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Summary Basis for Regulatory Action

Date:	June 13, 2024
From:	Jennifer Reed, PhD, CBER/OTP/OPPT
BLA STN:	125810/0
Applicant:	Biotest AG
Submission Receipt Date:	June 30, 2023
Action Due Date:	June 29, 2024
Proper Name:	immune globulin intravenous, human-dira
Proprietary Name:	YIMMUGO
Indication:	For the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age or older

* PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Clinical Evaluation

_____

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Lu Deng, CBER/OTP/OPPT Yambasu Brewah, CBER/OTP/OPPT Maria Luisa Virata, CBER/OTP/OPPT Leonid Parunov, CBER/OTP/OPPT Pei Zhang, CBER/OTP/OPPT Miriam Ngundi, CBER/OCBQ/DMPQ Neetu Dahiya, CBER/OCBQ/DMPQ Claire Wernly, CBER/OCBQ/DBSQC Emnet Yitbarek, CBER/OCBQ/DBSQC Jing Lin, CBER/OCBQ/DBSQC George Kastanis, CBER/OCBQ/DBSQC Parmesh Dutt, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DPV) • BIMO	Afsah Amin, CBER/OTP/OCE Yeowon Kim, CBER/OBPV/DPV Haecin Chun, CBER/OCBQ/BMB
Statistical • Clinical data (OBPV/DB)	Hairong (Helen) Shi, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Evi Struble, CBER/OTP/OPPT
Clinical Pharmacology	Yang Chang, CBER/OTP/OCE
Labeling **PNR Review** • Promotional (OCBQ/APLB)	Sonny Saini, CBER/OCBQ/DCM/APLB Oluchi Elekwachi, BER/OCBQ/DCM/APLB
Other Review(s) not captured above categories, for example: • Consults • FONSI	Fang Li, CDER/OTS/OCP/DPM Jingyu Yu, CDER/OTS/OCP/DPM
Advisory Committee Summary	N/A

Table of Contents

1. Introduction

YIMMUGO (IgG Next Generation; BT595) is a 10% intravenous immunoglobulin product intended for the treatment of primary humoral immunodeficiency (PI**)** in patients 2 years of age or older. At Biotest's facility in Dreieich, Germany, YIMMUGO is manufactured from large pools of human plasma via a (b) (4) cold ethanol fractionation process, with further purification by caprylic acid precipitation and chromatography steps. YIMMUGO is supplied in type (b) (4) glass vials of 50, 100, or 200 mL sizes. The product is reviewed under Biological License Application 125810, which was submitted on June 30, 2023, and assigned a standard 12-month review period. Biotest's Process Performance Qualification (PPQ) campaign was carried out in a new manufacturing space with a process (b) (4) designated Process (b) (4) These changes were implemented after the pivotal clinical trial was completed, using product manufactured via Process (b) (4) Additional manufacturing changes were initiated after the PPQ campaign was completed, presenting additional validation and comparability issues that were successfully addressed during the BLA review cycle.

The primary evidence of safety and efficacy was supported by Trial 991, a Phase 3, open-label, prospective, single-arm, multi-center study conducted in the U.S., Europe and Russia comparing annualized rate of SBI to historical standards. The trial enrolled 67 patients (49 adult and 18 pediatric) with PI. Patients received doses of YIMMUGO ranging from 200 mg to 833 mg per kg body weight (bw) every 3 (n=12) or 4 weeks

(n=55), for a treatment period of approximately 12 months. The pre-specified primary efficacy analysis threshold was met as the annualized acute serious bacterial infection (SBI) rate was less than one SBI per person-year. The secondary outcomes (rate of any infection, time to resolution of infection, antibiotic use, number of days missed from work or school, and hospitalizations) and pharmacokinetic (PK) data were overall supportive of the product's efficacy. There were no deaths reported during the study. Two serious adverse events (SAEs) related to the product administration were reported in two patients (anaphylactic reaction, severe neutropenia). A case of mild hemolysis and positive Coombs test was reported in one patient. It was noted that YIMMUGO maybe at higher risk of hemolysis due to higher (b) (4) (b) (4) with manufacturing using that caprylate/chromatography process. The risk was mitigated by labeling recommendations and enhanced pharmacovigilance by the applicant for all AEs involving hemolysis for a period of three years post-licensure.

