

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From: Yeowon A. Kim, MD, MHS
Medical Officer, Pharmacovigilance Branch 1
(PB1), DPV, OBPV, CBER, FDA

To: Jennifer Reed, PhD
Chair of the Review Committee
Office of Therapeutic Products

Through: Adamma Mba-Jonas, MD
Branch Chief, PB1

Meghna Alimchandani, MD
Deputy Director DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Applicant: Biotest AG

Product: YIMMUGO [(immune globulin intravenous,
human – dira), 10% liquid]

Application Type / Number BLA / STN 125810/0

Proposed Indication Primary humoral immunodeficiency in patients 2
years of age or older

Submission Date: 30 June 2023

Action Due Date: 29 June 2024

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the applicant's pharmacovigilance plan (PVP) submitted under the original BLA STN 125810/0 based on the safety profile of YIMMUGO. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) are warranted and/or if there will be agreed upon safety studies as Post-Marketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for YIMMUGO, should the indication for this product be approved. Please refer to Appendix A for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Primary immunodeficiency represents a heterogeneous group of disorders resulting from largely inherited defects of the immune system. These conditions are classified into 10 major categories, including immunodeficiencies affecting cellular and humoral immunity, combined immunodeficiencies with associated or syndromic features, predominantly antibody deficiencies, defects in intrinsic and innate immunity, bone marrow failure diseases, and phenocopies of primary immunodeficiency diseases (Sullivan et al. 2023). Primary humoral deficiencies, which are under the "predominantly antibody deficiencies" category, are characterized by B-cell-intrinsic abnormalities which result in decreased B cell numbers and/or impaired antibody production and increased susceptibility to infections (Chinn 2022). Replacement therapy with immunoglobulins, either administered intravenously or subcutaneously, is a mainstay of treatment for primary humoral deficiencies with absent or deficient antibody production.

3 PRODUCT INFORMATION

3.1 Product Description

YIMMUGO is a purified, sterile 10% (100 mg/mL) liquid preparation of polyclonal human immune globulin, containing at least 96% immune globulin G (IgG). It contains (b) (4) (b) (4) of IgA. YIMMUGO is intended for intravenous administration. Several steps are used in the manufacturing process to remove/inactivate adventitious viruses, including caprylic acid and low pH treatment, anion exchange chromatography, and nanofiltration. YIMMUGO is formulated in water for injection and contains glycine and polysorbate 80 as excipients. YIMMUGO does not contain carbohydrate stabilizers (e.g., sucrose, maltose) or preservatives.

3.2 Proposed Indication

The applicant's proposed indication statement as submitted to the original BLA 125810/0 is primary humoral immunodeficiency in patients 2 years of age or older. The intravenous dosing regimen is based on body weight: (b) (4) -800 mg/kg (b) (4) -8 mL/kg) every 3-4 weeks.

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the applicant for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

YIMMUGO was approved in Germany on 11 November 2022 and in Austria on 20 December 2022 for the following indications¹:

- Replacement therapy in adults, children, and adolescents in primary immunodeficiency syndromes with impaired antibody production or secondary immunodeficiencies in patients with severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of <4 g/L.
- Immunomodulation in adults, children, and adolescents with the following conditions: primary immune thrombocytopenia (ITP), Guillain Barré syndrome, Kawasaki disease, chronic inflammatory demyelinating polyradiculopathy (CIDP), and multifocal motor neuropathy (MMN).

Additionally, YIMMUGO is marketed in Hungary based on the German marketing authorization² and in the United Kingdom³.

5 DESCRIPTION OF YIMMUGO CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical Studies

The clinical study safety data reviewed are from the Summary of Clinical Safety (SCS) submitted to STN 125810/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the applicant data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125810/0 be approved. Please refer to the package insert for the final clinical safety data.

The applicant submitted data from two completed Phase 3 clinical studies: Trials 991 and 992. Trial 991 was a pivotal IND study that was conducted in adult and pediatric subjects with primary immunodeficiency disease (PID) from Europe and the United States (U.S.). Trial 992 was a non-IND study that was conducted in adult subjects with chronic ITP from Europe. Safety data were presented for each individual study and were also pooled for the two Phase 3 studies and presented as an integrated safety analysis. The integrated safety data will not be discussed in this memorandum; since the underlying medical condition(s), IGIV doses administered, and duration of IGIV treatment differ between the two studies, it is more informative to analyze the data separately by study.

Table 1. Summary of Clinical Studies Supporting the Safety of YIMMUGO*

Study	Number of Subjects	Description	Dosage Regimen/Treatment Duration
Trial 991 (IND study)	67 subjects (49 adults and 18 pediatric)	Phase 3, prospective, uncontrolled, open-label, multicenter study evaluating	0.2-0.8 g/kg body weight, intravenously administered

¹ Source: BLA 125810/0, Module 2.5, Clinical Overview, pages 14-15.

² Source: BLA 125810/0, Module 1.2, Cover Letter (dated 28 June 2023).

³ Source: BLA 125810/0.69, Module 1.11.2, Response to Pharmacovigilance Information Request #3.

Completed	subjects) with PID	the safety, efficacy, and pharmacokinetics of YIMMUGO in adult and pediatric individuals with PID.	every 3 or 4 weeks for approximately 12 months
Trial 992 (non-IND study) Completed	34 adult subjects with chronic primary ITP	Phase 3, prospective, randomized (two YIMMUGO dosing regimens in a 1:1 ratio), uncontrolled, multicenter study evaluating the safety and efficacy of YIMMUGO in adults with chronic primary ITP.	2.0 g/kg body weight, intravenously administered as either 1.0 g/kg body weight over 2 consecutive days or 0.4 g/kg body weight for 5 consecutive days

*Adapted from Table 1, Synopses of Individual Studies, STN 125810.0, Module 2.7.6

5.2 Review of Clinical Safety Data

5.2.1 Trial 991

Trial 991 was a Phase 3, prospective, uncontrolled, open-label, multicenter study evaluating the safety, efficacy, and pharmacokinetics (PK) of YIMMUGO in adult and pediatric subjects with PID. The primary objective of the study was to demonstrate that the mean rate of acute serious bacterial infections (SBIs) was <1.0 per subject-year. Subjects received YIMMUGO at doses between 0.2 and 0.7 g/kg body weight every 3 or 4 weeks for approximately 12 months. Safety outcome measurements consisted of adverse events (AEs), vital signs, physical examinations, and labs (which included viral serology, chemistry, hematology, coagulation, urinalysis, and intravascular hemolysis parameters). Descriptive statistics were used to summarize safety results. Exploratory confidence intervals (CIs) were calculated for select safety endpoints, including two-sided 90% CIs for the proportion of subjects with treatment-emergent adverse events (TEAEs) and infusional AEs (defined as AEs occurring from the start of infusion up to 72 hours after the end of infusion).

