulin for intravenous administration IgG Next Generation (BT595) as replacement therapy in patients with primary immunodeficiency disease.”
July 15, 2016	IND allowed to proceed.
October 17, 2016	iPSP submitted by the applicant.
June 6, 2017	iPSP agreement letter send to the applicant.
June 25, 2018	The applicant had a Type C meeting with the agency. FDA provided feedback on CMC-related issues including the comparability study for the new manufacturing process.
April 3, 2023	Pre-BLA meeting/teleconference held with the applicant. The agency stated that it was premature to determine if the applicant has fulfilled the PREA requirements as per the agreed iPSP without a complete review of BLA data.

Source: Original Table Created by Clinical Reviewer

Abbreviations: BLA, Biologics License Application; CMC, chemistry, manufacturing and controls; IgG, immunoglobulin G; IND, Investigational New Drug Application; iPSP, Initial Pediatric Study Plan.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was sufficiently organized and integrated to accommodate the conduct of a complete clinical review. It was submitted electronically and formatted as an electronic Common Technical Document according to the FDA

Guidance for Electronic Submissions. The submission contained the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The applicant reported that the study was conducted in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human patients and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, European Union Directives 2001/20/EC and 2005/28/EC, and the U.S. FDA Title 21 CFR, as well as the demands of national drug and data protection laws, other applicable regulatory requirements, and any new directives or regulations that became enforceable during the course of the study.

For Trial 991, the applicant reported 10 major protocol deviations. These included 3 of the 12 patients in the Q3W schedule group and 7 of the 55 patients in the Q4W schedule group. These 10 patients were excluded from per protocol set (PPS).

Table 3. Summary of Major Protocol Deviations

Nature of Deviation	Patient ID	Additional Comments
Eligibility violation	(b) (6)	13-year-old female had active infection and was receiving antibiotic therapy at the time of screening.
Eligibility violation	(b) (6)	6-year-old male had a specific antibody defect and not CVID.
Study procedure	(b) (6)	3-year-old male discontinued early due to withdrawal of guardian consent. Patient received 6 infusions.
Study procedure	(b) (6)	22-year-old female discontinued early from the study due SAE (severe neutropenia). Patient received one infusion only.
Eligibility violation	(b) (6)	41-year-old male had a suspected diagnosis of secondary immunodeficiency (history of B cell lymphoma and stem cell transplantation).
Study procedure	(b) (6)	34-year-old female discontinued early from the study due SAE (anaphylactic reaction). Patient received one infusion only.
Study procedure	(b) (6)	55-year-old male discontinued early from the study due SAE (toxic hepatitis). Patient received 12 infusions.
Eligibility violation Study procedure	(b) (6)	20-year-old female discontinued early from the study due to patient decision. Patient received 12 infusions. Additionally, the patient had an active infection and was receiving antibiotic therapy at the time of screening
Eligibility violation Study procedure	(b) (6)	28-year-old male discontinued early from the study due to patient decision. Patient received 2 infusions. Additionally, the patient had an active infection and was receiving antibiotic therapy at the time of screening
Study procedure	(b) (6)	38-year-old female discontinued early from the study due to patient decision. Patient received 5 infusions.

Source: Table created by the reviewer from information provided in Trial 991 CSR.

Abbreviations: CVID, common variable immunodeficiency; SAE, serious adverse event.

Reviewer Comments: It was noted that seven patients discontinued early from the study. The inadequate amount of study medication received by

these patients was addressed statistically by imputation and may have minimal impact on the efficacy results for YIMMUGO for the overall population. However, due to limited sample size of the pediatric population especially the young children (2 to <6-year-old), the early discontinuation may have significant impact on interpretation of efficacy data in this age group.

Additionally, it was noted that five patients had baseline total IgG trough level of <5 g/L. These deviations were regarded as minor since the patients had at least one total IgG trough level of ≥5 g/L during the 3 months prior to enrollment.

Bioresearch Monitoring Audit Summary

One domestic and three foreign clinical investigator sites of Trial 991 were selected for Bioresearch Monitoring inspection based on number of patients enrolled, previous inspectional history, and the data submitted in the BLA.

Per Bioresearch Monitoring Review “The inspections did not reveal significant issues that impact the data submitted in this original Biologics License Application (BLA).”

3.3 Financial Disclosures

Trial 991

Covered clinical study (name and/or number): Trial 991
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: 25
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>

<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p> <p>Is an attachment provided with details of the disclosable financial interests/arrangements? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant)</p> <p>Is a description of the steps taken to minimize potential bias provided? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)</p>
<p>Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u></p> <p>Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)</p>

Trial 992

<p>Covered clinical study (name and/or number): Trial 992</p>
<p>Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)</p>
<p>Total number of investigators identified: <u>22</u></p>
<p>Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u></p>
<p>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u></p>

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? Yes No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided? Yes No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? Yes No (Request explanation from applicant)

Reviewer's Comment: Per Form 3454, the sponsor certifies that the sponsor has not entered into any financial arrangements with the listed clinical investigators and that each listed clinical investigator did not disclose any such interests.

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

4.1 Chemistry, Manufacturing, and Controls

YIMMUGO is manufactured by using a modified (b) (4) cold ethanol fractionation process with caprylic acid preparation. It was noted that YIMMUGO IVIG lots used in clinical trials (Study 991 and Study 992) were manufactured by using Process (b) (4) and the full-scale manufacturing will be done by using Process (b) (4) which includes several changes in manufacturing parameters. Importantly, it was noted that the (b) (4) IVIG lots had (b) (4) (b) (4) compared to the (b) (4) IVIG lots (b) (4). This observation was supported by internal testing conducted by PDB1/DPD/OPPT/OTP/CBER. To address the risk of hemolysis, the applicant was advised by the CMC review team to either incorporate an (b) (4) (b) (4) or select plasma donors with (b) (4).

Reviewer Comment: There are several known risk factors for IVIG-associated hemolysis, which includes administration of high-dose IVIG, non-O blood group of the recipient, and manufacturing processes that lead to a (b) (4) in the final products. Published studies have reported that higher hemagglutinin titers are associated with hemolytic adverse events especially in immunoglobulin products purified via

caprylate/chromatography steps compared to products made without caprylate. While the IVIG lots produced by (b) (4) and (b) (4) are both below the FDA maximum allowable limit of (b) (4) the manufacturing process of YIMMUGO may be associated with an increased risk of hemolytic events. The clinical team agrees with the recommendation by the CMC review team to modify the YIMMUGO manufacturing process to either incorporate an (b) (4) or select plasma donors with (b) (4) which may potentially lower the risk of hemolysis associated with YIMMUGO administration.

4.2 Assay Validation

Please refer to the CMC review for details.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology/toxicology review for details. No non-clinical pharmacology/toxicology review issues were identified.

4.4 Clinical Pharmacology

The PK endpoints included (1) IgG trough levels (total IgG) before each administration of YIMMUGO (secondary efficacy endpoint) for all patients; (2) IgG trough levels at baseline and before the seventh/fifth infusion of the Q3W/Q4W schedule, respectively (except pediatric patients 2 to <6 years of age); (3) Antigen-specific IgG trough levels at baseline and before the seventh/fifth infusion of the Q3W/Q4W schedule, respectively (except pediatric patients 2 to <12 years of age); and (4) PK parameters at steady state which included maximum concentration (C_{max}), time to reach the maximum concentration (t_{max}), area under the concentration-time curve calculated from start to end of the dosing interval (AUC_{tau}) and extrapolated to infinity (AUC_{0-inf}), steady state clearance (CL_{ss}), and terminal elimination half-life ($t_{1/2}$), as well as other parameters.

The mean total IgG trough levels at steady state were above the targeted minimal trough level of 5 g/L and generally remained constant after reaching steady state. The PK profiles of patients aged 6 to <76 years were characterized by non-compartmental analyses (NCA). The applicant conducted population PK analysis to predict PK parameters for three young children (age 2 to < 6 years) and assess potential effect of the intrinsic and extrinsic factors on total IgG PK. It was noted that the PK sampling for pediatric patients aged <6 years of age was limited and there was uncertainty regarding the PK results from the modeling simulation. Please refer to the clinical pharmacology review memo for details.

Reviewer Comment: Based on the pharmacometrics review, the clinical reviewer believes that the PK data submitted in the young children cohort (2 to <6 years of age) may be insufficient to recommend approval of YIMMUGO in children who are 2 to <6 years of age. Population PK analyses were used to predict PK profiles of young children 2 to < 6 years old with sparse PK sampling. However, it was noted that the prediction of PK

parameters of total IgG in children 2 to < 6 years old may have uncertainty due to the small sample size in this population group.

4.4.1 Mechanism of Action

IVIG is manufactured through fractionation of large volumes of plasma pooled from thousands of healthy donors and contains immune antibodies and physiologic autoantibodies. Immune antibodies reflect the immunologic experience of the donor population. Hence the antibodies contained in IVIG will provide protection against many bacterial, viral, and other infectious agents. This fraction of IVIG preparations is useful for passive immunization as replacement therapy.

As IVIG is a blood product, there is also a risk of transmission of blood-borne infections. However, there have been no reports of transmission of HIV or hepatitis B or hepatitis C infection by IGIV therapy with the current safety measures.

4.4.2 Human Pharmacodynamics

YIMMUGO contains primarily IgG antibodies and has a distribution of immunoglobulin subclasses closely proportional to that of native human plasma. Administration of YIMMUGO increases recipients' IgG levels in a dose-dependent fashion.

4.4.3 Human Pharmacokinetics

Please refer to the clinical pharmacology review for details.

4.5 Statistical

The statistical reviewer reviewed the submitted data used to support the primary study endpoint analyses. No statistical concerns were identified. Please refer to the memo from the statistical reviewer.

4.6 Pharmacovigilance

Review of the available clinical and foreign post marketing safety data by the pharmacovigilance review team did not identify any safety concerns which would necessitate a Risk Evaluation and Mitigation Strategy (REMS) or a Post-marketing Requirement (PMR) study that is specifically designed to evaluate a particular safety issue as a primary endpoint. Further, no safety-related study as a post marketing commitment (PMC) was recommended by the team. The applicant was advised to conduct routine pharmacovigilance in accordance with 21 CFR 600.80 and enhanced pharmacovigilance for all AEs involving hemolysis for a period of three years post-licensure, as outlined in the applicant's Risk Management Plan for YIMMUGO (Human normal immunoglobulin (IVIg)), version 0.5. Please see pharmacovigilance memo for details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This original BLA submission included data from Trial 991 (PI), which served as the primary evidence of safety and efficacy. The submission also included data from Trial 992 in patients with ITP to support the safety of YIMMUGO. However, due to the differences in study population, dosing regimen, and follow-up duration, the data from Trial 992 was difficult to generalize to patients with PI. The clinical reviewer also reviewed study designs and data from clinical trials evaluating the safety, efficacy, and PK of the commercially available intravenous immunoglobulin products mentioned in [Section 2.3](#) of this document and the FDA IVIG guidance document.

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

- Module 1
 - 1.1 Forms
 - 1.1.2 Form 356
 - 1.1.3 Form 3397
 - 1.1.7 Form 3674: Certificate of Compliance
 - 1.2 Cover Letter
 - Cover letter
 - Reviewers Guide
 - 1.3 Administrative information
 - 1.3.4 Financial Certificate
 - 1.6 Meetings
 - 1.6.3 Pre-IND Type B Meeting Summary Jan 2016
 - 1.6.3 Type C Meeting Summary Oct 2016
 - 1.6.3 Type B Meeting Summary Aug 2022
 - 1.6.3 Pre-BLA Meeting Summary April 2023
 - 1.9 Pediatric administrative information
 - 1.9.4 Agreed initial Pediatric Study Plan (PSP) 20170606
 - 1.14 Labeling
 - 1.14.1.3 Draft Labeling text
 - 1.14.5 European Union Labeling text
- Module 2
 - 2.2 Introduction
 - 2.5 Clinical overview
 - 2.7 Clinical Summary
 - 2.7.3 Summary of Clinical efficacy
 - 2.7.4 Summary of Clinical Safety
 - 2.7.5 Literature References
 - 2.7.6 Synopsis of Individual Studies
- Module 5

- 5.2 Tabular listing of all Clinical Studies
- 5.3 Clinical Studies
 - 5.3.5.2 Study 991 Complete Clinical Study Report
 - 5.3.5.3 Integrated Summary of Safety
 - 5.3.5.4 Study 992 Complete Study Report
 - Appendix-16
 - Analysis Datasets
 - CFRs
- 5.4 Literature References

5.3 Table of Studies/Clinical Trials

Table 4. Studies/Clinical Trials

Type of Study	Study ID	Objective(s)	Study Design	Dose and ROA	Number of Patients	Study Population	Treatment Duration	Study Status
Efficacy, Safety, PK	BT595-991	To demonstrate that the rate of acute serious bacterial infections (i.e., the mean number of acute SBIs per patient-year) is less than 1.0, to provide substantial evidence of efficacy. To assess the safety and PK characteristics of BT595	Open, prospective, uncontrolled, multicenter	IgG Next Generation (BT595); 0.2-0.8 g/kg bw monthly as i.v. infusion in 3- or 4-week intervals for a treatment period of approx. 12 months	67 patients (2 to ≤75 years of age, 49 adults and 18 pediatric patients)	Patients with PI.	Approx. 12 months	Completed
Efficacy, Safety, (Efficacy in the EU only)	BT595-992	To assess the efficacy and safety of BT595 in adult patients with chronic primary ITP. To determine the rate of patients with an R, defined as a platelet count of $\geq 30 \times 10^9/L$ and at least a 2-fold increase of the baseline count, confirmed on at least 2 separate occasions at least 7 days apart, and the absence of bleeding.	Open, prospective, randomized (two dosing regimens in a 1:1 ratio), uncontrolled, multicenter	IgG Next Generation (BT595); 2 g/kg bw as i.v. infusion in either 1 g/kg bw for 2 consecutive days or 0.4 g/kg bw for 5 consecutive days	34 adult patients (18 to <75 years of age)	Patients with chronic primary ITP	2 to 5 days	Completed

Source: Table 1 from Module 2.7.6 (synopsis of individual studies)

Abbreviations: bw, body weight; EU, European Union; g, grams; IgG, immunoglobulin; ITP, immune thrombocytopenia; i.v., intravenous; kg, kilogram; L, liter; PI, primary immunodeficiency disease; PK, pharmacokinetics; R, response; SBI, serious bacterial infection.