2. Background

The intended use of YIMMUGO is replacement immunoglobulin therapy in patients with PI. PI is a form of primary immunodeficiency that is characterized by impaired B-cell immunity, with an impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, Severe Combined Immunodeficiency Disease (CVID), X-Linked Agammaglobulinemia (XLA), Common Variable Immunodeficiency Disease (CVID), Hyper-IgM Syndrome, Wiskott-Aldrich Syndrome, Chronic Granulomatous Disease (CGD), and IgG Subclass Deficiency. Patients with PI are at increased risk recurrent, severe bacterial infections, especially of the respiratory tract (2). The mainstay of treatment is lifelong maintenance immune globulin therapy to provide antibacterial antibodies (3,4). The safety profile of immunoglobulins, as a class, is well established, including a boxed warning for thrombosis, renal dysfunction and renal failure.

YIMMUGO is currently marketed in Germany, Austria, and the United Kingdom (UK) for treatment of PI.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	PS002860 January 26, 2016
2. IND submission	17046 June 17, 2016
3. Pre-BLA meeting	April 3, 2023
4. BLA 125810/0 submission	June 30, 2023
5. BLA filed	August 29, 2023
6. Mid-Cycle communication	December 22, 2023
7. Late-Cycle meeting	March 21, 2024
8. Action Due Date	June 29, 2024

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

YIMMUGO is a liquid formulation of 10% human IgG manufactured solely from U.S. Source Plasma. Manufacture begins with (b) (4) cold ethanol precipitation steps based on the (b) (4) process, with further purification accomplished by caprylic acid treatment followed by (b) (4) to remove precipitated proteins. After (b) (4) to inactivate viruses. Additional purification is performed with sequential anion exchange and cation exchange chromatography steps, followed by nanofiltration as an (b) (4) virus removal step. (b) (4) before the addition of Polysorbate 80. The (b) (4) is (b) (4) filling into type (b) (4) glass vials with nominal fill volumes of 50, 100, or 200 ml.

Biotest implemented a (b) (4) (Process (b) (4) Biotest's successful comparability evaluation of YIMMUGO manufactured via Process (b) (4) included (b) (4) PPQ drug product batches. The stability data set for Process (b) (4) batches support a shelf-life of 30 months at 5°C ± 3°C with a one-time period of storage up to 6 months at not more than 25°C.

Published data indicate that immunoglobulin products purified via caprylate / chromatography methods can contain higher levels of hemagglutinating antibodies associated with hemolytic adverse events (5). Excess hemagglutinating antibodies can be remedied by selection of (b) (4) source plasma, or inclusion of an (b) (4) (b) (4) chromatography step (5). A potential trend toward (b) (4) hemagglutinin levels in Process (b) (4) compared with Process (b) (4) batches was noted in the comparability data set. However, the levels of (b) (4) hemagglutinins remained within specifications. The trend toward (b) (4) hemagglutinin levels in Process (b) (4) batches was later attributed to a (b) (4) implemented between Process (b) (4) and Process (b) (4) the trend was therefore discounted.

Biotest was requested to narrow their process parameters, especially critical process parameters and key process parameters, to reflect what was covered by the PPQ lots. In-process testing is routinely performed, and process quality attributes are monitored at different stages during manufacture. It was noted that Biotest removed (b) (4) monitoring from many manufacturing steps after a microbial control strategy study. (b) (4) monitoring is required for all lots throughout the manufacturing process from plasma (b) (4) to drug product. A Post-Marketing Commitment (PMC) was requested to ensure the implementation of routine (b) (4) monitoring for test samples taken immediately prior to steps for bioburden reduction or sterilization, and at steps where potential microbial ingress could occur.

b. Testing Specifications

The Drug Product specifications for YIMMUGO were found to be acceptable after revisions. Biotest was requested to add a (b) (4) Assay, after which they added a validated (b) (4) assay and specification. They were also requested to add a (b) (4) test and specification, for which they agreed to do a PMC. Revisions to the measles virus neutralization potency, composition of immunoglobulins (IgG, IgA, IgM), and antibody to hepatitis B surface antigen specifications were also requested in order to be consistent with other US-licensed intravenous immunoglobulin products. The identity test was moved to the post-packaging stage to comply with 21 CFR 610.14 requirements.

The analytical methods and their validations and/or qualifications reviewed for the YIMMUGO (Immune Globulin Intravenous Human, 10% Liquid, IgG Next Generation [BT595]) (b) (4) (b) (4) Drug Product were found to be adequate for their intended use.