The study population consisted of 67 subjects (49 adults and 18 pediatric subjects) with PID from the U.S. and Europe. Exclusion criteria included the following: pregnancy (or unreliable contraceptive measures) or lactation; known intolerance to immunoglobulins, proteins of human origin, or components of the study product; acquired medical conditions known to cause secondary immune deficiency; active infection and antibiotic therapy at time of screening; systemic steroids or other immunosuppressants at enrollment; history of thrombotic events within 6 months prior to YIMMUGO administration or the presence of significant risk factors for thrombotic events; hepatitis B or C; and positive HIV test.

The mean age (SD) of adult subjects was 43.8 years (14.9), ranging from 20 to 74 years; 5 subjects (7.5%) were aged ≥65 years. The mean age (SD) of pediatric subjects was 9.6 years (4.2), ranging from 2 to 16 years; there were 3 subjects aged 2 to <6 years, 9 subjects aged 6 to <12 years, and 6 subjects aged 12 to 16 years. Overall, there were slightly more male (55.2%) than female subjects and there was a higher proportion of males (83.3%) in the pediatric subgroup compared to the adult subgroup

(44.9%). Most subjects were white (98.5%) and enrolled in European study sites (31.3% were enrolled in U.S. study sites and 7.5% were enrolled elsewhere). The majority of subjects (55 subjects, 82.0%) were on a every 4-week dosing schedule.

Treatment-emergent Adverse Events

Of the 67 subjects who received YIMMUGO in the Safety Analysis Set, 63 subjects (94.0%, 90% CI: 86.9% to 97.0%) experienced 458 treatment-emergent adverse events (TEAEs). Nineteen subjects (28.4%) had mild, 40 subjects had moderate (59.7%), and 4 subjects (6.0%) had severe TEAEs. The majority of TEAEs were mild or moderate in severity; 4 of 458 (0.9%) TEAEs were assessed as severe. The most common (frequency >5.0%) TEAEs (number of subjects, % of safety population) were headache (17 subjects, 25.4%); nasopharyngitis (16 subjects, 23.9%); upper respiratory tract infection (13 subjects, 19.4%); bronchitis and sinusitis (each 8 subjects, 11.9%); pharyngitis, viral upper respiratory tract infection, and diarrhoea (each 7 subjects, 10.4%); fatigue, oropharyngeal pain, influenza, and urinary tract infection (each 6 subjects, 9.0%); arthralgia and rhinorrhea (each 5 subjects, 7.5%); conjunctivitis, cough, extra dose administered, nausea, and vomiting, (each 4 subjects, 6.0%)⁴.

The applicant calculated the frequency of infusional AEs, which were defined as AEs occurring from the start of infusion up to 72 hours after the end of infusion. Thirty-nine subjects (58.2%, 90% CI: 47.4% to 68.4%) experienced infusional AEs⁵. Across all subjects, 74 of 923 infusions (8.0% [upper limit of the one-sided 95% CI: 9.6%]) were associated with ≥1 infusional AE. Most infusional AEs were mild or moderate; there was only 1 infusional AE assessed as severe⁶. Two subjects (3.0%) experienced infusional SAEs (neutropenia, which was also the only severe infusional AE, and anaphylactic reaction); both events led to study discontinuation and were assessed by the investigator to be related to YIMMUGO. The 2 infusional SAEs leading to study discontinuation are discussed in the subsection on study discontinuations. Infusional AEs reported in ≥3 subjects were headache (13 subjects, 19.4%); fatigue (5 subjects, 7.5%); extra dose administered and nausea (each 4 subjects, 6.0%); and blood pressure increased and nasopharyngitis (3 subjects, 4.5%)⁷.

Reviewer comment: A large proportion of TEAEs (41.2%, 189/458 events) were infections, which is expected for the study population; the majority of subjects (70.1%) reported TEAEs in the MedDRA SOC of infections and infestations. Subgroup analysis

⁴ Source: BLA 125810/0, Module 5.3.5.2, Clinical Study Report for Study-991-PID, Table 12-6, pages 229-230.

⁵ The applicant also calculated the summative frequency of infusional AEs, TEAEs assessed by the investigator to be related to YIMMUGO, and TEAEs with missing causality assessment, which were collectively referred to as “FDA-specified adverse reactions (ARs)” by the applicant. Since all TEAEs assessed as related to YIMMUGO also happened to infusional AEs, and there were no TEAEs with missing causality assessment (note: for Trials 991 and 992, any TEAEs with missing causality assessment were imputed as related to YIMMUGO), events meeting the “FDA-specified AR” criteria were the same as those meeting the definition of infusional AEs.

⁶ Source: BLA 125810/0, Module 5.3.5.2, Clinical Study Report for Study-991-PID, Table 12-10, page 216.

⁷ Source: BLA 125810/0, Module 5.3.5.2, Clinical Study Report for Study-991-PID, Table 12-17, page 232.

by dosing interval was limited by the small number of subjects (n=12) who were on a 3-week dosing schedule. Overall, the profile/pattern of TEAEs are consistent with marketed IGIV products; the most common non-infection TEAEs associated with YIMMUGO (including headache, diarrhoea, fatigue, oropharyngeal pain, arthralgia, nausea, and vomiting) are labeled ARs for marketed IGIV products.