5.4 Consultations

5.4.1 Advisory Committee Meeting

No Advisory Committee Meeting was held.

5.4.2 External Consults/Collaborations

The Center for Drug Evaluation and Research's Division of Pharmacometrics was consulted to analyze the population PK data. The population PK analysis included the total IgG concentrations of 67 patients from Trial 991, comprising 47 adults and 18 pediatric patients. The final population model was used to predict PK parameters for young children 2 to <6 years of age. It was noted by the pharmacometrics reviewer that there may be uncertainty in the prediction of PK parameters for young children 2 to <6 years of age due to the small sample size in this population group.

Reviewer's Comment: The clinical reviewer agrees with Pharmacometrics reviewer regarding the uncertainty of PK parameters in the youngest population group (young children 2 to <6 years of age).

5.5 Literature Reviewed

Borte M, Melamed IR, Pulka G, et al (2017). Efficacy and safety of human intravenous immunoglobulin 10% (Panzyga®) in patients with primary immunodeficiency diseases: a two-stage, multicenter, prospective, open-label study. *J Clin Immunol*; 37(6):603-12.

Kreuz W, Erdös M, Rossi P, et al (2010). A multi-centre study of efficacy and safety of Intratect®, a novel intravenous immunoglobulin preparation. *Clin Exp Immunol*; 161(3):512-7.

Krivan G, Chernyshova L, Kostyuchenko L, et al (2017). A Multicentre Study on the Efficacy, Safety and Pharmacokinetics of IqYmune®, a Highly Purified 10% Liquid Intravenous Immunoglobulin, in Patients with Primary Immune Deficiency. *J Clin Immunol*; 37(6):539-47.

Romberg, V., Hoefflerer, L., El Menyawi I. Effects of the manufacturing process on the anti-A isoagglutinin titers in intravenous immunoglobulin products. *Transfusion* 2015 Jul; 55 Suppl 2: S105-9. Doi: 10.1111/trf.13115.

Wasserman RL, Lumry W, Harris J 3rd, et al (2016). Efficacy, Safety, and Pharmacokinetics of a new 10% liquid intravenous immunoglobulin containing high titer neutralizing antibody to RSV and other respiratory viruses in patients with primary immunodeficiency disease. *J Clin Immunol*; 36(6):590-9.

Wasserman RL, Church JA, Stein M, et al (2012). Safety, efficacy, and PK of a new 10% liquid intravenous immunoglobulin (IVIg) in patients with primary immunodeficiency. *J Clin Immunol*; 32(4):663-9.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Trial 991: An open-label, prospective, multicenter study investigating clinical efficacy, safety, and PK properties of the human normal immunoglobulin for intravenous administration YIMMUGO as replacement therapy in patients with PI.

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to demonstrate that the rate of acute SBIs (i.e., the mean number of acute SBIs per patient-year) is less than 1.0, to provide substantial evidence of efficacy.

The secondary objectives of this study, in addition to further efficacy assessments, were to assess the safety and PK characteristics of YIMMUGO.

Primary Endpoint

Rate of acute SBIs, i.e., the mean number of acute SBIs per patient-year. Acute SBIs included:

- Bacteremia or sepsis.
- Bacterial meningitis.
- Osteomyelitis/septic arthritis.
- Bacterial pneumonia.
- Visceral abscess.

Specific diagnostic criteria for these infection types as per FDA IVIG guidance were used.

Secondary Endpoints

- IgG trough levels (total IgG) before each infusion (local laboratory assessment).
- Rate of any infections (number per patient-year).
- Rate of nonserious infections (number per patient-year), defined as all infections not fulfilling the FDA guidance on diagnostic criteria for serious infection types.
- Time to resolution of infections (days).
- Antibiotic treatment (number of days antibiotic treatment was received per patient-month and per patient-year).
- Rate of time lost from school/work due to infections and their treatment (number of days per patient-month and per patient-year [both 365 and 220 days]).
- Hospitalizations (number of days per patient-month and per patient-year overall and due to infection).
- Fever episodes (number of days per patient-year).

Exploratory Endpoints

- PedsQL (child self-report and/or parent proxy report): completed by all pediatric patients (2 through 4 years of age, 5 through 7 years of age, 8 through 12 years of age, and 13 through 18 years of age).
- The 3-level version of EQ-5D (EQ-5D-3L) completed by all adult patients (18 through 75 years of age).
- Youth version of the EQ-5D (EQ-5D-Y): completed by pediatric patients (4 through 17 years of age, inclusive). The parent proxy version for children 4 through 7 years of age was not used.

Pharmacokinetics Endpoints

- IgG trough levels (total IgG) before each administration (secondary efficacy endpoint), as assessed by the local laboratory, for all patients.
- IgG trough levels (subclasses 1-4, central laboratory) at baseline and before the seventh/fifth infusion of the Q3W/Q4W schedule, respectively (except for pediatric patients 2 to <6 years of age).
- Antigen-specific IgG trough levels (anti-pneumococcal capsular polysaccharide, anti-haemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-hepatitis B surface antigen/hepatitis B; central laboratory) at baseline and before the seventh/fifth infusion of the Q3W/Q4W schedule, respectively (except for pediatric patients up to 11 years of age, inclusive [European Medicines Agency, EMA, guidance]; 2 to <12 years of age [FDA guidance]).
- PK parameters at steady state for: a) total IgG (patients 2 to <76 years of age), b) IgG subclasses 1-4 (patients 6 to <76 years of age), and c) the 6 analyzed antigen-specific IgGs (patients 12 to <76 years of age). PK parameters included maximum concentration (C_{max}), time to reach the maximum concentration (t_{max}), area under the concentration-time curve calculated from start to end of the dosing interval (AUC_{tau}) and extrapolated to infinity (AUC_{0-inf}), steady state clearance (CL_{ss}), and terminal elimination half-life ($t_{1/2}$), as well as other parameters.

Safety Endpoints

- Adverse events
 - Number, severity, causality, and seriousness of infusional AEs (including nonproduct-related); i.e., AEs temporally associated with the infusion (occurring during infusion or within 1, 24, or 72 hours after the end of infusion).
 - Number of related infusional AEs (occurring during infusion or within 1, 24, and 72 hours after the end of infusion).
 - Number and percentage of infusions temporally (within 72 hours) associated with one or more TEAEs.
 - Number of AEs during the infusion, by infusion rate and by time to onset.

- Number, severity, causality, and seriousness of all AEs.
- Number, severity, causality, and seriousness of all TEAEs.
- Number of noninfusional AEs (occurring more than 72 hours after the end of infusion).
- Changes in safety laboratory parameters (outside reference range and clinically relevant).
- Number of positive intravascular hemolysis test results.
- Changes in vital sign parameters.
- Changes in physical examination parameters.

6.1.2 Design Overview

The trial was a multicenter, multinational, prospective, open-label, historically controlled study conducted in United States, Europe, and Asia.

Reviewer Comment: The selected endpoints and study design were consistent with FDA IVIG guidance.

6.1.3 Population

Summary of the Inclusion Criteria

- Patients 2 to 7 years of age.
- Diagnosis of PI with impaired antibody production.
- Established IVIG replacement therapy for at least 3 months prior to the start of YIMMUGO with a constant dose that did not change by $\pm 20\%$ with regular dosage interval, and at least one trough level of ≥ 5 g/L during the previous 3 months.

Summary of the Exclusion Criteria

- Acquired medical conditions known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, as well as protein-losing enteropathies and hypoalbuminemia.
- Active infection and receiving antibiotic therapy for the treatment of this infection at the time of screening.
- Therapy with systemic steroids or other immunosuppressant drugs at the time of enrollment (current daily use of corticosteroids, i.e., >10 mg prednisone equivalent/day for >30 days. Intermittent corticosteroid use during the study was allowable, if medically necessary).
- History of thrombotic events (including myocardial infarction, cerebral vascular accident [including stroke], pulmonary embolism, and deep vein thrombosis) within the 6 months before treatment start with BT595 or the presence of significant risk factors for thrombotic events.
- Therapy with live-attenuated virus vaccines within 3 months before the start of the study.
- Selective, absolute IgA deficiency or known antibodies to IgA.
- Positive diagnosis of hepatitis B or hepatitis C.

- Positive HIV test.

Reviewer Comment: The eligibility criteria were typical for IVIG trials and were appropriate to determine the safety and efficacy in the target population. No patients enrolled in the trial were naïve to IVIG therapy. This conforms with other development programs for similar products, but likely results in an overestimation of safety and tolerability. However, there were several eligibility violations during the trial including three patients who had active infection and were receiving antibiotic therapy, one patient with specific antibody defect, and one with a possible secondary immune deficiency due to B cell lymphoma and stem cell transplantation.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The patients received YIMMUGO at doses between 0.2 and 0.8 g per kg bw (2 to 8 mL/kg bw), either at a Q3W or Q4W schedule, for a treatment period of approximately 12 months. The initial dose and dosage interval had to be consistent with the patient's pre-study IVIG treatment and was only to be changed due to changes in weight or if medically indicated. YIMMUGO was administered as intravenous infusion at an initial infusion rate of 0.3 mL/kg/h for 30 minutes, to be increased to 1.4 mL/kg/h for a further 30 minutes. If well tolerated, the infusion rate could then be gradually increased to a maximum of 2 mL/kg/h for the remainder of the first infusion. From the second infusion onwards, patients' infusion rates could be individually tailored at the investigator's discretion, but each infusion had to start again at the initial infusion rate of 0.3 mL/kg. In patients who tolerated the infusion rate of 2 mL/kg/h well during the first infusion, the rate could be gradually increased to 4 mL/kg/h and, if still tolerated well, gradually increased to 6 mL/kg/h, to a maximum of 8 mL/kg/h.

6.1.5 Directions for Use

Not applicable

6.1.6 Sites and Centers

Table 5. List of Principal Investigators and Investigative Sites With Recruitment Data

Site Number	Principal Investigator Name	Site Address and Contact Details at the Time of Clinical Study	Number of Patients Enrolled	Number of Patients Eligible	Number of Patients Treated who Prematurely Discontinued IP
0101	Suez, Daniel	Allergy, Asthma and Immunology Clinic PA, 1115 Kinwest Parkway, Suite #100, Irving, 75063, Texas, USA, p: 001-972-401-0545, f: 001-214-306-6453, dsuez@dsallergy.com	0	0	0
0102	Lumry, William	AARA Research Centre, 10100 North Central Expressway, Suite #125, Dallas, 75231, Texas, USA, p: 001-214-365-0365, f: 001-214-365-0360, LumryMD@aararesearch.com	5	4	0
0103	Melamed, Isaac	IMMUNOe Research Centers - Centennial, 6801 South Yosemite Street, Centennial, 80112, Colorado, USA, p: (b) (6) f: (b) (6), melamedi@immunoe.com	9	7	0
0104	Schroeder, Harry	The Kirklin Clinic of UAB Hospital, 2000 6 th Avenue South, Birmingham, 35233, Alabama, USA, p: (b) (6) hschroeder@uabmc.edu	2	1	0
0105	Rehman, Syed	Toledo Institute of Clinical Research, 7247 West Central Avenue, Toledo, 43617, Ohio, USA, p: 001-419-843-8815, f: 001-419-843-8816, (b) (6) @yahoo.com	2	2	0
0106	Harris, James	The South Bend Clinic, 211 North Eddy Street, South Bend, 46617, Indiana, USA, p: 001-574-239-1576, f: 001-574-204-6439, jharris@southbendclinic.com	5	3	0
0110	Koterba, Alan	Allergy Associates of Palm Beaches P.A, 840 US Highway 1, Suite 230 - 250, North Palm Beach, 33408, Florida, USA, p: (b) (6) (b) (6) f: (b) (6) akoterba@pballergy.com	0	0	0
0111	Moy, James	Rush University Medical Centre, University Consultants in Allergy and Immunology, 1725 W. Harrison Street, Room 117, Chicago, 60612, Illinois, USA, p: (b) (6) f: (b) (6) james_moy@rush.edu	4	2	0
0114	Melamed, Isaac	IMMUNOe Research Centers, 3260 East 104th Avenue, Thornton, 80233, Colorado, USA, p: 001-303-771-9000, f: 001-303-452-4392, melamedi@immunoe.com	1	0	0