Table 2: YIMMUGO Drug Product Specifications

Determination	Requirement	Method
(b) (4) (post-packaging identity test)	Complies	(b) (4)
Antibody to hepatitis B surface antigen	(b) (4)	(b) (4)
Polio virus neutralization (b) (4)	(b) (4) CBER Ref. Std. (b) (4)	(b) (4)
Measles virus neutralization potency, (b) (4) (b) (4)	(b) (4) CBER Ref. Std. (b) (4)	(b) (4)
Diphtheria toxin neutralization potency, (b) (4) (b) (4)	(b) (4)	(b) (4)
Coloration	(b) (4)	(b) (4)
Clarity and Opalescence	(b) (4)	(b) (4)
Visible particles	Clear and practically free from particles	(b) (4)
Extractable volume	NLT nominal	(b) (4)

pH	(b) (4) (4.4-5.2)	(b) (4)
Osmolality	(b) (4) (280-380 mosmol/kg)	(b) (4)
Total Protein	(b) (4) (90-110 g/L)	(b) (4)
(b) (4) human IgG	Positive	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Composition of immunoglobulins IgG IgA IgM	(b) (4) NMT 0.3 mg/mL (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sterility	Sterile	(b) (4)
Pyrogens	Pyrogen free	(b) (4)
Excipient: Polysorbate 80	(b) (4) (2-20 µg/ml)	(b) (4)

Excipient: Glycine	(b) (4) (270-330 mmol/L)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Notes: NLT, not less than; NMT, not more than

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of YIMMUGO are listed in the table below. The activities performed and inspectional histories are noted in the table.

Table 3: Activities Performed and Inspectional Histories

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Biotest AG Landsteinerstraße 5, 63303 Dreieich, Germany (b) (4) *DP manufacture, primary packaging and labeling, and DP release testing*	3001034985	315031799	PLI	OCBQ/DMPQ December 2023 VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waiver	ORA/OPQO (b) (4) VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waiver	ORA/OPQO (b) (4) NAI
(b) (4)	(b) (4)	(b) (4)	Waiver	ORA/OPQO

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
(b) (4) *DP release testing*				(b) (4) VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) VAI

Acronym key: DMPQ - Division of Manufacturing and Product Quality; DP – drug product; DS – drug substance; NAI – No Action Indicated; OBPO – Office of Biological Products Operations; OCBQ - Office of Compliance and Biologics Quality; OPQO – Office of Pharmaceutical Quality Operations; ORA – Office of Regulatory Affairs; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated

OCBQ/DMPQ conducted a PLI of Biotest AG from December 04 – 15, 2023. A Form FDA 483 list of observations was issued at the end of the inspection, and the corrective actions were reviewed. All inspectional issues were resolved, and the inspection was classified as VAI.

ORA/OPQO performed a pre-approval inspection of (b) (4) (b) (4) from (b) (4) All inspectional issues were resolved, and the inspection was classified as VAI.

ORA/OPQO performed the most recent FDA surveillance inspection of (b) (4) (b) (4) from (b) (4) A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

ORA/OPQO performed the most recent FDA surveillance inspection of (b) (4) (b) (4) from (b) (4) All inspectional issues were resolved, and the inspection was classified as VAI.

ORA/OBPO performed the surveillance inspection of (b) (4) (b) (4) from (b) (4) All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The YIMMUGO DP is filled into (b) (4) 100, (b) (4) mL clear, colorless Type (b) (4) glass vials (b) (4) The vials are closed with 32 mm Type (b) (4) bromobutyl rubber stoppers that are siliconized (b) (4) and sealed with 32 mm aluminum crimp seals equipped with a plastic flip-off (b) (4)

(b) (4) performed the container closure integrity testing at the (b) (4) facility, employing a (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

A categorical exclusion from Environmental Assessment / Environmental Impact Statement was requested by the firm under 21 CFR 25.31. FDA concluded that the request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

In vitro primary pharmacodynamic studies were performed to assess Fab- and Fc functions of YIMMUGO. The results of these studies demonstrate functionality of YIMMUGO and its potential to neutralize pathogens of relevance in the PID indication.

One single-dose toxicity and safety pharmacology study was performed in Sprague Dawley rats with YIMMUGO. In this study, 2 g/kg YIMMUGO was given as an intravenous infusion. The animals were assessed one and fourteen days after infusion for systemic and local toxicity. No unexpected toxicities were observed in this study.

Toxicity of excipients was assessed via a literature review. There are no safety concerns related to potential toxicity of excipients and other impurities in the final formulation of YIMMUGO.

There are no pharmacology and toxicology issues that would prevent YIMMUGO from being approved.