Serious Adverse Events

Nine subjects (13.4%) had a total of 12 SAEs. Three adult subjects had SAEs of neutropenia, anaphylactic reaction, and hepatitis toxic that led to study discontinuation; the SAEs are discussed in the following subsection on study discontinuations. The remaining 9 SAEs in 6 subjects were gastrointestinal viral infection, rheumatoid arthritis, anal abscess, meniscus injury, systemic scleroderma, chronic sinusitis, thermal burn, dehydration, and appendicitis. The SAEs of thermal burn, gastrointestinal viral infection, dehydration, and appendicitis occurred in 2 pediatric subjects (the latter 3 events occurred in one subject, with dehydration and appendicitis occurring in temporal proximity).

Reviewer comment: *The 9 SAEs that did not result in study discontinuation were assessed by the investigator to be not related to YIMMUGO. This reviewer agrees with the investigator's causality assessment since the events are infections for which individuals with PID are known to be at increased risk (gastrointestinal viral infection, anal abscess, and chronic sinusitis), represent pre-existing conditions (rheumatoid arthritis, systemic scleroderma, chronic pansinusitis), have a clear precipitant (meniscus injury, thermal burn), or do not have a plausible biologic explanation to be caused by YIMMUGO (appendicitis).*

Deaths and Discontinuations from the Study

There were no deaths reported in Trial 991.

A total of 7 subjects (10.4%) discontinued Trial 991; 3 subjects discontinued due to SAEs, 3 subjects discontinued due to subject decision, and informed consent was withdrawn for 1 subject. The 3 discontinuations due to SAEs of neutropenia, anaphylactic reaction, and hepatitis toxic, are summarized below. The SAEs of neutropenia and anaphylactic reaction were infusional AEs that were assessed by the investigator to be related to YIMMUGO.

- Subject (b) (6) was a 22-year-old female with a medical history of PID, thrombocytopenia, and neutropenia (the latter two were ongoing since 2016), who was on a 3-week interval dosing schedule and discontinued from the study after experiencing worsening of neutropenia after the first infusion of YIMMUGO. The event started 3.5 hours after the first infusion and resolved within 9 days. The subject's neutrophil count dropped from $1.5 \times 10^9/L$ (reference range: $1.8-7.5 \times 10^9/L$) 2 hours pre-infusion to $0.6 \times 10^9/L$ 3.5 hours after the start of infusion. The subject was asymptomatic during the event and her neutrophil count returned to baseline level ($1.2 \times 10^9/L$) on Day 8.

Reviewer comment: *This reviewer agrees with the investigator's assessment that the worsening neutropenia is related to YIMMUGO. Although there are confounding factors/other potential causes of neutropenia in this case, including PID and the participant's preexisting neutropenia, the timing of the event and biologic plausibility support that the SAE is likely due to YIMMUGO. Neutropenia is a known class effect of IGIVs and is thought to be caused by neutrophil margination to the vascular wall upon activation by complement or immune globulins or immune clearance mediated by antineutrophil antibodies or antibodies to sialic acid-binding Ig-like lectin 9 in IGIVs. Most cases of neutropenia associated with IGIVs are transient and do not require intervention (Perez et al. 2022).*

- Subject (b) (6) was a 34-year-old female on a 4-week interval dosing schedule who discontinued from the study after experiencing an anaphylactic reaction during the first infusion of YIMMUGO. Within the first 10 minutes of infusion, the subject developed coughing, vomiting, headache, hypotension (blood pressure 70/40 mmHg), tachycardia (102 beats/minute), and pelvic pain. The infusion was stopped and the subject was given prednisolone and drotaverine (an antispasmodic drug), with subsequent normalization of heart rate and blood pressure. The subject was hospitalized for monitoring.

Reviewer comment: *This reviewer agrees with the investigator's assessment that the anaphylactic reaction was related to YIMMUGO. Of note, the participant did not have a history of allergies or IgA deficiency and had previously tolerated other IGIV products without issues. Hypersensitivity, including anaphylaxis, is a known class effect of IGIVs.*

- Subject (b) (6) was a 56-year-old male with a medical history of diabetes (type not specified), alcohol abuse and poisoning, and psychological trauma who developed hepatitis 260 days after the first infusion of YIMMUGO and was discontinued from the study 84 days later due to hepatitis, alcohol abuse, and poor compliance. The subject had an increase in liver enzymes, mainly gamma-glutamyltransferase (GGT), in the setting of increased alcohol intake and alcohol abuse; GGT was increased to >10-fold of the upper limit of normal (ULN) (from baseline value of >3 ULN), with milder elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin. Per the applicant, no signs of acute viral hepatitis were found.

Reviewer comment: *This reviewer agrees with the investigator's assessment that the hepatitis was likely alcohol-related and not related to YIMMUGO. Although exact lab values were not specified in the narrative, the substantial elevations in GGT and accompanied by milder elevations of serum AST and ALT are consistent with alcoholic hepatitis.*

Adverse Events of Special Interest

Protocol-specified adverse events of special interest (AESIs) were defined as thromboembolic events (TEEs) and hemolysis. Hemolysis was defined as a decrease in hemoglobin ≥ 2.0 g/dL from screening in conjunction with serum haptoglobin below the

lower limit of normal (LLN) and increase in lactate dehydrogenase (LDH) from screening. Adverse events of special interest were required to be reported to the study sponsor within 24 hours of study site awareness of the event. In analyzing AESIs, the applicant used Standardized MedDRA Queries (SMQs); the embolic and thrombotic events SMQ and thrombophlebitis SMQ (broad scope) were used to identify TEEs and the haemolytic disorders SMQ (broad scope) was used to identify events of hemolysis.