Site Number	Principal Investigator Name	Site Address and Contact Details at the Time of Clinical Study	Number of Patients Enrolled	Number of Patients Eligible	Number of Patients Treated who Prematurely Discontinued IP
0115	Lieberman, Jay	LeBonheur Children's Hospital, 51 North Dunlap, Suite #400, Memphis, 38105, Tennessee, USA, p: (b) (6) f: (b) (6) (b) (6) jlieber1@uthsc.edu	1	1	0
0116	Church, Joseph	Children's Hospital Los Angeles, Division of Clinical Immunology and Allergy, MS #75, 4650 Sunset Boulevard, Los Angeles, 90027, California, USA, p: (b) (6) (b) (6) @chla.usc.edu	1	1	0
0702	Shcherbina, Anna	Federal Research and Clinical Centre of Children, Haematology, Immunology and Oncology, 1 Samora Mashela Street, Moscow, 117997, Moskovskaya Oblast', RUS, p: (b) (6) f: (b) (6) (b) (6) @hotmail.com	6	6	3
0703	Skorokhodkina, Olesya	Kazan Republican Clinical Hospital, 140 Orenburgkoe shosse, Kazan, 620149, Tatarstan, RUS, p: (b) (6) f: 007-(b) (6) (b) (6) @rambler.ru	0	0	0
0704	Klimusheva, Natalia	Regional Clinical Hospital, Volgogradskaya Str. 185, Ekatarinburg, 420064, Sverdlovskaya Oblast', RUS, p: (b) (6) (b) (6) (b) (6) (b) (6) @okb1.ru	6	5	1
3401	Lopez Hoyos, Marcos	Hospital Universitario Marques de Valdeilla, Av. De Valdecilla s/n, Santander, Cantabria, 39008, Cantabria, ESP, p: 0034-942 202 520, f: 0034-942-315-517, mlopezhoyos@humv.es	0	0	0
3402	Pons de Ves, Jaime	Hospital Universitari Son Espases, Carretera de Valldemossa, 79, Palma, Illes Balears, 7120, Balearic Islands, ESP, p: (b) (6) (b) (6) @ssib.es	0	0	0
3403	Soler Palacin, Pere	Hospital Vall d'Hebron, Paseo de la Vall d'Hebron, 119 - 129, Barcelona, 8035, Barcelona, ESP, p: (b) (6) (b) (6) psoler@vhebron.net	2	2	0
3405	Fernandez-Cruz, Eduardo	Hospital General Universitario Gregorio Maranon, Calle de Dr. Esquerdo, 46, Madrid, 28007, Madrid, ESP, p: (b) (6) (b) (6) f: (b) (6) (b) (6) eduardo.fernandezcruz@salud.madrid.org	1	1	1

Site Number	Principal Investigator Name	Site Address and Contact Details at the Time of Clinical Study	Number of Patients Enrolled	Number of Patients Eligible	Number of Patients Treated who Prematurely Discontinued IP
3602	Krivan, Gergely	Del-pesti Centrumkorhaz - Orzagos Hematologiai es infektologiai Intezet, Gyermekhematologiai es oszejttranszplantacios osztaly, Albert Florian u. 5 - 7, Budapest, 1097, Budapest, HUN, p: (b) (6) (b) (6) f: (b) (6), (b) (6)@hu.inter.net	29	25	1
3603	Csurke, Ildiko	Szabolcs-Szatmar-Bereg Megyei Korhazak es Egyetemi Oktatokorhaz Gyermkosztaly, Szent Istvan u. 68, Nyiregyhaza, 4400, Nyiregyhaza, HUN, p: (b) (6) (b) (6) @gmail.com	2	2	0
3605	Simon, Reka*	Borod-Abauj-Zemplen Megyei Korhaz es Egyetemi Oktato Korhaz, Gyermek-onkohaematologiai-es csontvelotranszplantacios osztaly, Szentpeteri kapu 72 - 76, Miskolc, 3526, Miskolc, HUN, p: (b) (6), f: (b) (6) (b) (6) (b) (6) @gmail.com	1	1	0
4901	Horneff, Gerd	Asklepios Klinik, Zentrum fuer allegemeine Paediatric und Neonatologie Arnold-Janssen-Str. 29, Sankt Augustin, 53757, North Rhine-Westphalia, DEU, p: (b) (6), f: (b) (6) (b) (6) g.horneff@asklepios.com	0	0	0
4902	Behrens, Frank	CIRI - Centrum fuer innovative Diagnostik und Therapie - Rheumatologie / Immunologie Theodor-Stern-Kai 7, Haus 33B der Universitaetsklinik, Frankfurt am Main, 60590, Hesse, DEU, p: (b) (6) f: (b) (6) info@ciri-clinical.de	0	0	0
4904	Warnatz, Klaus	Universitaetsklinikum Freiburg, Department fuer Innere Medizin, Klinik fuer Rheumatologie und Klinische Immunologie - Studienambulanz, Hugstetter Str. 55, Freiburg, 79106, Baden-Wuerttemberg, DEU, p: (b) (6) f: (b) (6) (b) (6) (b) (6) @uniklinik-freiburg.de	1	1	0
4905	Borte, Michael	Klinikum St. Georg Leipzig, Klinik fuer Kinder- und Jugendmedizin, Immun Defekt Centrum Leipzig (IDCL), Delitzscher Strasse 141, Leipzig, 4129, Saxony, DEU, p: (b) (6) (b) (6) f: (b) (6) (b) (6) @sanktgeorg.de	3	3	1

Data source: Adapted from list of investigators provided by the applicant in Module 1.3

The 67 eligible and treated patients were enrolled at 17 sites in the following countries: 21 patients in the United States, 28 patients in Hungary, four patients in Germany, three patients in Spain, six patients in the European part of Russia (41 patients in total in Europe), and five patients in the Asian part of Russia.

6.1.7 Surveillance/Monitoring

The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, the Declaration of Helsinki, with local regulatory requirements and 21 CFR 312, and in accordance with standard operating procedures for clinical research at Biotest AG and the contract research organization (b) (4)

(b) (4) An independent data safety and monitoring board provided oversight to ensure safety of the patients during the trial.

YIMMUGO was administered intravenously by staff at the clinical sites. All patients were monitored during the infusion. Table 6 below lists the details of the schedule of assessment for each planned visit.

Table 6. Study Schedule and Schedule of Assessments

Study Schedule/Assessments Period	Screening	Treatment ^a	Treatment ^a	Closing (Follow-up) ^a
Visit	V 1	V 2		
Q3W			V 3 to V 19	V 20
Q4W			V 3 to V 15	V 16
Week	W -4 to W0	W 0		
Q3W			W 3 to W 51	Up to W 54
Q4W			W 4 to W 52	Up to W 56
Day	D -28 to D 0	D 1		
Q3W			D 22 to D 358 (approx.)	Up to D 379 (approx.)
Q4W			D 29 to D 365 (approx.)	Up to D 393 (approx.)
Informed consent/assent	x			
Eligibility criteria (inclusion/exclusion)	x			
Demographic data (incl. gender, date of birth, ethnic origin, height)	x	x		
Medical and surgical history (incl. drug and disease history, previous medication)	x	x		
Physical examination ^b	x	x	x	x
Vital signs (pulse, BP, temperature, RR)	x	x ^c	x ^c	x
Body weight	x	x	x	
Pregnancy test ^d	x	x	x	x
Safety laboratory (hematology, coagulation, clinical chemistry, urinalysis)	x	x ^e	x	x
Intravascular hemolysis parameters (incl. Coombs test, haptoglobin, hemoglobin, hemosiderin)	x		x ^f	x
Viral safety (retention samples)	x			x
Virus serology (hepatitis B, hepatitis C, HIV)	x			
Infusion of BT595		x	x	
Immunoglobulin G trough levels (total IgG)	x	x ^e	x	x
Immunoglobulin G trough levels (subclasses 1-4)		x ^g	x ^g	
Specific antibody trough levels		x ^h	x ^h	
Patient diary (paper) dispensed		x	x	
Collection and review of patient diary (paper)			x	x
Health-related quality of life assessment		x	x	x
Concomitant medications	x	x	x	x

Study Schedule/Assessments Period	Screening	Treatment ^a	Treatment ^a	Closing (Follow-up) ^a
Adverse events		x	x	x
PK for total IgG, IgG subclasses, and 6 analyzed antigen-specific IgGs		x	x	x ⁱ

Source: Trial 991 CSR (Table 9-1).

- a. A time window of ± 2 days was allowed for the treatment visits and the closing (follow-up) visit; however, this time window was not applied for the PK assessments. Pharmacokinetic assessments followed timepoint specific time windows.
- b. The physical examination was followed-up with a verbal exchange (face-to-face) between the patient and the investigator 1 hour after the end of each infusion, and a verbal exchange (by telephone) 24 and 72 hours after the end of each infusion.
- c. Vital signs (pulse, BP, RR) were assessed within 30 minutes before each infusion, 15 to 30 minutes after the start of each infusion, 15 to 30 minutes after the end of each infusion, and 15 to 30 minutes after the start of any change in the infusion rate. Where the change in infusion rate was sooner than a 15-minute interval, vital signs were measured prior to the change. The vital sign, temperature, was recorded within 30 minutes before each infusion only.
- d. A serum human chorionic gonadotropin pregnancy test was performed for all female patients ≥ 12 years of age or if menstruation had occurred at or before screening. Urine pregnancy dipstick tests were performed at all other study visits.
- e. Additional samples for safety laboratory assessments and total IgG were taken at the end of the first BT595 infusion.
- f. For detecting any hemolytic outcome, the first 10 (adult) patients who received ≥ 2 infusions were followed up on the following visit (V3, V4) by analyzing Coombs test and test of haptoglobin.
- g. Samples were taken from patients ≥ 6 years of age at baseline and before the seventh/fifth infusion of the Q3W/Q4W schedule, respectively (i.e., this sample was the same sample as the predose sample for PK analysis).
- h. Samples were taken from patients (12 to < 76 years of age) at baseline and before the seventh/fifth infusion of the Q3W/Q4W schedule, respectively (i.e., this sample was the same sample as the predose sample for PK analysis).
- i. At the seventh infusion (Week 18 [Q3W schedule]) or fifth infusion (Week 16 [Q4W schedule]), serum samples for the PK analysis of total IgG, IgG subclasses 1-4, and 6 analyzed antigen-specific IgGs (i.e., for: anti-pneumococcal capsular polysaccharide, anti-haemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-hepatitis B surface antigen/hepatitis B) were drawn from patients (total IgG and IgG subclasses 1-4 for patients ≥ 6 years of age; antigen-specific IgG levels for patients ≥ 12 years of age) at the following time points: predose. Ten to 30 minutes before the infusion, 10 to 30 minutes postinfusion (end of infusion), 4 and 24 hours postinfusion, and at 4, 7, 14, 21 days. For the Q3W and the Q4W schedule and 28 days postinfusion (Q4W schedule only). For young children (2 to < 6 years of age), optional sparse sampling for PK analysis of total IgG only may have been performed at flexible time points within specified time windows after the end of the infusion.

Abbreviations: approx., approximately; BL, baseline; BP, blood pressure; D, day; HIV, human immunodeficiency virus; IgG, immunoglobulin G; incl, including; PK, pharmacokinetic; Q3W, 3 weeks; Q4W, 4 weeks; RR, respiratory rate; V, visit; W, week.

6.1.8 Endpoints and Criteria for Study Success

Efficacy Endpoints

Primary Endpoint

The primary efficacy endpoint was the rate of acute SBIs per patient-year. Acute SBIs were diagnosed as per FDA guidance criteria (FDA, 2008) and included the following:

- Bacteremia or sepsis.
- Bacterial meningitis.
- Osteomyelitis/septic arthritis.
- Bacterial pneumonia.
- Visceral abscess.

The rate of <1 SBI per patient-year was required to successfully demonstrate the efficacy of YIMMUGO.

Secondary Endpoints

- IgG trough levels (total IgG) before each infusion.
- Rate of any infections (number per patient-year).
- Rate of nonserious infections (number per patient-year), defined as all infections not fulfilling the FDA guidance on diagnostic criteria for serious infection types.
- Time to resolution of infections (days).
- Antibiotic treatment (number of days of antibiotic treatment received per patient-month and per patient-year).
- Rate of time lost from school/work due to infections and their treatment (number of days per patient-month and per patient-year [both 365 and 220 days]).
- Hospitalizations (number of days per patient-month and per patient-year overall and due to infection).
- Fever episodes (number of days per patient-year).

Reviewer Comment: The primary and secondary endpoints conform to the FDA IVIG guidance to support marketing approval of IVIG products for replacement therapy in patients with PI.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review memo.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The following population sets were used for analysis.

- SAF: All patients who had received ≥ 1 dose of study medication.