5. Clinical Pharmacology

YIMMUGO contains a broad spectrum of opsonic and neutralizing immunoglobulin G (IgG) antibodies against various infectious agents reflecting the IgG activity found in the donor population. As YIMMUGO is manufactured from pooled donors, it has an IgG subclass distribution similar to that of native human plasma. Therapeutic dosing of IGIV, including YIMMUGO, can restore abnormally low IgG levels to the normal range. Standard pharmacodynamic studies were not performed.

The PK of YIMMUGO was assessed by non-compartmental analyses (NCA) at steady-state in 57 patients with PI aged 6 to <76 years who were receiving doses of 280mg/kg to 800mg/kg. The mean half-life was 24.8-29.9 days depending on treatment schedule. The mean clearance (baseline uncorrected) was 1.4 mL/day/kg for the 21 day dosing regimen and 1.3 mL/day/kg for the 28 day dosing regimen. The mean steady state total trough IgG concentrations was above 5mg/L. Population PK modeling was done to predict PK parameters for young children, age 2 to <6 years. This covariate analysis did not identify a relationship between PK parameters, age and sex.

Overall, the clinical pharmacology data supports the approval of YIMMUGO as replacement therapy for children 2 years of age and older with PI based on a dosing regimen of 300-800 mg/kg every 21 or 28 days, to be adjusted based on IgG trough values and clinical response.

6. Clinical/Statistical

a. Clinical Program

The primary evidence of safety and efficacy for this BLA comes from Study 991, a Phase 3, open-label, prospective, single-arm, multi-center study conducted in the U.S., Europe and Russia under IND 17046 comparing annualized rate of SBI to historical standards. The study planned to enroll patients 2 to 75 years of age with PI who had been on stable doses of IGIV therapy for at least 3 months, and had therapeutic IgG trough levels (i.e., at least one IgG trough level of ≥5g/L during the previous 3 months). Patients were to receive YIMMUGO at doses equivalent to their prior IGIV therapy, between 0.2 to 0.8 g per kg body weight (bw) and according to their pre-study IGIV administration schedule and frequency, either every 3-weeks (Q3W) or every 4-weeks (Q4W) for a period of 12 months; doses adjusted for changes in weight or as medically indicated.

The primary efficacy endpoint was annualized rate of serious bacterial infections (SBI), defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscesses, or bacterial meningitis. Secondary efficacy variables included occurrence of any infection of any kind or seriousness, time to resolution of infections, use of antibiotics, the number of days of work/school missed, and the number and days of hospitalizations.

The study enrolled 67 patients, 49 adults and 18 children. The mean age of study participants was 35 years, with patients ranging from 2 to 74 years of age. The study population was predominantly White (n=66; 98.5%), with males representing 55% of the population. The most common underlying cause of PI was CVID (n=53; 80%). During the study, patients received YIMMUGO doses between 200 mg to 833 mg per kg body weight (bw) every 3 (n=12) or 4 weeks (n=55), for a treatment period of approximately 12 months. Infusions were initiated at a rate of 0.5 mg/kg/min (0.005 mL/kg/min) for the first 30 minutes, and, if tolerated, could be increased to a maximum tolerated rate not exceeding 13 mg/kg/min (0.13mLl/kg/min). During the study, 12 (18%) patients had medical indications for a dose increase. This included 10 patients who had low IgG levels (including 7 patients who had trough levels <5 g/L) and 2 patients who had infections. One patient required a dose reduction due to an adverse reaction (worsening of fatigue).

The study demonstrated that treatment with YIMMUGO resulted in less than one SBI per person-year. A total of five acute SBIs occurred in 3 adults and 2 children. All five acute SBIs were bacterial pneumonia. A summary of efficacy outcomes is shown in Table 4.

Table 4: Summary of Efficacy Results in Trial 991

Category	Results
Number of Patients	67 patients with 67.6 years on study
Infections	
Annualized rate of acute SBIs	0.07 acute SBIs/person-year (upper one-sided 99% confidence limit of 0.21)
Annualized rate of other infections	2.7 infections/person-year
Time to resolution of infection*	7 (1, 172) days†
Antibiotics	
Number of patients with therapeutic antibiotic use	35 patients (52.2%)
Number of days on therapeutic antibiotics*	9.5 (3, 35) days
Time lost from work/school	
Number of patients who lost ≥1 day due to infection	26 patients (38.8%)
Number of days lost from work/school due to infection*	6 (1, 85) days
Hospitalizations due to infection	
Number of patients with hospitalizations due to infection	3 patients (4.5%)
Number of days hospitalized*	2 (2, 20) days
Annualized rate of hospitalization due to infection	0.36 days/person-year

*Number of days presented in median (min, max) among patients with events of a duration of ≥1 day; maximum duration was used if there were multiple events.
†Two patients had unresolved infections at the last follow-up visit.