There were no investigator reports of TEEs and the applicant's MedDRA SMQ search for TEEs did not identify any events. There were no investigator reports of hemolysis or any subjects who met the protocol-specified laboratory criteria of hemolysis. The applicant's MedDRA SMQ search for hemolysis identified 2 events (decreased haptoglobin and Coombs direct test positive), each in one subject:

- Subject (b) (6) was a 10-year-old female with unknown ABO blood type⁸ who had a TEAE of decreased haptoglobin (0.13 g/L) at the final study visit; concurrently, LDH was elevated (578 U/L) but the Coombs test was negative and the hemoglobin (12.7 g/dL) was within normal range although decreased by 1.2 g/dL from 28 days prior.

Reviewer comment: *The clinical significance of the decreased haptoglobin and elevated LDH values at the final study visit are unclear, particularly in context of the normal hemoglobin value and negative Coombs test. The clinical review team did not assess the event as treatment-emergent hemolysis.*

- Subject (b) (6) was a 28-year-old female with unknown ABO blood type, ITP, and iron deficiency anemia who had a 2.4 g/dL decrease in Hb from baseline⁹ (11.6 g/dL) to Week 52 (9.2 g/dL, nadir value) and a TEAE of Coombs direct test positive at the Week 56 final study visit. Haptoglobin, LDH, and plasma-free Hb were normal at the end of the study, and hemoglobin was 9.8 g/dL. Of note, LDH was elevated (644 U/L) at Week 40; a concurrent hemoglobin level was not available but was 9.9 g/dL and 9.8 g/dL at Weeks 36 and 44, respectively).

Reviewer comment: *The clinical review team identified Subject (b) (6) (discussed above) as having suspected mild treatment-emergent hemolysis. Subject (b) (6) 2.4 g/dL decrease in hemoglobin followed by a positive Coombs test 4 weeks later is suggestive of immune/antibody-mediated hemolysis. In their IR response, the applicant stated that Subject (b) (6)'s iron deficiency anemia and history of autoimmune hemolytic anemia were more likely explanations for the positive Coombs test and decreased hemoglobin, citing that all other indicators for hemolysis were unremarkable at Week 56 and that hemoglobin was comparable to prior visits (the subject's hemoglobin was 10.0 g/dL at screening, which was lower than the baseline value of*

⁸ The applicant stated that the ABO blood types of Subjects (b) (6) in Trial 991 were unknown. Source: BLA 125810/0.46, Module 1.11.2, Response to Clinical Information Request #3.

⁹ Baseline was defined as the last available value before the first infusion of study drug and could be any visit between screening (initial visit) and Day 1.

11.6 g/dL)¹⁰. Although the normal haptoglobin and LDH values at Week 56 are inconsistent with intravascular hemolysis, normal haptoglobin and LDH levels can be seen in extravascular hemolysis (Krishnadasan 2021), and IGIV-related hemolysis may involve both intravascular and extravascular hemolytic mechanisms (Padmore 2012, Flegel 2015). Although positive Coombs test without clinically apparent hemolysis occasionally may be seen in healthy individuals and in 1-15% of hospitalized patients (Hannon 2012, Zarandona et al. 2006), IGIV-related hemolysis cannot be ruled out in this case due to the lack of a clear alternative explanation for the positive Coombs test and decrease in hemoglobin.

This reviewer notes that the assessment of hemolysis in Subjects (b) (6) was limited by the incomplete hemolysis labs that were obtained during the nadir hemoglobin levels. Additionally, a reticulocyte index may have been helpful to distinguish between iron deficiency anemia and hemolysis, and an eluate to confirm the specificity of the antibodies implicated in the positive Coombs test.

Additional AESIs of concern to this reviewer included other adverse reactions (ARs) which have been reported for immune globulin products, including hypersensitivity, neutropenia/leukopenia, renal dysfunction/failure, transfusion-related acute lung injury (TRALI), aseptic meningitis syndrome (AMS), and transmissible infectious agents. Per the applicant, there were no additional events of hypersensitivity or neutropenia/leukopenia observed with YIMMUGO during the clinical studies, aside from the 1 event each of anaphylaxis and neutropenia in Trial 991, which were discussed in the study discontinuations subsection of this memo. Additionally, the applicant stated that there were no events of renal dysfunction, renal failure, or increased serum creatinine levels; TRALI; or AMS observed with YIMMUGO in either study. There were no AEs of transmissible infectious agents reported by the applicant.

Reviewer comment: The use of premedication was discouraged in Trial 991 and was limited to situations concerning participant safety. Only one subject in Trial 991 received premedication with acetaminophen and dexchlorpheniramine for a history of previous infusion reactions. Hypersensitivity is an important identified risk in the applicant's proposed pharmacovigilance plan (PVP) and renal dysfunction/failure is included in the Boxed Warning as well as the Warnings and Precautions section of the proposed USPI. Of note, YIMMUGO does not contain sucrose, which has been implicated in acute renal dysfunction/failure in the setting of IGIV administration.

Pregnancies

There were no pregnancies or lactating subjects reported for Trial 991.

Subgroup Analyses

Overall, subgroup analyses were limited by small sample sizes. Per the applicant, subgroup analyses by age, gender, and geographic region did not raise notable safety concerns or clinically relevant differences.

¹⁰ Source: BLA 125810/0.39, Module 1.11.2, Response to Clinical Information Request #2.

Reviewer comment: *Subgroup analysis by age was limited by the small number of pediatric (n=18) and geriatric (age ≥65 years, n=5) subjects. The proportion of subjects experiencing TEAEs was comparable between the pediatric (100%, 18/18 subjects) and overall adult (91.8%, 45/49 subjects) subgroups. However, a higher proportion (83.3%, 15/18 subjects) of pediatric subjects experienced infusional AEs compared to overall adults (49.0%, 24/49 subjects). Four of the 5 (80%) geriatric subjects experienced infusional AEs. Headache, which was the most frequent non-infection TEAE overall, was reported more frequently in pediatric subjects (44.4%, 8/18 subjects) than in adults (18.4%, 9/49 subjects). It is unclear whether differences in TEAEs between the pediatric and adult subgroups are of clinical significance or are due to random chance. Please refer to the clinical review memo for a detailed assessment of safety and efficacy for the pediatric subgroup.*