- Full analysis set (FAS): All patients following the principle of intention-to-treat.
- PPS: All patients who were compliant with the current protocol without any major protocol deviations.
- PK trough set: All patients following the principles of the SAF for whom ≥ 1 trough concentration of total IgG in the age group 2 to <76 years of age and/or subclass IgG in the age group 6 to <76 years of age (local laboratory) was available.
- Specific IgG trough PK set: All patients 12 to <76 years of age for whom at least 1 trough concentration of ≥ 1 specific IgG from central laboratory was available.
- Dense PK subset: All patients who received all planned doses following the principles of the FAS and for whom at least one concentration of total IgG, IgG subclasses 1-4, or the analyzed antigen-specific IgGs (anti-pneumococcal capsular polysaccharide, anti-haemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B), measured in the dense sampling period (i.e., after/at the seventh infusion of the Q3W schedule or after/at the fifth infusion of the Q4W schedule, including the predose concentrations) was available. PK parameters were derived using the Dense PK subset.

Table 7. Population Analysis Sets

Population Set	N
SAF	67
FAS	67
PPS	57
PK trough set	67
Specific IgG trough PK set	54
Dense PK subset	57

Data source: Table created by the reviewer.

Abbreviations: FAS, full analysis set; IgG, immunoglobulin G; n, number of patients in a specified category; N, number of patients; PK, pharmacokinetics; PPS, per protocol set; SAF, safety population set

6.1.10.1.1 Demographics

The study enrolled 67 patients between 2 to 74 years of age, with a mean of 34.6 years of age. Forty-nine were adult patients (≥ 17 years of age), six were adolescents (12 to <17 years of age), nine were children (6 to <12 years of age), and three were young children (2 to <6 years of age). The study population was predominantly White (n=66; 98.5%), with males representing 55.2% of the population. Forty-one patients were enrolled from European sites, 21 from U.S. sites, and five from Asian sites. Table 8 provides details of study population demographics.

Table 8. Study Population Demographics

Criteria	Adults (n=49)	Pediatric Patients 2 to <6 Years of Age (n=3)	Pediatric Patients 6 to <12 Years of Age (n=9)	Pediatric Patients 12 to <17 Years of Age (n=6)	Overall (N=67)
Age at screening, years					
Mean (SD)	43.8 (14.9)	2.7 (0.6)	9.2 (2.0)	13.7 (1.6)	34.6 (20)
Median	42.0	3.0	10.0	13.5	37.0
Min – Max	20 – 74	2 – 3	6 – 11	12 – 16	2 – 74
Gender, n (%)					
Male	22 (44.9)	3 (100)	8 (88.9)	4 (66.7)	37 (55.2)
Female	27 (55.1)	0	1 (11.1)	2 (33.3)	30 (44.8)
Region, n (%)					
United States	16 (32.7)	0	2 (22.2)	3 (50.0)	21 (31.3)
Europe	28 (57.1)	3 (100)	7 (77.8)	3 (50.0)	41 (61.2)
Asia (1 site in Russia)	5 (10.2)	0	0	0	5 (7.5)
Height, cm					
Mean (SD)	168.2 (9.3)	95.6 (5.5)	142.4(13.9)	167.0 (7.9)	161.4 (19.4)
Median	170.00	95.80	142.50	168.55	164.00
Min – Max	149.0 – 185.0	90.0 – 101.0	122.0 – 159.0	158.0 – 178.3	90.0 – 185.0
Weight, kg					
Mean (SD)	69.0 (20.1)	15.7 (3.4)	42.6(16.5)	63.0 (16.2)	62.6 (23.0)
Median	64.5	15.5	38.0	66.0	62.0
Min – Max	40.0 – 127.0	12.5 – 19.2	25.0 – 69.1	40.6 – 85.1	12.5 – 127.0
BMI, kg/m ²					
Mean (SD)	24.3 (6.6)	17.1 (1.7)	20.4 (5.4)	22.4 (5)	23.3 (6.4)
Median	23.1	16.9	20.8	23.3	22.3
Min – Max	16.1 – 45.3	15.4 – 18.8	13.3 – 28.4	16.2 – 29.6	13.3 – 45.3
Race, n (%)					
White	49 (100)	3 (100)	8 (88.9)	6 (100)	66 (98.5)
Asian	0	0	1 (11.1)	0	1 (1.5)

Data source: Trial 991 CSR Table 11-2 (with modification to 1 decimal place)

Abbreviations: BMI, body mass index; cm, centimeters; kg, kilogram; Max, maximum; min, minimum; SD, standard deviation.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The most common underlying cause of PI was CVID (n=53; 79.1%). The other etiologies included XLA (n=10; 14.9%); congenital agammaglobulinaemia (n=2; 3%); congenital hypogammaglobulinaemia (n=1; 1.5%); and specific antibody defect (n=1; 1.5%). The time since diagnosis ranged between 8 to 492 months in adult patients and 4 to 136 months in pediatric patients. The minimum time since diagnosis of 4 months was imputed from a patient with an incomplete documented date of diagnosis of XLA (Patient (b) (6)). However, the applicant notes that the patient had received previous IVIG reference therapy for 6.6 months.

The IgG trough levels at baseline ranged between 0.6 to 17.3 g/L in adult patients and between 5.3 to 11.4 g/L in pediatric patients. The lower range of baseline IgG levels in the adult cohort was due to the five patients who had baseline total IgG trough levels of <5 g/L. These deviations were noted as minor

protocol deviations because the patients had at least one total IgG trough level of ≥ 5 g/L during the previous 3 months and fulfilled the study inclusion criteria.

All patients received IVIG preparations from different manufacturers listed in Table 9. The most common IVIG preparations used by the study patients was Intratect followed by Privigen. Of the 67 patients overall, four patients had received IVIGs for <6 months and 4 other patients had not received the same IVIG at a constant dose for the last 3 months.

Table 9. Summary of Previous Immunoglobulin Replacement Therapy

Type of Previous Established IVIG Therapy, n (%)	Q3W Schedule (n=12)	Q4W Schedule (n=55)	Overall (N=67)
Intratect			
Intratect 10%	1 (8.3)	11 (20.0)	12 (17.9)
Intratect (NOS)	0	9 (16.4)	9 (13.4)
Octagam			
Octagam 5%	4 (33.3)	3 (5.5)	7 (10.4)
Octagam 10%	3 (25.0)	4 (7.3)	7 (10.4)
Octagam (NOS)	0	3 (5.5)	3 (4.5)
Privigen			
Privigen 10%	2 (16.7)	8 (14.5)	10 (14.9)
Gamunex			
Gamunex-C	0	1 (1.8)	1 (1.5)
Gamunex (NOS)	2 (16.7)	4 (7.3)	6 (9.0)
Humaglobin	0	3 (5.5)	3 (4.5)
Carimune	1 (8.3)	2 (3.6)	3 (4.5)
IG vena	0	2 (3.6)	2 (3.0)
Bivigam 10%	0	1 (1.8)	1 (1.5)
Flebogamma	0	1 (1.8)	1 (1.5)
Immunovenin	0	1 (1.8)	1 (1.5)
Plangamma 5%	1 (8.3)	0	1 (1.5)
IVIG (NOS)	0	5 (9.1)	5 (7.5)

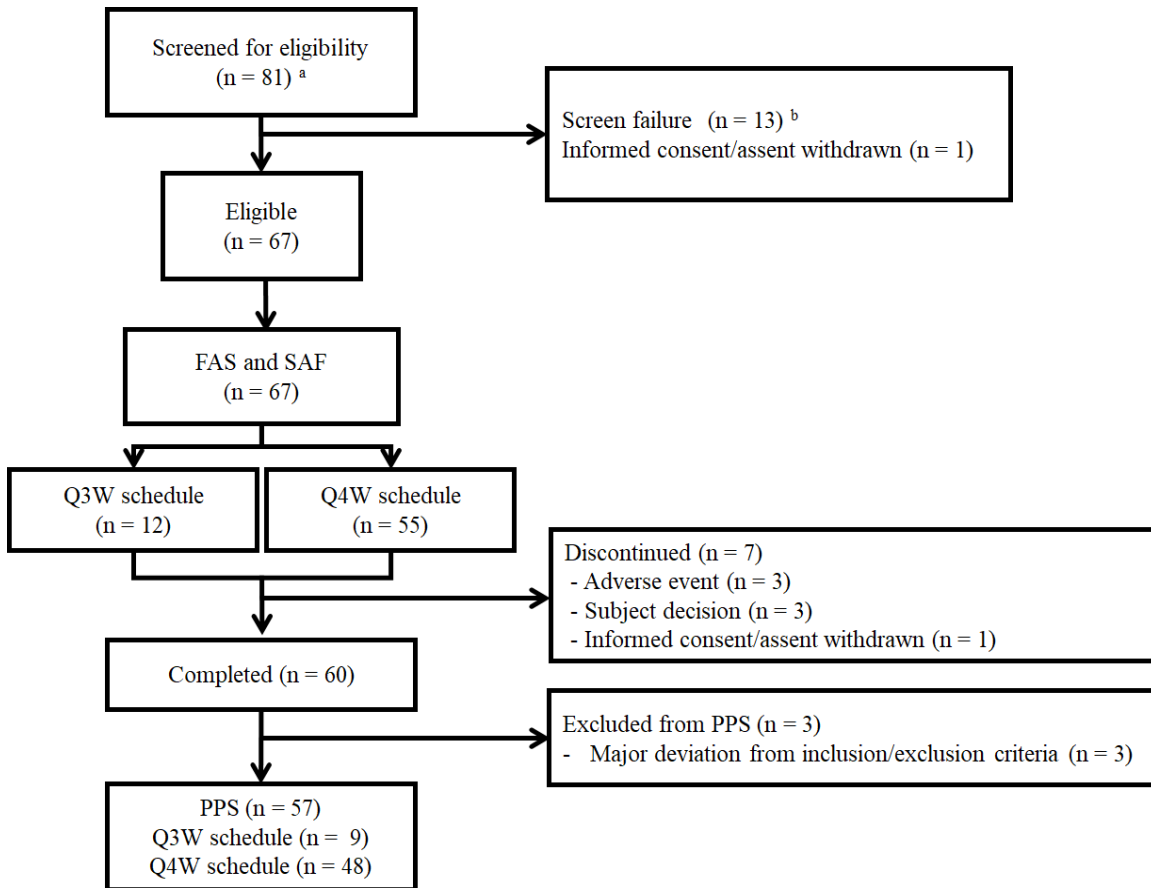
Source: Trial 991 CSR Table 11-6

Abbreviations: IG, immunoglobulin; IVIG, immunoglobulin for intravenous administration; n, number of patients in a specified category; N, number of patients; NOS, not otherwise specified; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation

The most frequently used concomitant medications ($\geq 20\%$ of patients) included anti-inflammatory and antirheumatic products (28 patients, 41.8%); vitamins (27 patients, 40.3%); analgesics (24 patients, 35.8%); cough and cold preparations (24 patients, 35.8%); nasal preparations (23 patients, 34.3%); anti-anemic preparations (i.e., iron preparations and vitamin B12 plus folic acid; 19 patients, 28.4%); antihistamines for systemic use (16 patients, 23.9%); agents acting on the renin-angiotensin system (15 patients, 22.4%); drugs for acid-related disorders (15 patients, 22.4%); and drugs against obstructive airway diseases (15 patients, 22.4%).

6.1.10.1.3 Patient Disposition

Figure 1. Patient Disposition



Source: Trial 991 CSR (Figure 10-1)

Note: The 67 eligible patients included one patient who was rescreened and enrolled under a different patient ID (Patient (b) (6)), initial patient ID (b) (6)).

^a total of 81 patients were screened and enrolled (82 screening procedures and patient IDs due to 1 rescreened patient).

^b The 13 screen failures who did not meet eligibility criteria included one patient who discontinued prior to the first infusion due to a nontreatment-emergent AE of acute pneumonia (Patient (b) (6)). In addition to these 13 patients, one patient withdrew his/her consent/assent prior to the first infusion and did not continue into the treatment phase (Patient (b) (6)).

Abbreviations: AE, adverse event; FAS, full analysis set; n, number of patients in a specified category; PPS, per protocol set; Q3W, every 3 weeks; Q4W, every 4 weeks; SAF, safety population set.

6.1.11 Efficacy Analyses

All 67 patients received ≥ 1 dose of YIMMUGO and were included in the SAF, FAS, and PK trough population and were included in the efficacy analysis.

Reviewer Comment: It was noted that 55 patients received YIMMUGO at the Q4W interval and 12 patients received it at the Q3W interval. Because of the difference in the number of patients in each treatment group, a separate efficacy analysis based on Q3W and Q4W treatment may not provide any meaningful comparative information; therefore, a subgroup analysis based on treatment schedule was not done by the reviewer.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary analysis intended to demonstrate that the SBI rate (upper limit of the 1-sided 99% CI) was <1.0 per patient-year in the overall FAS (irrespective of treatment schedule or age group). The applicant reported a single SBI in an adult patient and the unadjusted SBI rate of 0.01 per patient-year.