The safety population set (SAF) consisted of all patients who received at least one dose of YIMMUGO (n=67). A total of 923 YIMMUGO infusions were administered during the trial. No deaths were reported. Two serious adverse events (SAEs) related to the product administration was reported in two patients (anaphylactic reaction, severe neutropenia). Both SAEs led these patients to discontinue participation in the study. Mild hemolysis and positive Coombs test were reported in one patient. Overall, 93 adverse reactions (ARs) occurred in 39 patients. The most common ARs observed in >5% of patients included headache, upper respiratory infections, fatigue, nausea, and increased blood pressure.

The study design is consistent with the FDA guidance for studies supporting marketing applications for IVIG therapies for the treatment of primary immunodeficiency disease (PI) (6). Based on the clinical and clinical pharmacology data included in the BLA, there is a favorable benefit-risk profile to support approval of YIMMUGO for the treatment of patients with PI 2 years of age and older.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for one domestic and three foreign clinical investigator study sites that participated in the conduct of Protocol 991. The inspections

did not reveal significant issues that impact the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

The safety, efficacy, and PK data for children 2 to <17 years of age from Study 991 is considered adequate by the division to support approval for children who are at least 2 years of age with PI. The pediatric study requirement for age 0 to <2 years is waived as PI is rarely diagnosed in this age group, and therefore conducting studies in this age group are impossible or highly impractical. No additional pediatric studies are being required under PREA.

d. Other Special Populations

No other special populations are under consideration for the use of this IGIV product.

7. Safety and Pharmacovigilance

Pharmacovigilance

YIMMUGO is marketed in Germany, Austria, and the United Kingdom. In addition to the event of hemolysis noted during Study 991, review of global postmarketing safety data revealed an additional hemolysis event.

Review of the available clinical and foreign postmarketing safety data 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. There is no safety-related study as an agreed upon postmarketing commitment (PMC) at this time. The applicant will 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*.

8. Labeling

The proposed proprietary name, YIMMUGO, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on September 20, 2023, and was determined to be acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on September 27, 2023.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed USPI, package and container labels on April 11, 2024, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

This application was not referred to an Advisory Committee because our review of information submitted in the BLA, including the clinical study design and trial results, did

not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review committee recommends approval of YIMMUGO for the treatment of primary humoral immunodeficiency (PI) in patients 2 years or older with the following postmarketing commitments:

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

1. Biotest commits to completing implementation of (b) (4) sampling and testing as indicated in Amendment STN 125810/0.47, before production of the first commercial U.S. YIMMUGO lot, and to submit the related change controls in the first Annual Report by August 31, 2025.

   Final Report Submission: August 31, 2025

2. Biotest commits to completing (b) (4) evaluations with effective (b) (4) for samples (b) (4) the YIMMUGO (b) (4) (b) (4) and to submit the study report as a Postmarketing Commitment Submission - Final Study Report by June 30, 2025.

   Final Report Submission: June 30, 2025

3. Biotest commits to completing a (b) (4) validation study for (b) (4) which is used for the drug substance (b) (4) and to submit the final validation study report as a Changes Being Effected (CBE) supplement by November 30, 2024. Biotest also commits to place the lot processed with the maximum (b) (4) (b) (4) on stability. Interim stability data will be submitted annually as a Postmarketing Commitment Submission – Status Update. A final stability study report will be submitted by May 31, 2027, as a Postmarketing Submission – Final Study Report. Any stability failures will be reported within 45 days of the occurrence as a Postmarketing Commitment Submission – Status Update.

   Changes Being Effected (CBE) Supplement Submission: November 30, 2024

   Final Validation Report Submission: November 30, 2024

   Final Stability Report Submission: May 31, 2027

4. Biotest commits to performing concurrent (b) (4) validation studies for the (b) (4) at Step (b) (4) and Step (b) (4) respectively. The interim results of the studies will be submitted annually in the Annual Report. The final validation study reports will be submitted as a CBE supplement no later than June 30, 2026. Biotest commits to notifying the FDA of any (b) (4) failures within 45 days of the occurrence as a Postmarketing Commitment Submission - Status Update.