5.2.2 Trial 992

Trial 992 was a Phase 3, prospective, open-label, multicenter study evaluating the safety and efficacy of YIMMUGO in adult subjects with chronic ITP. The primary objective of the study was to determine the subject response rate (defined as a platelet count of $\geq 30 \times 10^9/L$ and ≥ 2 -fold increase of the baseline count, confirmed on ≥ 2 separate occasions at least 7 days apart, and the absence of bleeding). The exclusion criteria were similar to those of Trial 992. Notable exclusion criteria included high-dose corticosteroid or other immunosuppressant therapy within 1 month prior to study start; a history of thrombotic events within 6 months prior to the start of YIMMUGO or the presence of significant risk factors for thrombotic events; and absolute IgA deficiency or known antibodies to IgA. Subjects were randomized in a 1:1 ratio to one of the following YIMMUGO dosing regimens (the total dose for both regimens was 2.0 g/kg body weight per treatment course): 1.0 g/kg body weight administered intravenously over 2 consecutive days or 0.4 g/kg body weight for 5 consecutive days. Safety outcome measurements were similar to that of Trial 991. The final study visit was 36 days after the first YIMMUGO infusion.

The mean age (SD) of the 34 subjects in the Safety Analysis Set was 45.7 (16.9) years, ranging from 19 to 74 years. There were 7 subjects (20.6%) aged ≥ 65 years. There were more female (58.8%) than male subjects.

Treatment-emergent Adverse Events

Overall, 27 of 34 subjects (79.4%, 90% CI: 64.8% to 89.9%) experienced TEAEs. Twenty-six subjects (76.5%) had mild TEAEs, and there were 5 subjects (14.7%) each who had moderate and severe TEAEs. The majority of TEAEs were mild to moderate in severity; 6 of 34 (7.1%) TEAEs were assessed as severe. The majority of the most common (frequency $>10\%$) TEAEs were those conceptually related to ITP: petechiae (23.5%); gingival bleeding (14.7%); and ecchymosis, platelet count decreased, and subcutaneous hematoma (each 11.8%). Excluding these events, TEAEs reported by $\geq 5\%$ of subjects in decreasing order of frequency were headache (7 subjects, 20.6%), intravascular hemolysis (5 subjects, 14.7%), Coombs test positive (4 subjects, 11.8%), rash (3 subjects, 8.8%), oropharyngeal pain (2 subjects, 5.9%), and red blood cell sedimentation rate increased (2 subjects, 5.9%). Of the 6 severe TEAEs (in 5 subjects),

5 events were likely reflective of the underlying illness (ITP): platelet count decreased (3 subjects), ITP (1 subject), and platelet count decrease (1 subject). The sixth severe TEAE was transient intravascular hemolysis, which is discussed in the Trial 992 AESI subsection of this memo.

Nineteen subjects (55.9%, 90% CI: 40.5% to 70.5%) reported infusional AEs. There was one infusional SAE of anemia and one non-serious infusional AE of anemia; the SAE of anemia is discussed in the Trial 992 SAE subsection of this memo. The most frequent infusional AE was headache (7 subjects, 20.6%). Excluding bleeding events, the only other infusional AEs reported in ≥ 1 subject was Coombs test positive and red blood cell sedimentation rate increased, which were reported in 2 subjects (5.9%) each.

One subject (2.9%) (Subject (b) (6)) had a non-serious TEAE of asthma leading to YIMMUGO discontinuation after the fourth infusion. The subject was a 41-year-old female with a past medical history of ITP and asthma. On Day 4 of the 5-day infusion schedule, the subject experienced worsening asthma symptoms, initially reported as dyspnea. A CT scan of the thorax was negative for TEE. The event was assessed by the investigator to be unrelated to YIMMUGO. The subject missed the last infusion but completed the study. Per the applicant, there were no other instances of YIMMUGO dose modifications or interruptions due to TEAEs¹¹.

Reviewer comment: *Although Subject (b) (6) dyspnea is likely due to an asthma flare/exacerbation, it is unclear whether product-related hypersensitivity may have contributed to her symptoms. The narrative did not mention any other associated symptoms and signs. Overall, the profile/pattern of TEAEs reported in Trial 992 were consistent with the study population's underlying medical condition of ITP or were known AEs associated with immune globulins.*

Serious Adverse Events

One subject (2.9%), subject (b) (6) experienced an SAE of anemia, which was assessed by the investigator to be unrelated to YIMMUGO. The subject was a 64-year-old group A male with ITP who had a drop in hemoglobin from 16.1 g/dL at screening to 12.9 g/dL on Day 8, which was three days after the last YIMMUGO infusion. Concurrent hemolysis labs on Day 8 were notable for elevated LDH (569 U/L) and low serum haptoglobin (0.1 g/L); Coombs test was negative. The subject's hemoglobin level further decreased to 10.5 g/dL ten days after the last infusion. Per the applicant, there was no clinical evidence of acute bleeding. The subject was given folic acid for anemia and the event was considered resolved a month later.

Reviewer comment: *This reviewer disagrees with the investigator's assessment that the anemia was unrelated to YIMMUGO. The participant's non-O blood group and exposure to higher immunomodulatory doses of IGIV are risk factors for IGIV-related hemolysis (Perez et al. 2022). While it is possible that the participant's anemia could have been caused by an internal bleeding event due to ITP, IGIV-related hemolysis*

¹¹ Source: BLA 125810/0, Source: BLA 125810/0, Module 5.3.5.4, Clinical Study Report for Study-992-ITP, page 98.

cannot be ruled out in the setting elevated LDH and decreased haptoglobin (the Coombs test may be negative following a severe hemolytic episode in which all antibody-coated red blood cells have been destroyed).

Deaths and Discontinuations from the Study

There were no deaths reported in Trial 992. One subject discontinued the study due to subject decision (i.e., not for a medical reason).

Adverse Events of Special Interest

Similar to Trial 991, protocol specified AESIs were defined as TEEs and hemolysis in Trial 992. There were no investigator reports of TEEs and the applicant's MedDRA SMQ search for TEEs did not identify any events.