Synopsis of SBI in Patient (b) (6)

The single reported SBI occurred in a 60-year-old White male from the United States who aspirated after a single episode of alcohol ingestion the night before the onset of symptoms. He presented with an acute onset of cough and fever but had no prodromal symptoms or involvement of other parts of his respiratory tract that would have suggested a viral etiology. The X-ray revealed an infiltrate in the right upper lobe of the lung. Because of the location of the infiltrate, in association with a history of reflux and alcohol ingestion, the diagnosis of bacterial pneumonia secondary to aspiration was made and as per the FDA diagnostic criteria for bacterial pneumonia, the event was classified as an SBI.

During our review, four additional events of possible SBIs were identified in two adult and two pediatric patients. These events are summarized below.

Patient (b) (6)

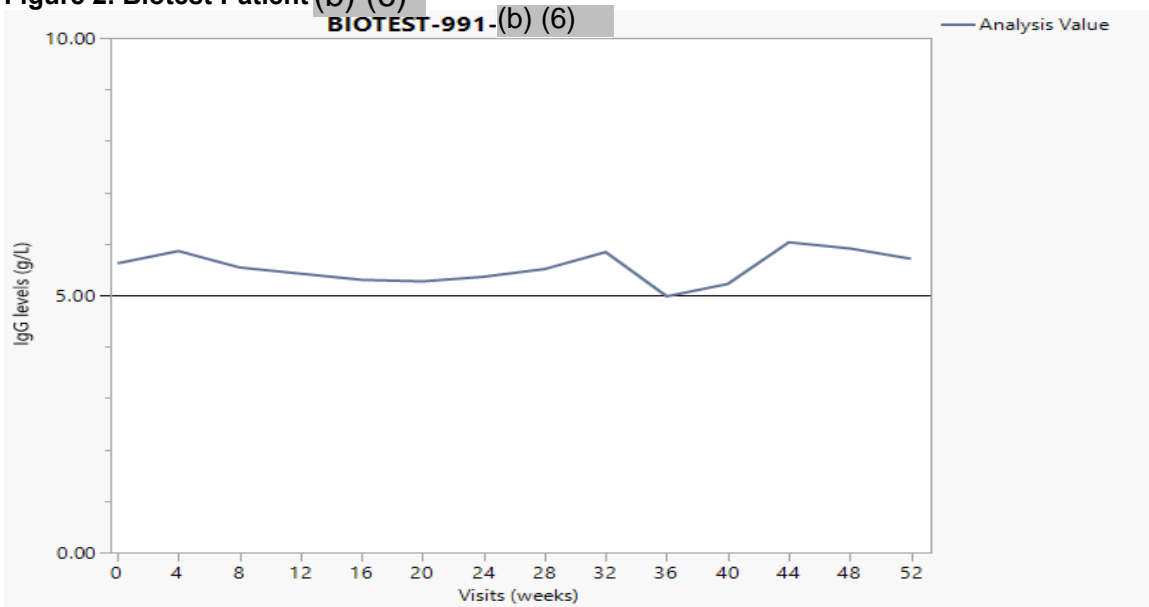
A 69-year-old White female with CVID who was receiving YIMMUGO at the Q3W treatment schedule. Relevant concomitant diseases included allergic rhinitis and asthma. Relevant concomitant medication included albuterol (inhalation). The patient experienced bronchitis of moderate severity 7 days after infusion-14. No fever was reported. The patient was started on oral levofloxacin and oral prednisone 5 days after the onset of symptoms and was examined and investigated 15 days after the onset of bronchitis at the next scheduled visit when the symptoms were reported to be resolved. At the scheduled visit, the laboratory assessment reported elevated WBC counts ($13.03 \times 10^9/L$) and elevated neutrophils ($9.87 \times 10^9/L$). No imaging studies were done. Because of the incomplete workup at the onset of the AE, the possibility of underlying bacterial pneumonia and SBI cannot be ruled out in this patient.

Patient (b) (6)

A 43-year-old White male with CVID who was receiving YIMMUGO at the Q4W treatment schedule. Relevant concomitant diseases comprised chronic obstructive pulmonary disease. Relevant past medical history included several episodes of pneumonia and respiratory tract infection. Relevant concomitant medication included Symbicort. Twenty-one days after infusion-11 of YIMMUGO, the patient experienced bronchitis of moderate severity and reported a 7-day history of fever. He was started on oral levofloxacin and was later examined at the next scheduled visit (week 48) 7 days after the onset of symptoms. At the scheduled visit, the laboratory assessment reported elevated WBC counts ($16.88 \times 10^9/L$), neutrophils ($13.7 \times 10^9/L$), and erythrocyte sedimentation rate (11 mm/hr). No imaging studies were done. Additionally, the patient had a dose adjustment at week 40 due to low IgG levels (4.98 g/L). Because of the history of

fever, reported laboratory parameters along with the reported low IgG levels preceding the AE, in the absence of a complete workup including imaging studies at the onset of AE, the possibility of underlying bacterial pneumonia and SBI cannot be ruled out in this patient.

Figure 2. Biotest Patient (b) (6)

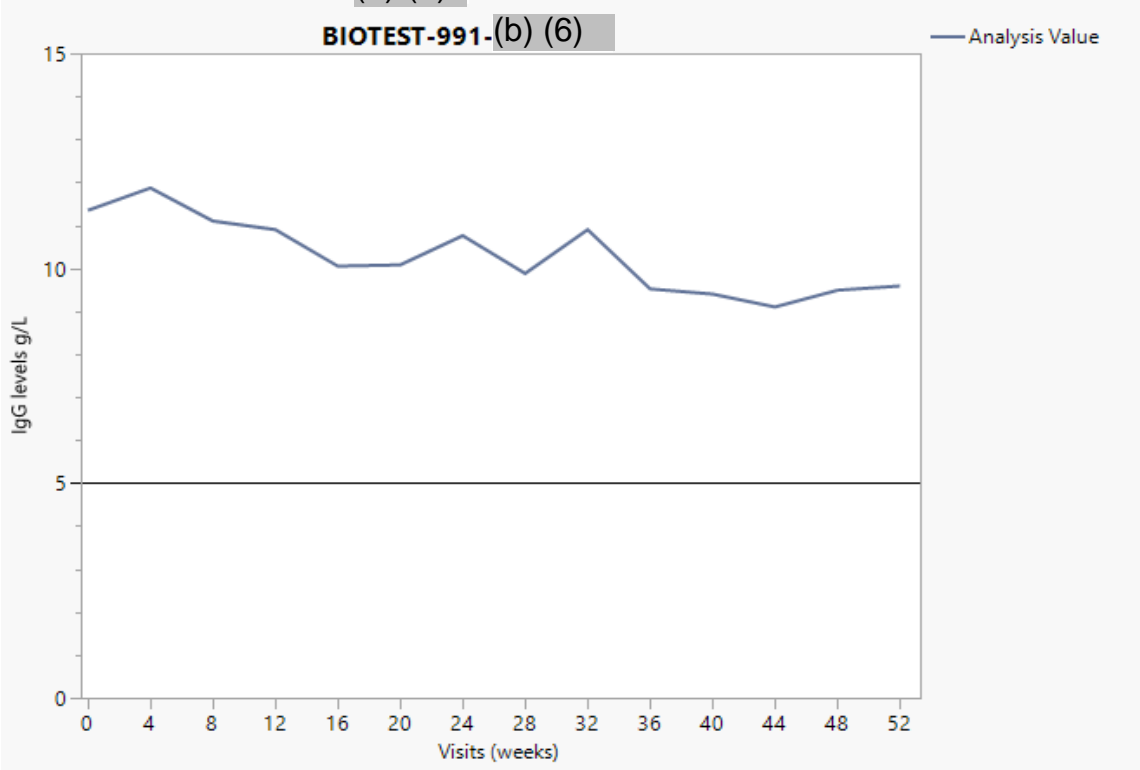


Source: Graph created by the reviewer using ADAM dataset.
Abbreviations: g, grams; IgG, immunoglobulin G; L, liter.

Patient (b) (6)

A 12-year-old female with CVID who was receiving YIMMUGO at the Q4W treatment regimen. Relevant past medical history includes chronic bronchitis and several episodes of upper respiratory tract infections. Seventeen days after the infusion at week 36, the patient experienced bronchitis of moderate severity. No associated fever was reported. The patient was started on oral Augmentin. The patient was examined at the next scheduled visit 10 days after the onset of her symptoms. It was noted that the patient's IgG levels started dropping after week 4 and remained at a lower level at onset of the reported AE (week 36 to week 40). Because of the incomplete workup at the onset of AE, the possibility of underlying bacterial pneumonia and SBI cannot be ruled out in this patient.

Figure 3. Biotest for Patient (b) (6)



Source: Graph created by the reviewer using ADAM dataset
Abbreviations: g, grams; IgG, immunoglobulin G; L, liter.

Patient (b) (6)

A 3-year-old male patient with XLA who was receiving YIMMUGO at the Q4W treatment regimen. Relevant past medical history included bronchopneumonia and asthma. This patient reported a total of 18 infections including three episodes of bronchitis. Eighteen days after the study infusion at week 44, the patient experienced his third episode of bronchitis with associated fever for 5 days. The patient was started on oral Augmentin but was not examined or investigated. The patient was examined at the next scheduled visit at week 48. The physical examination reported abnormal lung findings, and elevated erythrocyte sedimentation rate (14 mm/hr). No imaging studies were done at the visit. It was also noted that the patient's dose of YIMMUGO was adjusted at week 4 due to infections and again at week 48. Because of the incomplete workup at the onset of AE, the possibility of underlying bacterial pneumonia and SBI cannot be ruled out in this patient.

Table 10. Serious Bacterial Infection Events in Trial 991

Patient	Age (years)	Type of SBI	Infusion Number prior to SBI	Dose of YIMMUGO prior to SBI (mg/kg)	IgG Trough level prior to SBI (g/L)
1	60	Bacterial Pneumonia	6	450	8.27
2	69	Bacterial Pneumonia	14	400	7.53
3	43	Bacterial Pneumonia	11	830	5.22
4	12	Bacterial Pneumonia	10	270	9.52
5	3	Bacterial Pneumonia	12	490	12.3

Source: Table created by the reviewer.

Abbreviations: g, grams; IgG, immunoglobulin G; L, liter; mg, milligram; SBI, serious bacterial infection.

Reviewer Primary Efficacy Analysis

The efficacy analysis was conducted by including the newly identified cases of possible SBI to a total of five SBIs in five patients. With total person-years of 67.59, the annual SBI rate was calculated to be 0.074 with a 99% CI of 0.21. Table 11 below summarizes the revised primary efficacy analysis including five SBI events.

Table 11. Revised Primary Efficacy Analysis

Criteria	Adults (n=49)	2 to <6 Years of Age (n=3)	6 to <12 Years of Age (n=9)	12 to <17 Years of Age (n=6)	Overall (N=67)
Total exposure (patient-years)	48.6	2.6	9.9	6.5	67.6
Number of patients with ≥1 acute SBI	3	1	0	1	5
SBI rate per patient-year (99% CI)	0.06 (0.24)	0.38 (3.92)	0	0.15 (1.58)	0.074 (0.21)

Source: Table created by the reviewer.

Abbreviations: CI, confidence interval; N, number of patients; SBI, serious bacterial infection.

6.1.11.2 Analyses of Secondary Endpoints

IgG Trough Levels (Total IgG) Before Each Infusion

All 67 patients were included in the analysis. For patients with trough levels below the targeted minimal trough level of 5 g/L, dose adjustments for the next infusion were allowed at the investigator's discretion. A total of 19 events of low IgG trough levels (<5 g/L) were reported during the study. Additionally, a total of 10 patients (nine adults and one pediatric patient) had a dose adjustment due to low IgG levels. Table 12 below summarizes the patients who had low IgG levels before study drug infusion.

Table 12. Events of Low IgG Levels Reported During the Trial

Criteria	Adults (n=49)	Patients 2 to <6 Years of Age (n=3)	Patients 6 to <12 Years of Age (n=9)	Patients 12 to <17 Years of Age ^a (n=6)	Overall (N=67)
Screening, n (%)	5 (10.2)	0	0	0	5 (7.5)
Baseline (before infusion 1 or at screening), n (%)	5 (10.2)	0	0	0	5 (7.5)
Before infusion number ^b , n (%)					
2	4 (8.2)	0	0	0	4 (6.0)
3	4 (8.2)	0	0	0	4 (6.0)
4	2 (4.1)	0	0	0	2 (3.0)
5	2 (4.1)	0	0	0	2 (3.0)
6	3 (6.1)	0	0	0	3 (4.5)
7	0	0	1 (11.1)	0	1 (1.5)
10	2 (4.1)	0	0	0	2 (3.0)
13	1 (2.0)	0	0	0	1 (1.5)

Source: Trial 991 CSR Table 11-9

^a Adolescents were defined as 12 to <17 years of age according to FDA guidance, and 12 to <18 years of age according to EMA guidance. Since the only patient 17 years of age at screening (initial visit) withdrew consent prior to the first BT595 infusion, the number of patients in the FAS qualifying as adolescents and adults comply with both FDA and EMA age group categorizations.

^b Only infusions where ≥1 patient had IgG trough levels below <5 g/L are presented.