   Changes Being Effected (CBE) Supplement Submission: June 30, 2026

5. Biotest commits to performing a concurrent (b) (4) validation study for the (b) (4) (b) (4) Interim results will be submitted annually in the Annual Report. The final validation study report will be submitted as a Changes Being Effected (CBE) supplement not later than June 30, 2026. Biotest commits to notifying the FDA of any (b) (4) failures within 45 days of the occurrence as a Postmarketing Commitment Submission - Status Update.

   Changes Being Effected (CBE) Supplement Submission: June 30, 2026

6. Biotest commits to submitting a validation study final report to confirm the proposed maximum (b) (4) for the (b) (4) (b) (4) as a Changes Being Effected (CBE) supplement by June 30, 2026. Biotest commits to notifying the FDA of any (b) (4) failures within 45 days of the occurrence as a Postmarketing Commitment Submission - Status Update.

   Changes Being Effected (CBE) Supplement Submission: June 30, 2026

7. Biotest commits to implementing the (b) (4) test for Drug Product lot release and setting the specification based on Drug Product testing results. The (b) (4) method SOP and the final validation study report for testing DP will be submitted as a Prior Approval Supplement (PAS) no later than September 30, 2024. In the interim, Biotest commits to testing for (b) (4) in the (b) (4) (b) (4) with a specified limit of (b) (4) until the PAS is approved.

   Prior Approval Supplement (PAS) Submission: September 30, 2024

8. Biotest commits to performing a (b) (4) study to support product (b) (4) during (b) (4) for the (b) (4) and to submit the study report as a Postmarketing Commitment Submission - Final Study Report by August 31, 2024.

   Final Report Submission: August 31, 2024

9. Biotest commits to performing a complete virus clearance validation study for the (b) (4) step with a (b) (4) range from (b) (4) and conducting a robustness study with a (b) (4) greater than (b) (4) using the (b) (4) collected from commercial scale production of YIMMUGO as testing materials.

The final study reports will be submitted as a Changes Being Effected (CBE) supplement no later than October 31, 2024.

Changes Being Effected (CBE) Supplement Submission: October 31, 2024

10. Biotest commits to providing the complete stability data supporting BT595 PPQ drug product batches manufactured from US plasma in study BE-Q-301j-95/03 as a Postmarketing Commitment Submission – Final Study Report by December 31, 2024.

    Final Report Submission: December 31, 2024

11. Biotest commits to providing the complete leachables data supporting BT595 PPQ drug product batches manufactured from US plasma in study BE-186-95/01 as a Postmarketing Commitment Submission – Final Study Report by December 31, 2024.

    Final Report Submission: December 31, 2024

12. Biotest commits to providing the final CAPA report for 200195300 as a Postmarketing Commitment Submission – Final Study Report by November 30, 2024.

    Final Report Submission: November 30, 2024

b. Benefit/Risk Assessment

Data submitted in the BLA provide substantial evidence of effectiveness and safety in patients with PI 2 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.

c. Recommendation for Postmarketing Activities

The review team determined that YIMMUGO does not require a PMR safety study under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) or a REMS. There is no safety-related study as an agreed upon postmarketing commitment (PMC) at this time. The applicant will conduct routine and enhanced pharmacovigilance activities, in accordance with 21 CFR 600.80, as outlined in the *Risk Management Plan for* YIMMUGO *(Human normal immunoglobulin (IVIg)), version 0.5.* Regarding the latter, the applicant will be required to conduct enhanced pharmacovigilance activities for AEs

involving hemolysis for a period of 3 years post-licensure. Enhanced pharmacovigilance activities will consist of 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.

12. References

1. Quinn J., Modell V., Orange J.S., et al. Growth in diagnosis and treatment of primary immunodeficiency within the global Jeffrey Modell Centers Network. Allergy Asthma Clin Immunol 2022 Mar 4; 18(1):19. doi: 10.1186/s13233-022-00662-6.

2. Sil A., Basu S., Joshi V,, et al. Immunoglobulin replacement therapies in inborn errors of immunity: a review. Front Pediatr 2024; Feb 15:12:1368755. doi: 10.3389/fped.2024.1368755.

3. Perez E.E., Orange J.S., Bonilla FI, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J. Allergy Clin Immunol 2017 Mar;139(3S):S1-S46. doi: 10.1016/j.jaci.2016.09.023.4. Matucci A., Maggi E., Vulaggio A. Mechanisms of action of IG preparations: immunomodulatory and anti-inflammatory effects. Front Immunol 2014; 5: 690. doi: 10.3389/fimmu.2014.00690.

4. Romberg, V., Hoefferer, 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.

5. 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