There were 5 subjects (14.7%) with investigator reported AESIs of hemolysis (2 events of intravascular hemolysis and 3 events of hemolysis); all events were non-serious and assessed by the investigator as related to YIMMUGO. Two of the five subjects (Subject IDs (b) (6) and (b) (6)) exhibited clinical signs of hemolysis (icterus and dark urine). The narratives are summarized below:

- Subject (b) (6) was a 37-year-old female with unknown ABO blood type who was on a 5-day infusion schedule. On Day 8, three days after the final infusion, the subject had a 3.4 g/dL decrease in hemoglobin from baseline (13.5 g/dL), positive Coombs test, high LDH (2750 U/L), high total bilirubin (109 umol/L), high direct bilirubin (20 umol/L), and increased reticulocytes (14.7%). Hemoglobin decreased further to 9.6 g/dL on Day 15. Grade 2 icterus was reported. The event resolved after 15 days.
- Subject (b) (6) was a 68-year-old male with unknown ABO blood type who was on a 2-day infusion schedule. On Day 8, six days after the final infusion, the subject had a 2.6 g/dL decrease in hemoglobin from baseline, positive Coombs test, low haptoglobin (0.1 g/L), and high LDH (493 U/L). The subject did not have any clinical symptoms and the event resolved after 8 days.
- Subject (b) (6) was a 35-year-old male with unknown ABO blood type who was on a 2-day infusion schedule. On Day 8, six days after the final infusion, the subject had a 2.0 g/dL decrease in hemoglobin from baseline, low haptoglobin (0.005 g/L), and high direct bilirubin (5.2 umol/L); total bilirubin and LDH were normal and Coombs test and urine hemosiderin were negative. Reticulocytes were increased (4.5%). The subject was asymptomatic and the event resolved after 13 days.
- Subject (b) (6) was a 47-year-old group A male who was on a 2-day infusion schedule. Four days after the last infusion, the subject developed dark urine and on was found to have a 3.8 g/dL decrease in hemoglobin from baseline on Day 8. Other concurrent lab abnormalities included high total (30 umol/L) and direct (4.7 umol/L) bilirubin, low haptoglobin (0.01 g/L), and increased reticulocytes. Coombs test was negative. The subject was asymptomatic and the event resolved after 7 days.
- Subject (b) (6) was a 50-year-old group A female on a 2-day infusion schedule. On Day 8, six days after the final infusion, the subject had a 4.3 g/dL decrease in

hemoglobin from baseline, low haptoglobin (0.02 g/L), high LDH (769 U/L), and positive Coombs test. The event resolved 15 days after.

The applicant's MedDRA SMQ for haemolytic disorders identified all 5 cases of the investigator-reported cases of hemolysis discussed previously as well as 4 additional events of positive Coombs test in 4 subjects (11.8%).

Reviewer comment: *This reviewer agrees that the five investigator reported cases of hemolysis were likely related to YIMMUGO. Risk factors for IGIV-related hemolysis include high-dose infusions (1 to 2 g/kg/day) and non-O blood group. Four (of the 5) investigator reported cases of hemolysis were in the 2-day dosing schedule group, and 2 subjects were blood group A (ABO blood type was not specified for the other 3 subjects). In their response to Clinical Information Request #2, the applicant clarified that a total of 12 subjects had a positive Coombs test on Day 8; of these 12 subjects, 3 subjects (Subject IDs (b) (6)) had AESIs of hemolysis (which were discussed above)¹². The applicant stated that the other 9 subjects with positive Coombs tests did not experience clinically significant decreases in hemoglobin or any lab values suggestive of hemolysis.*

Pregnancies

There were no pregnancies or lactating subjects reported for Trial 992.

6 SUMMARY OF FOREIGN POSTMARKETING EXPERIENCE

6.1 Applicant's Analysis

The International Birth Date for YIMMUGO is 11 November 2022, which is the date it was first approved in Germany. In addition to Germany, YIMMUGO is marketed in Austria, Hungary, and the United Kingdom. The submitted Periodic Safety Update Report (PSUR) (covering the reporting period 11 November 2022 to 10 May 2023) and an updated cumulative summary of foreign postmarketing experience for YIMMUGO (covering the reporting period 11 November 2022 to 24 March 2024) were reviewed. As of 24 March 2024, the estimated cumulative patient exposure in the postmarketing setting is 23,577 doses, corresponding to 1,814 patient years¹³.

During the PSUR reporting interval, one batch of YIMMUGO (batch (b) (4)) was voluntarily withdrawn on (b) (4) by the applicant due to an increased number of hypersensitivity AEs reported for the batch. Per the applicant, all 20 individual case study reports (corresponding to 46 events, all from Germany) received during the PSUR reporting interval were of hypersensitivity or hypersensitivity associated symptoms and involved the withdrawn batch. There were 11 reports of hypersensitivity, 1 report of severe anaphylactic reaction, and 8 reports of cutaneous hypersensitivity reactions such as urticaria, rash, and pruritis. Five cases (25%) were serious and involved respiratory symptoms (dyspnea, wheezing, throat tightness) and/or hypotension. Per the applicant, quality investigations were unremarkable to date.

¹² Source: BLA 125810/0.39, Module 1.11.2, Response to Clinical Information Request #2, pages 4-6.

¹³ Source: BLA 125810/0.69, Module 1.11.2, Response to Pharmacovigilance Information Request #3.

During the time interval since the PSUR (11 May 2023 to 24 March 2024), there were 18 individual case study reports corresponding to 33 events. Four events were serious, with the latter two occurring in one case: urticaria, shunt thrombosis, haemolytic anaemia, and thromboembolism. The most common (≥ 3 events) non-serious AEs were chills (n=5 events), nausea (n=4), and headache (n=3).