Abbreviations: n, number of patients in a specified category; N, number of patient.

Reviewer Comment: It was noted that several patients required dose adjustment due to low IgG levels. Additionally, a total of 26 patients (21 adults and 5 pediatric patients) were reported to have a drop in IgG trough level of more than 1 g/L from baseline at least once during the trial. Because the correlation between IgG trough levels and the rate of infection is individualized, it was difficult to determine if the rate of infections were impacted by the variability in IgG levels and requirement for dose adjustments noted in the trials participants.

Rate of Any Infections

Among the 67 patients, 48 patients reported a total of 189 treatment-emergent infections during the study. The annualized rate of treatment-emergent infections was reported to be 2.80 per patient-year. The mean annualized rate of treatment-emergent infections per patient was noted to be highest in the young children 2 to <6 years of age (6.72) and lowest in adults (2.24). Further, the annual rate of infection per patient was highest in the winter (3.62) and spring 3.00). Four of the 189 treatment-emergent infections reported were serious infections requiring hospitalization.

Rate of Nonserious Infections

Nonserious infections were defined as all infections not fulfilling the FDA guidance on diagnostic criteria for serious infection types. Overall, 185 out of 189 treatment-emergent infections were nonserious. The overall annual rate of nonserious infection per patient was 2.58 with the highest rate in the young children 2 to <6 years of age (6.10) and lowest in adults (2.20).

Time to Resolution of Infections

The median time to resolution of infections was 7 days (range 1 to 342 days). Two infections (acute gastric ulcer and chronic pansinusitis) were not resolved by the end of the study and were therefore censored. The maximum time to resolution of 342 days was due to imputed data on a pediatric patient with incomplete stop date. The maximum time to resolution in pediatric patients with non-imputed start or stop date was 64 days and in adults, the maximum time to resolution was 81 days.

Antibiotic Treatment

Overall, 39 patients received a total of 115 antibiotic treatments during the study including both prophylactic and therapeutic antibiotics. It was noted that six patients had a long antibiotic treatment period (≥ 35 days with a single antibiotic). These included three adults and two pediatric patients. The details of individual patients are provided below.

- Patient (b) (6) : A 53-year-old White male patient from Hungary in the Q4W schedule group received prophylactic antibiotic treatment throughout the study (399 days) to prevent infections due to his PI.
- Patient (b) (6) : An 11-year-old White male patient from the United States in the Q4W schedule group received prophylactic antibiotic treatment with azithromycin throughout the study (409 days) to prevent infections due to his XLA. In addition, the patient received mupirocin for the treatment of a staphylococcal skin infection for an imputed duration of 342 days (imputation due to incomplete stop date).
- Patient (b) (6) : A 20-year-old White female patient from Russia in the Q4W schedule group received antibiotic treatment on a regular basis throughout the study (314 days) as treatment for a pre-existing chronic bronchitis. The patient was excluded from the PPS.
- Patient (b) (6) : A 13-year-old White female patient from the United States in the Q3W schedule group received several different antibiotics from the start of the study onwards and for up to 189 days as treatment for a pre-existing Lyme disease. The patient was excluded from the PPS.
- Patient (b) (6) : A 28-year-old White male patient from Russia in the Q4W schedule group received antibiotic treatment for 57 days during the study as treatment for a pre-existing chronic bronchitis. The patient was excluded from the PPS.
- Patient (b) (6) : A 59-year-old White female patient from the United States in the Q3W schedule group received prophylactic antibiotic treatment, which was started prior to the first infusion, for a single imputed period of 43 days to prevent infections (imputation due to missing stop date).

Reviewer Comment: The antibiotic use may have been overestimated since multiple patients were on prophylactic antibiotic therapy during the trial. Further, the long treatment duration of antibiotics noted in these patients may have impacted the efficacy outcome and the rate of SBI in trial

patients. However, because of the small number of patients with prolonged use of antibiotics, the impact on efficacy was estimated to be minimal.

Rate of Time Lost from School/Work Due to Infections

Overall, 26 out of 67 patients lost at least 1 day from work/school due to infection. The maximum number of days lost in adults was 21 days, in adolescents (12 to <17 years of age) was 40, in children (6 to <12 years of age) was 18, and in young children (2 to <6 years of age) was 85 days. The higher number of days for adolescents and young children was due to one patient in each group who lost 40 and 85 days, respectively.

Hospitalizations

A total of six patients required eight hospitalizations with a total of 47 hospitalization days. All hospitalizations were <21 days. The overall annualized rate of hospitalization days was 0.70 per patient-year. Four patients who required hospitalization were adults and two were pediatric patients.

Four hospitalizations in three patients were due to infections. The annualized rate of hospitalization days due to infection was 0.36 per patient-year. The details of the three patients with hospitalizations due to infections are listed below.

- A 3-year-old White male patient from Hungary (Patient (b) (6)) had two infection SAEs requiring hospitalization. The first SAE was an appendicitis that required hospitalization for 19 days. The event was treated with three parenteral antibiotics for 16 days (cefuroxime and metronidazole for 8 days, and imipenem for another 8 days). The second SAE was a gastrointestinal viral infection that required hospitalization for 1 day, required no antibiotic therapy, and lasted a total of 2 days.
- A 45-year-old White female patient from Hungary (Patient (b) (6)) had an SAE of anal abscess that required hospitalization for 2 days and lasted a total of 9 days. The patient received oral metronidazole twice for 8 and 10 days. The patient was hospitalized for an additional 6 days due to reasons not related to infections.
- A 41-year-old White male patient from Hungary (Patient (b) (6)) had an SAE of chronic sinusitis that required hospitalization for 2 days, required no antibiotic therapy, and lasted a total of 2 days.

Fever Episodes

Overall, 14 patients had 27 episodes of fever with a total of 114 fever days. The overall annual rate of fever was 0.40.

6.1.11.3 Subpopulation Analyses

A subpopulation analysis of the study population was conducted to compare the efficacy results in adults compared to pediatric patients 2 to <17 years of age. Table 13 provides a summary of efficacy analysis by age groups.

Table 13. Efficacy Analysis by Age Groups

Criteria	Adults (n=49)	Patients 2 to <6 Years of Age (n=3)	Patients 6 to <12 Years of Age (n=9)	Patients 12 to <17 Years of Age (n=6)	Overall (N=67)
Total exposure					
Patient years	48.6	2.6	9.9	6.5	67.6
Rate of serious bacterial infection					
Number of patients	3	1	0	1	5
SBI rate per patient year (99% CI)	0.06 (0.24)	0.38 (3.92)	0	0.15 (1.58)	0.07 (0.21)
Total IgG trough levels before each infusion, mean (SD)					
Baseline (before first infusion)	8.1 (3.2)	8.5 (0.8)	7.9 (1.5)	9.5 (2.0)	8.2 (2.9)
Steady state (before fifth infusion)	8.9 (4.0)	9.7 (1.4)	8.5 (1)	9.5(1.8)	8.9 (3.5)
Rate of any infections					
N (%) with ≥1 infection	33 (67.3)	3 (100)	6 (66.7)	6 (100)	48 (71.6)
Rate per patient-year	2.4	7.7	3.2	3.0	2.8
Time to resolution of any infections, Kaplan-Meier analysis					
Days, median	8.0	6.0	7.0	10.0	7.0
[95% CI]	[7.0; 9.0]	[4.0; 9.0]	[5.0; 8.0]	[7.0; 14.0]	[7.0; 8.0]
Antibiotic treatment (includes prophylactic treatment)					
n (%) with antibiotic treatment	28 (57.1)	3 (100)	4 (44.4)	4 (66.7)	39 (58.2)
Days per patient-year	28.2	18.0	55.9	36.0	32.6
Rate of time lost from school/work due to infections and their treatment					
n (%) with any time lost (≥1 day)	14 (28.6)	2 (66.7)	6 (66.7)	4 (66.7)	26 (38.8)
Days lost per patient-year					
1 year (365 days)	1.9	33.8	4.5	10.8	4.3
Hospitalizations due to infections					
n (%) with hospitalization	2 (4.1)	1 (33.3)	0	0	3 (4.5)
Days per patient-year	0.1	7.7	0.00	0.00	0.4

Source: Adapted from Trial 991 CSR table-11.8. (Modified to one or two decimal point)

Abbreviations: CI, confidence interval; IgG, immunoglobulin G; n, number of patients in a specified category; N, number of patients; SBI, serious bacterial infection; SD, standard deviation.

Reviewer Comment: Because of the small number of patients in pediatric cohorts, any meaningful comparison was not possible. However, it was noted that the young children cohort (2 to <6 years of age) had only two evaluable patients. One of those patients had 18 infections (including one possible SBI) and had to be hospitalized due to infection. With a possible lack of efficacy signals, the efficacy in young children 2 to <6 years of age was not determined.

6.1.11.4 Dropouts and/or Discontinuations

Out of the 67 enrolled patients, 60 patients completed the study. A total of seven patients discontinued early. Three adult patients discontinued due to an SAE of anaphylactic reaction, severe worsening of neutropenia, and toxic hepatitis. Three adult patients discontinued due to patient decision, and informed consent was withdrawn for one pediatric patient.

6.1.11.5 Exploratory and Post Hoc Analyses

The applicant assessed the following as health-related quality of life measures as exploratory endpoints in the trial.

- PedsQL completed by pediatric patients 2 to 18 years of age and/or parent proxy. The mean (standard deviation) PedsQL™ total score increased from 91.7 (14.43) at baseline to 94.2 (8.14) at the last protocol-defined infusion (infusion 18) in the Q3W schedule group and increased from 81.0 (10.65) at baseline to 86.4 (12.05) at the last protocol-defined infusion (infusion 14) in the Q4W schedule group.
- EQ-5D-3L was completed by adult patients 18 to 75 years of age and EQ-5D-Y completed by pediatric patients 4 to 17 years of age. No meaningful changes were noted from baseline to last protocol-defined infusion for both EQ-5D-3L and EQ-5D-Y.

6.1.12 Safety Analyses

6.1.12.1 Methods

The SAF consisted of all patients who received ≥ 1 dose of YIMMUGO (n=67). The safety endpoints were assessed descriptively. The patients were monitored for AEs at the clinical site for at least 1 hour after the end of infusion. Any AEs following the discharge from the site were reported continuously through patient diary between site visits. The proportion of patients with TEAEs, infusional AEs, and non-infusional AEs were calculated with 2-sided 90% CI.

6.1.12.2 Overview of Adverse Events

A total of 923 YIMMUGO infusions were administered during the trial. The mean overall duration of exposure was 67.59 patient-years. Overall, 63 out of 67 patients experienced a total of 458 TEAEs. Table 14 below summarizes the TEAEs by standard of care.

Table 14. Summary of TEAEs in Safety Population Set (n=67)

System Organ Class (Preferred Term)	Number of Patients, n (%)	Number of Events
Any TEAE	63 (94.0)	458
Infections and infestations	47 (70.1)	172
Nasopharyngitis	16 (23.9)	24
Upper respiratory tract infection	13 (19.4)	24
Bronchitis	8 (11.9)	12
Sinusitis	8 (11.9)	11
Pharyngitis	7 (10.4)	8
Viral upper respiratory tract infection	7 (10.4)	7
Influenza	6 (9.0)	6
Urinary tract infection	6 (9.0)	8
Conjunctivitis	4 (6.0)	6
Gastrointestinal disorders	24 (35.8)	38
Diarrhoea	7 (10.4)	8
Nausea	4 (6.0)	6
Vomiting	4 (6.0)	4
Nervous system disorders	21 (31.3)	47
Headache	17 (25.4)	41
Respiratory, thoracic, and mediastinal disorders	20 (29.9)	62
Oropharyngeal pain	6 (9.0)	9
Rhinorrhoea	5 (7.5)	5
Cough	4 (6.0)	5
Musculoskeletal and connective tissue disorders	14 (20.9)	23
Arthralgia	5 (7.5)	5
Injury, poisoning and procedural complications	12 (17.9)	14
Extra dose administered	4 (6.0)	4
Investigations	11 (16.4)	15
General disorders and administration site conditions	9 (13.4)	20
Fatigue	6 (9.0)	10
Psychiatric disorders	6 (9.0)	8
Skin and subcutaneous tissue disorders	6 (9.0)	11
Blood and lymphatic system disorders	5 (7.5)	5
Metabolism and nutrition disorders	5 (7.5)	5
Surgical and medical procedures	5 (7.5)	5
Ear and labyrinth disorders	4 (6.0)	6
Reproductive system and breast disorders	4 (6.0)	6
Vascular disorders	4 (6.0)	5

Source: Adapted from table 12-16 provided in Trial 991 CSR

Abbreviations: n, number of patients in a specified category; N, number of patients; TEAE, treatment-emergent adverse events.

A total of 93 events in 39 patients were FDA-specified ARs defined as any TEAE which meets at least one of the following.

- Adverse events temporally associated with the infusion are AEs occurring during intravenous administration or within 72 hours after the end of infusion.
- Adverse events considered by the investigator to be related to YIMMUGO administration.

- Adverse events for which the investigator’s causality assessment was missing.

Table 15 summarizes the ARs reported in ≥5% of patients.

Table 15. ARs Reported in ≥5% of Patients

Adverse Reaction MedDRA Preferred Term	Number (%) of Patients With AR (N=67)	Number (%) of Infusions With AR (N _{inf} =923)
≥1 AR	39 (58)	93 (10)
Headache	13 (19)	22 (2)
Upper respiratory tract infections	8 (12)	8(<1)
Fatigue	5 (8)	8 (<1)
Nausea	4 (6)	5 (<1)
Increased blood pressure	4 (6)	4 (<1)

Source: Table created by the reviewer based on internal adjudication of ARs
Abbreviations: AR, adverse reaction; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; N_{inf}, number of infusions.

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 12 SAEs were reported in nine patients during the trial. Of these two were assessed to be related to the product administration and led to the patient discontinuing YIMMUGO. The summary of SAEs in these patients is shown below.

- Patient (b) (6) : 34-year-female with CVID assigned to received YIMMUGO at Q4W interval experienced anaphylactic reaction after the first infusion. The event was reported to have been resolved within 2.3 hours following treatment with prednisolone and drotaverine. The patient discontinued from the study.
- Patient (b) (6) : 22-year-female with CVID assigned to received YIMMUGO at Q3W interval experienced severe neutropenia after the first infusion. The neutrophil count dropped from $1.5 \times 10^9/L$ (reference range $1.8-7.5 \times 10^9/L$) prior infusion to $0.6 \times 10^9/L$ after the start of the first infusion. The event was reported to have been resolved after 9 days. The patient discontinued from the study.

The remaining 10 SAEs not related to the product administration included alcohol-induced toxic hepatitis, acute appendicitis, dehydration, gastrointestinal infection, rheumatoid arthritis, perianal abscess, meniscus injury, worsening of systemic sclerosis, chronic sinusitis, and severe thermal burn.

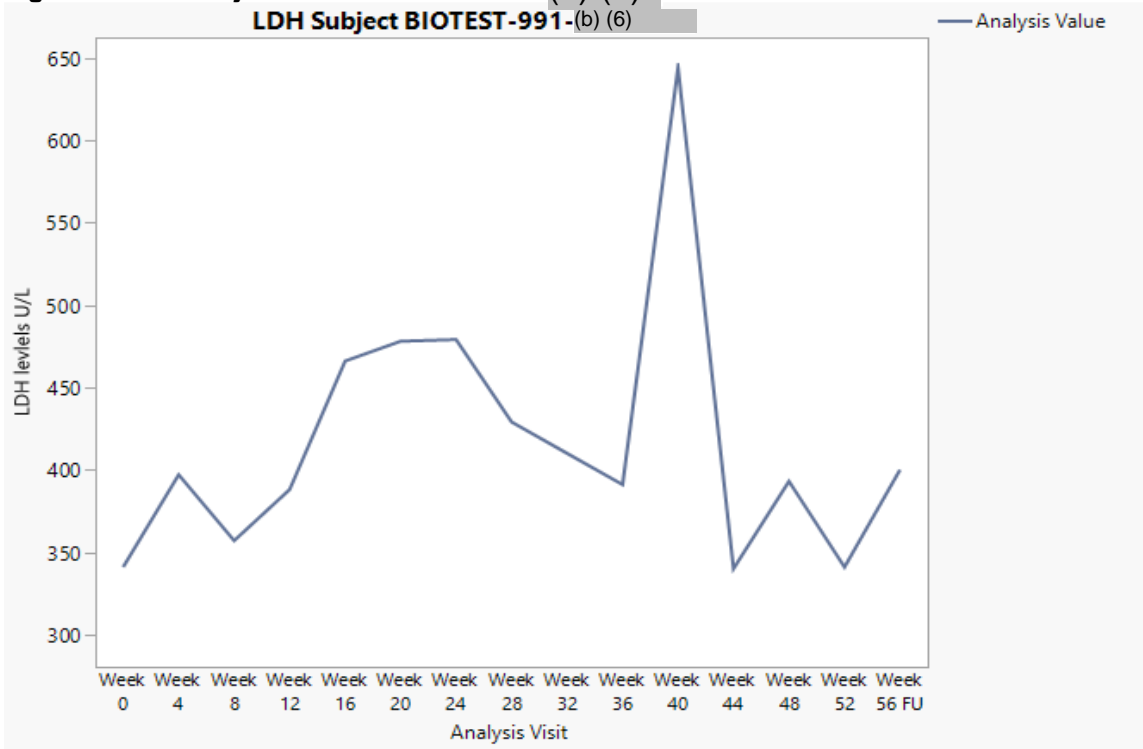
6.1.12.5 Adverse Events of Special Interest

The trial assessed thromboembolic events and hemolysis as adverse events of special interest. These events were retrieved from the database by using Standardized MedDRA Queries. No thromboembolic or hemolytic events were reported by the applicant. However, during the internal review and adjudication,

one case of possible mild hemolysis was identified. The event is summarized below.

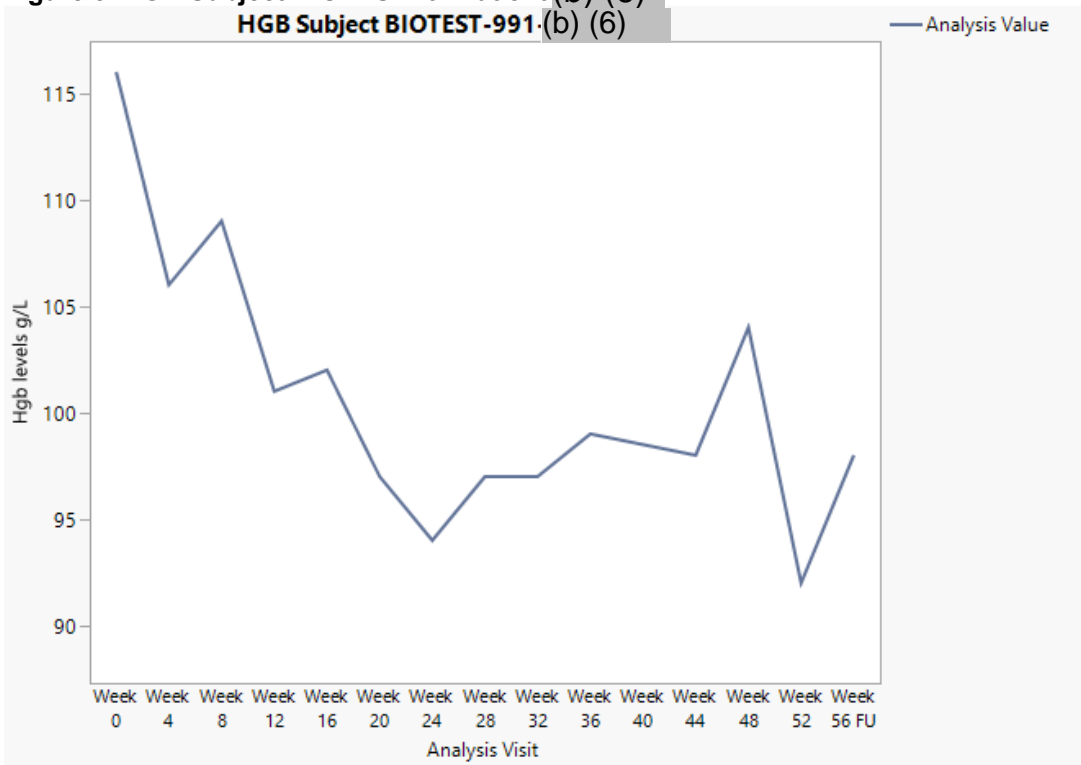
- Patient (b) (6) : Twenty-eight-year-old female who received YIMMUGO at the Q4W treatment schedule. A drop in hemoglobin levels was noted starting at week 12 to week 44. The lowest level of hemoglobin reported was 92 g/L, a 24 g/L decrease from baseline (116 g/L) along with a rise in lactate dehydrogenase levels with highest level reported at week 40 (644 u/L; BL 460 u/L). Serum haptoglobin was not evaluated until the last visit at week 56. The Coombs test was negative at screening and positive at week 56. The patient received vitamin B12 and Aktiferrin treatment with no noted improvement in hemoglobin levels. Based on the noted laboratory parameters, the possibility of hemolytic anemia in this patient cannot be ruled out.

Figure 4. LDH Subject BIOTEST for Patient (b) (6)



Source: Graph created by the reviewer using ADAM dataset
Abbreviations: L, liter; LDH, lactate dehydrogenase; U, units.

Figure 5. HGB Subject BIOTEST for Patient (b) (6)
HGB Subject BIOTEST-991 (b) (6)



Source: Graph created by the reviewer using ADAM dataset
Abbreviations: g, grams; HGB, hemoglobin; L, liter.

6.1.12.6 Clinical Test Results

One patient had a positive Coombs test during the study.

6.1.12.7 Dropouts and/or Discontinuations

A total of seven patients discontinued early from the study. Three of the patients discontinued due to SAE (anaphylactic reaction, severe neutropenia, and toxic hepatitis), three patients discontinued due to patient's decision and one patient withdrew consent.

Reviewer Comment: Of the seven patients who discontinued early from the study, two patients received only one infusion, one patient received two infusions, and two received five and six infusions. The impact of inadequate amount of study medication received by these patients on the safety and efficacy results was assessed to be low.

6.1.13 Study Summary and Conclusions

The study met its objective because incidence of serious acute bacterial infections was less than 1.0 per patient per year (in accordance with Agency guidance) disproving the null hypothesis. The secondary efficacy endpoints and safety data are comparable to other approved immunoglobulin products. Because of factors related to the manufacturing of YIMUUGO, the final product is

reported to have (b) (4) . Therefore, YIMMUGO may be considered to constitute a risk of causing hemolytic events.

6.2 Trial #2

Trial 992: This was an open-label, prospective, randomized, multicenter study investigating the clinical efficacy and safety of the YIMMUGO in patients with chronic primary ITP. The primary objective of the study was to assess the rate of patients with a response defined as a platelet count of $\geq 30 \times 10^9/L$ and at least a 2-fold increase of the baseline count, confirmed on at least two separate occasions at least 7 days apart, and the absence of bleeding. The trial enrolled a total of 34 patients with refractory ITP who received either 1 g/kg bw per day for 2 consecutive days or 0.4 g/kg bw per day for 5 consecutive days (i.e., a total dose of 2 g/kg bw per treatment course). The patients were followed for a total of 36 days after the first YIMMUGO infusion.

The results from Trial 992 were submitted by the applicant to support the safety of YIMMUGO. A total of 115 infusions to 34 patients were included in the safety analysis. No deaths were reported. One SAE was reported in a patient (anemia). Additionally, six patients were reported to have hemolytic events and 12 patients tested positive for Coombs test during the study. Patients with hemolytic events are summarized in Table 16 below.

Table 16. Patients With Hemolytic Events in Trial 992

Patient ID	Decrease in Hgb (g/L)	Haptoglobin (g/L)	Plasma Free Hgb (g/L)	LDH (U/L)	Bilirubin (Umol/L)	Hemo-siderin	Coombs Test
(b) (6)	47	0.1	0.418	498-2750	109	Pos	Pos
(b) (6)	37	0.1	0.096	445-493	31	Neg	Pos
(b) (6)	20	0.005	0.3	371-414	16.8	Neg	Neg
(b) (6)	39	0.01	0.6	312-511	30	Neg	Neg
(b) (6)	69	0.02	0.1	457-769	17	Pos	Pos
(b) (6)	32	0.1	n/a	569-565	25.7	Neg	Neg
Normal Range	0	0.4-1.7	Nil	140-280	1.71-20.5	Neg	Neg

Source: Table created by the reviewer

Abbreviations: g, grams; Hgb, hemoglobin; L, liter; LDH, lactate dehydrogenase; na, not available; Neg, negative; Pos, positive; U, unit.

Reviewer Comment: *Because of the significant differences in the study population, higher dose administration, and limited follow-up duration, it was difficult to generalize the results from Trial 992 to patients with PI. However, the high number of hemolytic events noted during the study may indicate that YIMMUGO is associated with increased risk of causing hemolytic events especially at high dose levels.*

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated summary of efficacy was submitted, nor was it required.

8. INTEGRATED OVERVIEW OF SAFETY

The applicant submitted an integrated safety summary to include data from Trial 991 and Trial 992. However, only data from Trial 991 was considered to evaluate the safety of YIMMUGO in the target indication. See [Section 6](#) for the detailed safety review.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproductive studies have not been conducted with YIMMUGO. It is not known whether YIMMUGO can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. YIMMUGO should be given to pregnant women only if clearly needed.