The events of haemolytic anaemia and thromboembolism occurred in the same patient; a 53-year-old female with unknown ABO blood type and multifocal motor neuropathy who received immunomodulatory doses of YIMMUGO (2.3 g/kg) over 5 days experienced both thromboembolism and haemolytic anaemia 2 days after the last dose of YIMMUGO. Per the applicant, the patient did not experience any clinical symptoms and no treatment was reported. Notable labs included a decrease in hemoglobin from 16.4 g/dL to 7.2 g/dL, accompanied by a decrease in haptoglobin (to 0.1 g/L) and increases in LDH (to >500 U/L) and bilirubin. The patient also had a right renal vein thrombus detected on CT scan.

Limited information was provided on the case of shunt thrombosis. The subject had a history of scleromyxedema and prior shunt thrombosis and was diagnosed with shunt thrombosis during dialysis two months after starting YIMMUGO. It is unclear whether the patient had an arteriovenous fistula or a synthetic graft for hemodialysis access.

Reviewer comment: *The majority of foreign postmarketing cases for YIMMUGO involved hypersensitivity events, which resulted in the voluntary withdrawal of a batch of YIMMUGO (b) (4) for increased number of hypersensitivity AEs. Overall, 5 of 22 hypersensitivity reaction cases were assessed as serious and involved generalized urticaria, respiratory, and/or systemic symptoms. The applicant stated that since the voluntary withdrawal of the implicated batch of YIMMUGO, the number of hypersensitivity reactions has returned to baseline.*

It is this reviewer's opinion that the two postmarketing cases of TEEs could possibly be related to YIMMUGO, although the patient with shunt thrombosis had predisposing risk factors for thrombosis (previous thromboembolism, chronic kidney disease, and hemodialysis access). It is unclear whether the patient who experienced shunt thrombosis had an arteriovenous fistula or a synthetic graft for hemodialysis access. Thrombosis is a known complication of both, although rates of thrombosis are higher for synthetic grafts compared with fistulas.

7 APPLICANT'S PHARMACOVIGILANCE PLAN

The applicant submitted an initial pharmacovigilance plan (PVP) (EU Risk Management Plan for Yimmugo (Human normal immunoglobulin (IVIg))), version 0.2, dated 26 August 2022) proposing routine pharmacovigilance (PV) activities, which includes the review and reporting of adverse reactions from the postmarketing setting, signal detection and management, periodic safety reports, and literature review¹⁴. Following Information

¹⁴ Source: BLA 125810/0.13, Module 1.11.1, Description of the Routine Pharmacovigilance Activities, dated 19 September 2023.

Requests from OBPV/DPV to add “use in pregnancy and lactation” as missing information, reclassify “hemolytic anemia” as an important identified risk, and add thromboembolic events as an important potential risk, the applicant submitted a revised PVP, version 0.5. The revised PVP, version 0.5, will be the focus of this review. The applicant’s summary of important identified risks, important potential risks, and missing information is outlined in Table 2.

Table 2. Applicant’s Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important Identified Risk	Hypersensitivity, including anaphylaxis	<p>Routine risk minimization measures, including routine risk communication (including labeling)</p> <p>Routine PV activities, including specific adverse reaction follow-up questionnaires</p> <p>Additional PV activities: none</p>
Important Identified Risk	Hemolytic anemia	<p>Routine risk minimization measures, including routine risk communication (including labeling)</p> <p>Routine PV activities, including specific adverse reaction follow-up questionnaires</p> <p>Additional PV activities: FDA-required enhanced PV activities for 3 years following licensure, which consists of the following activities:</p> <ul style="list-style-type: none"> • Submission of expedited reports (i.e., 15-day reports) for all AEs involving hemolysis, regardless of label status or seriousness • Submission of license holder’s assessment

		(based on interval and cumulative data) of the risk of hemolysis, with specific analysis of this risk among patients with primary humoral immunodeficiency, in periodic safety reports
Important Potential Risk	Thromboembolic events	Routine risk minimization measures, including routine risk communication (including labeling), and routine PV activities. Additional PV activities: none
Missing Information	Use in pregnancy and lactation	Routine risk minimization measures, including routine risk communication (including labeling) Routine PV activities, including follow-up questionnaires regarding pregnancy outcomes Additional PV activities: none

*Adapted from Risk Management Plan for Yimmugo (Human normal immunoglobulin (IVIg)), version 0.5, Module 1.16.1.

8 ANALYSIS OF APPLICANT’S PHARMACOVIGILANCE PLAN

8.1 Important Identified Risks

8.1.1 Hypersensitivity Including Anaphylaxis

Hypersensitivity reactions are a known AR with immune globulin products; severe hypersensitivity reactions (including anaphylaxis) are less frequent than mild allergic-type reactions. Although hypersensitivity is a known AR for immunoglobulin products, product lots associated with an increased frequency of hypersensitivity reactions can pose a safety issue to patients. There was one event of anaphylaxis in Trial 991. Additionally, one batch of YIMMUGO (batch (b) (4)) was voluntarily withdrawn on

(b) (4) by the applicant due to an increased number of hypersensitivity AEs reported for the batch.

Hypersensitivity is an important identified risk in the applicant's proposed pharmacovigilance plan (PVP). The applicant proposes to use an event-specific questionnaire to follow-up on postmarketing reports of hypersensitivity. Hypersensitivity, including anaphylaxis, is included in the WARNINGS AND PRECAUTIONS section and in the ADVERSE REACTIONS section of the proposed USPI. The applicant's proposed risk minimization activities are acceptable.

8.1.2 Hemolytic Anemia

Hemolysis, including clinically significant hemolytic anemia, can occur with IGIV products. Plasma derivatives may contain blood group antibodies which can bind to recipient red blood cells and induce hemolysis. Risk factors for IGIV-related hemolysis include high-dose infusions (1 to 2 g/kg/day), high IGIV doses, female sex, and non-O blood group (Perez et al. 2022). In Trial 991, there were no investigator reports of hemolysis or any subjects who met the protocol-specified laboratory criteria of hemolysis. However, Subject (b) (6) had a drop in hemoglobin accompanied by other lab findings supportive of hemolysis, for which the applicant did not have a clear alternative explanation; the subject was assessed by the clinical review team as having suspected treatment-emergent hemolysis. In Trial 992, 5 subjects (14.7%) had investigator reported AESIs of hemolysis, of which 2 subjects had clinical signs of hemolysis (icterus and dark urine). There was an additional subject (Subject (b) (6)) in Trial 992 who had anemia and laboratory findings consistent with hemolysis (decrease in hemoglobin in conjunction with elevated LDH and low haptoglobin). The absence of investigator reported AESIs of hemolysis in Trial 991 may be explained by the IGIV doses used in the study; Trial 991 used lower replacement doses compared Trial 992, which used higher IGIV doses used in the setting of immunomodulation for treatment of ITP.