9.1.2 Use During Lactation

No human data are available to indicate the presence or absence of drug-associated risk. The developmental and health benefits of breastfeeding should be considered along with the other clinical needs for YIMMUGO and any potential adverse effects on the breastfed infant from YIMMUGO or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

The applicant had an Agreed iPSP for a partial waiver for patients 0 to <2 years of age with PI, which was considered justified by the Agency because the studies are impossible or highly impracticable in this pediatric population. Moreover, it was agreed that efficacy, safety, and PK data will be investigated in study 991 in pediatric patient 2 to <17 years of age. However, the applicant had requested a deferral for pediatric group 2 to <17 years in case sufficient PK and safety data cannot be collected from pediatric patients in study 991. In such case, an additional pediatric study will be initiated to complete PK and safety information in each age subgroup of the pediatric population. Further, it was established that to adequately characterize PK using a population PK modeling analysis, at least 9 to 18 pediatric patients (3 to 6 patients each, aged 2 to <6 years, 6 to <12 years and 12 to <17 years) will be enrolled in study 991. The Trial 991 enrolled a total of 18 pediatric patients. A summary of the pediatric data based on age groups is as follows:

Two to <6 years of age: A total of three patients in this age group were enrolled and treated. One child (b) (6) received only 6 infusions and had limited data to conduct any meaningful assessment. The second child (b) (6) reported a total of 18 infections during the trial including two events requiring hospitalization and seven events requiring antibiotic therapy. The patient's dose was adjusted due to infection at week 4, but this did not appear to have improved the rate of infection. Overall, the child lost 85 days from school/daycare during the study period. Additionally, there was lack of workup (no physical exam, laboratory, or imaging) for one event of bronchitis with a concomitant 5-day history of fever to determine if the event could be classified as an SBI. The third child (b) (6) maintained the IgG trough levels during the trial with only two mild infections reported.

Six to <12 years of age: A total of nine patients in this age group were enrolled and treated. Two children (b) (6) had to undergo dose adjustment due to low IgG levels and infections. No SBI or hospitalizations were reported. It was noted that five out of nine (55%) patients appeared to have lower IgG trough levels compared to baseline especially in the latter half of the treatment cycle when the prior IVIG product may no longer have carryover effect. The overall rate of any infection was reported to be 3.2, with four children requiring antibiotic treatment.

12 to <17 years of age: A total of six adolescents were enrolled and treated. The applicant did not report any SBIs or hospitalizations. However, one adolescent

(b) (6) had a case of moderate bronchitis; the workup was insufficient to determine if this represented an SBI. In this age group, the overall rate of any infection was reported to be 3.1, and four adolescents required antibiotic treatment. Of note, one adolescent patient (b) (6) lost 40 days from school due to infections. Also, one adolescent patient (b) (6) had a hemolytic event, for which blood transfusion was not needed.

Reviewer Comment: After review of the pediatric data from Trial 991, the reviewer is concerned that there is insufficient clinical, safety, and PK data to support approval for children 2 to 16 years of age. While the applicant did not identify any SBIs, there were two possible cases identified by the review division (in a 3 year old and in a 12 year old).

Of the three children 2 to <6 year olds, there was clinical efficacy in only one child as one patient (b) (6) withdrew prior to achieving steady-state on YIMMUGO, one patient (b) (6) had a potential SBI and multiple infections and prolonged school/daycare absence due to infections. Therefore, the reviewer recommends not approving this in children 2 to <6 years of age and requesting additional efficacy and safety clinical data by issuing a PREA PMR.

For the 6 to 17 year olds, the PK and efficacy generally appear similar to adults, and approval in this pediatric age group may be considered.

Summary of pediatric study data was presented to Pediatric Review Committee (PeRC) on March 19, 2024. The PeRC advised that if the product is approved by the division in adults, then a partial waiver should be granted to pediatric patients from birth to less than 2 years of age on the basis that necessary studies are impossible or highly impracticable. Further, with only 2 evaluable patients in 2 to <6 year old cohort, the PeRC agreed with the division's recommendation for a deferral pediatric study under PREA for this age group.

9.1.4 Immunocompromised Patients

Not applicable as the product is indicated for patients with immunodeficiency. All patients have PI.

9.1.5 Geriatric Use

Five adults ≥65 years of age were enrolled and treated with YIMMUGO in the study. Sample size is too small to derive meaningful conclusions.

10. CONCLUSIONS

Trial 991 was conducted according to FDA guidance and is adequately designed to demonstrate safety and efficacy of YIMMUGO for the treatment of patients with PI. The study met its primary objective by demonstrating that the upper one-sided 99% confidence limit for the rate of acute SBIs (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) meeting FDA criteria was less than 1.0 per patient per year in the

population of patients with PI receiving YIMMUGO infusions at Q3W or Q4W intervals for 12 months. Efficacy was supported by secondary endpoints demonstrating low rate of any infection, antibiotic use, hospitalization, and days missed from work/school.

The infusions of YIMMUGO were well tolerated with no fatal events reported. It was noted that the manufacturing of YIMMUGO leads to a high titer of anti-A and anti-B and therefore, use of the product may create a higher risk for hemolytic events. However, in Trial 991, the type and frequency of AEs reported were consistent with the known safety profile of other licensed IVIG treatments. Therefore, the clinical reviewer recommends the following:

- Granting a license for the use of YIMMUGO for treating patients 6 years of age and older with PI.
- Partial waiver of requirement for clinical studies in children <2 years of age
- Post Marketing Requirement (under PREA) to conduct a PK, safety, and efficacy study in young children 2 to 6 years of age.
- Labeling recommendation for high dose restriction due to the hemolytic events noted with the administration of high doses of YIMMUGO.
- Enhanced pharmacovigilance to monitor and better understand the hemolytic risk associated with YIMMUGO administration.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 17. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> PI represents a heterogeneous group of disorders resulting from inherited defects of the immune system. Patients with PI are at increased risk for recurrent, severe infections. 	<ul style="list-style-type: none"> PI diseases are serious, chronic conditions associated with considerable morbidity and mortality. IgG replacement therapy (administered either intravenously or subcutaneously) has been shown to reduce the incidence of serious infections through the provision of passive immunity and prolonged lifespan.
Unmet Medical Need	<ul style="list-style-type: none"> Numerous marketed IgG products (both intravenous and subcutaneous forms) have demonstrated efficacy with serious bacterial infection rates less than 1.0 per patient-year. 	<ul style="list-style-type: none"> Currently, there is not an unmet medical need. However, given the potential for supply-chain disruptions and shortages, there is a public health benefit for having additional immunoglobulin replacement products on the market.
Clinical Benefit	<ul style="list-style-type: none"> An open-label, single-arm, prospective, multicenter study evaluated the safety, efficacy, and pharmacokinetics of YIMMUGO in patients 2 years of age and older with PI compared to historical standards. Study participants received IVIG infusions at Q4W or Q3W intervals for 12 months. There was a total of five possible SBIs reported during a cumulative total follow-up of 67.6 patient-years, resulting in an incidence of acute SBIs of 0.074 events per patient per year (upper one -sided 99% confidence limit of 0.21). Overall, the secondary efficacy outcome measures (rate of any infections, antibiotic use, hospitalizations, and days missed from school) in patients treated with YIMMUGO were supportive of the primary efficacy outcome. PK data was noted to be insufficient to infer safety and efficacy conclusions in the age group 2 to <6 years of age 	<ul style="list-style-type: none"> The study met its objective because the incidence of serious acute bacterial infections in patients with PI treated with the investigational product YIMMUGO was less than 1.0 per patient per year (in accordance with Agency guidance) disproving the null hypothesis. The product was shown to be effective at preventing SBIs in patients with PI over 6 years of age and older.
Risk	<ul style="list-style-type: none"> Class-specific risks for immunoglobulin products (AESI) include the following: thrombosis, hypersensitivity reactions, acute renal failure, hyperproteinemia, aseptic meningitis, hemolysis, TRALI, transmissible infectious agent, laboratory test interference. The most common systemic AE seen in >5% of patients were headache, upper respiratory tract infections, fatigue, nausea, and increased blood pressure. The manufacturing process allows for IgA up to 300 micrograms per milliliter. There may be a possible increased risk of anaphylaxis due to higher IgA content. There was one case of anaphylaxis in the trial but given size of clinical trial there is uncertainty with regard to extent of risk of anaphylaxis with this product in the post-market setting. The manufacturing process of YIMMUGO leads to a (b) (4) and therefore, the product may be at a higher risk for causing hemolytic events but given size of trial the extent of the hemolysis risk with this product is unclear. 	<ul style="list-style-type: none"> ARs with YIMMUGO are similar to other IVIG products. Higher risk for product related hemolytic events specially with higher dose levels.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	<p>The risks of YIMMUGO can be managed by:</p> <ul style="list-style-type: none"> • Clinical monitoring throughout the infusion • Periodic laboratory monitoring of renal function and for hemolysis. • YIMMUGO specific warnings and high dose restrictions on the label. • Post market enhanced pharmacovigilance and AE reporting. • Patients should be educated and monitored for signs and symptoms of hypersensitivity, hemolysis, thrombosis, aseptic meningitis, and TRALI. 	<ul style="list-style-type: none"> • Risk mitigation with product changes as suggested by CMC would be preferred but given the uncertainties of hemolysis risk at proposed doses for PI, labeling recommendations and enhanced pharmacovigilance are adequate. • Other risk mitigation through labelling recommendations and clinical monitoring adequate to manage the risks.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; IgG; immune globulin G; IVIG, intravenous immunoglobulin; Q3W, 3 week; Q4W, 4 week; PI, primary humoral immunodeficiency; PK, pharmacokinetics; SBI, serious bacterial infection; TRALI, transfusion-related acute lung injury.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA provide substantial evidence of effectiveness and safety in patients with PI 6 years and older. YIMMUGO is effective in reducing the number of SBIs to less than one per patient per year in patients with PI. The most commonly reported adverse reactions (occurring within 72 hours of infusion) were headache, upper respiratory infections, fatigue, nausea, and increased blood pressure. Adverse reactions were consistent with those anticipated with this class of products and were self-limited with YIMMUGO. For immunoglobulin therapy for PI, the Agency accepts a single adequate and well-controlled (AWC) trial with confirmatory data from other AWC trials within the class for the same indication. Overall, the benefits outweigh the risks of YIMMUGO, and the benefit-risk profile is favorable. During the clinical trial, the observed risk profile is consistent with this class of products. However, it is important to note that while hemolysis is a known risk for this class of products, the manufacturing process for YIMMUGO with caprylic acid preparation without mitigation leads to (b) (4) and therefore, the product may be at a higher risk for hemolytic events compared to other IVIG products.

11.3 Discussion of Regulatory Options

The regulatory options for this application are approval for patients 2 years of age and older with PI, approval for a subset of the requested population (i.e., adults, adults and a subset of children with PI), or a complete response letter. Because of the limited data in pediatric population 2 to <6 years of age, the reviewer recommends approving YIMMUGO for adults and pediatric patients 6 years of age and older with PI and issuing a PREA PMR to collect additional data in children 2-<6 years of age with PI.

11.4 Recommendations on Regulatory Actions

This reviewer recommends approval of STN125810.0 in patients with PI 6 years of age and older with labeling changes as listed below.

Division Director Note: I concur with the clinical reviewer's summary assessment of the safety and efficacy of YIMMUGO. While I acknowledge the limited available PK data in patients 2 to <6 years of age, my overall assessment is that approval in this younger age group is supported based on the available data (see clinical pharmacology reviewer memo).

11.5 Labeling Review and Recommendations

The reviewer recommends the following changes to the proposed draft label:

- Section 1 (Indication and Usage): Recommend limiting indication to patients with PI who are 6 years of age and older.
- Section 2 (Dosage and Administration):

- Recommend modifying the lower limit of YIMMUGO in label to 300 mg/kg bw because of limited data to support a dose below 300 mg/kg bw in Trial 991.
- Recommend revision to Table-1 to provide details on the maintenance infusion rate for first and second infusions and maximum infusion rates.
- Recommend including a maximum dose restriction of not exceeding 800 mg/kg because of the high number of hemolytic events noted with the use of high dose levels.
- Section 5 (Warnings and Precautions): Recommend reordering the subsections to first include events that were observed with YIMMUGO in clinical trials (hemolysis and hypersensitivity). Further, recommend using product specific language when describing these adverse events instead of general class language.
- Section 6 (ARs): Recommend modification to the ARs based on the adjudication by the reviewer. Further, recommend revising the list post marketing ARs to be consistent with previous approved IVIG label.
- Section 7 (Drug Interactions): Recommend including interactions with other intravenous products, and rationale to limit concomitant use of loop diuretics.
- Section 14 (Clinical Studies): Recommend including demographics of study population, description of primary endpoint, dose adjustment and patient discontinuations during the trial. Further, recommend including a table to describe the efficacy results for improved readability.

11.6 Recommendations on Postmarketing Actions

Post-marketing requirements are necessary for completion of deferred pediatric studies, required under PREA (21 CFR 314.55(b) and 601.27(b)) for the age range 2 to <6 years of age.

Division Director Note: Because the Applicant's requested indication will be approved, there is not a need to conduct post-marketing studies in the 2 to <6 year of age group. The pediatric study requirement for ages from birth to less than 2 years of age are waived because the number of patients diagnosed with primary humoral immunodeficiency in this age group is so small.

Further, because of the potentially increased risk associated hemolysis, the reviewer recommends that the applicant conduct routine and enhanced pharmacovigilance activities which may include 1) expedited reporting of all AEs involving hemolysis, regardless of label status or seriousness and 2) the applicant's assessment of the risk of hemolysis, with specific analyses of this risk

among patients receiving YIMMUGO for primary humoral immunodeficiency, in periodic safety reports.