Routine risk minimization measures proposed by the applicant includes risk communication in the USPI. The WARNINGS AND PRECAUTIONS section of the proposed USPI includes a subsection on hemolysis, including risk factors for hemolysis (high doses (e.g., ≥ 2 g/kg), non-O blood group) and suggestions for monitoring. Hemolysis is also included in the ADVERSE REACTIONS section (in both *Clinical Trials Experience* and *Postmarketing Experience* subsections). Given that hemolysis has occurred with YIMMUGO in both the clinical trial and postmarketing settings, and that YIMMUGO conformance lots for US distribution post-licensure were found to have hemagglutinin titers (b) (4) comparable to lots of another marketed IGIV product which was withdrawn for hemolysis¹⁵, the applicant will be required by FDA to conduct enhanced pharmacovigilance activities for all AEs involving hemolysis for a period of 3 years following licensure if the product is approved.

¹⁵ OPBV-OTP Safety Assessment Meeting: Immune globulins and hemolysis: YIMMUGO (original BLA undergoing review), 05 April 2024.

8.2 Important Potential Risks

8.2.1 Thromboembolic Events

Immune globulin products carry a Boxed Warning regarding the risk of thromboembolic events (TEEs). Risk factors for TEEs in the setting of immune globulin administration include hereditary hypercoagulable states, hyperviscosity, malignancy, indwelling catheters, autoimmunity or connective tissue disease, older age, estrogen use, previous thrombotic events, and immobilization (Stiehm 2013). Additionally, increased levels of procoagulant activity have been implicated in some TEEs in the past, specifically with the IGIV product OCTAGAM.

There were no investigator reports of TEEs and the applicant's MedDRA SMQ search for TEEs did not identify any events in either Trial 991 or 992. As of 24 March 2024, there were two reports of TEEs in the postmarketing setting. Routine risk minimization measures proposed by the applicant includes risk communication in the USPI. The proposed USPI includes a Boxed Warning addressing thrombosis and the WARNINGS AND PRECAUTIONS section includes a subsection on thrombosis. Thromboembolic events are also included in the *Postmarketing Experience* subsection. The applicant's proposed risk minimization activities are acceptable.

8.3 Important Missing Information

8.3.1 Use in Pregnancy and Lactation

Although pregnant or lactating individuals were excluded from the clinical trials of YIMMUGO, it is expected that these individuals will be treated with YIMMUGO if it is approved. Individuals with PID may become pregnant, and pregnant and lactating individuals may develop neuroimmunologic or autoimmune conditions which may be treated with immune globulin products.

The placental transfer of IgG in humans starts around 13 weeks gestation, with fetal IgG levels reaching 50% of maternal levels by 32 weeks and exceeding maternal plasma IgG levels at birth (Palmeira et al. 2012). Human breast milk contains transferred IgG and IgM antibodies, although secretory IgA antibodies accounts for the majority of breast milk antibodies (Andreas et al. 2015). The applicant did not conduct any preclinical studies assessing the potential effects of YIMMUGO on reproductive function or embryofetal, perinatal, and postnatal development, stating that 1) such studies are not warranted as immunoglobulins are endogenous proteins and 2) the immunogenic potential of human IgG in animals limit such studies¹⁶. There were no reported pregnancies or lactating subjects in the clinical trials of YIMMUGO.

The applicant proposes routine pharmacovigilance for the important missing information of use in pregnancy and lactation. Proposed risk minimization measures include risk communication in the USPI; the relevant subsections reflect that there are no data available to indicate the presence or absence of drug-associated risk in pregnant or lactating individuals. In addition to recording all case reports involving pregnancy and

¹⁶ Source: BLA 125810/0, Module 2.4, Nonclinical Overview, page 13.

lactation in the global safety database, the applicant will use follow-up questionnaires to obtain information regarding pregnancy outcome. The applicant's proposal to conduct routine pharmacovigilance is acceptable, considering that immune globulins are endogenous proteins in humans that are known to be transferred across the placenta and secreted in breast milk, with protective effects on the fetus and neonate (Atyeo et al. 2021).

9 DPV ASSESSMENT

The submitted data show that overall, the safety profile of YIMMUGO is comparable to other marketed IGIV products. The FDA's review of foreign postmarketing data did not reveal any new or concerning safety-related findings. Hypersensitivity events and hemolysis have been observed during the clinical trial and postmarketing settings, with the majority of hemolysis events occurring in the setting of higher immunomodulatory doses. Both hypersensitivity and hemolytic anemia are included as important identified risks in the applicant's PVP, and in the event of approval, the applicant will be required to conduct enhanced pharmacovigilance activities for all AEs involving hemolysis for a period of 3 years post-licensure. Regarding other adverse reactions that have been reported with immune globulin products, there were two postmarketing reports of TEEs. Thromboembolic events are included as an important potential risk in the applicant's PVP. Given the small number of thromboembolic events, it is reasonable to monitor for additional events post-approval through routine pharmacovigilance. Use in pregnancy and lactation is included as important missing information in the applicant's PVP, for which OBPV/DPV agrees with the applicant's proposal for routine risk minimization, including labeling.

10 DPV RECOMMENDATIONS

The proposed pharmacovigilance plan for YIMMUGO (version 0.5, dated 06 May 2024) is adequate should the proposed indication of primary humoral deficiency in patients 2 years of age or older be approved. The available data do not indicate a safety signal which would require either a Risk Evaluation and Mitigation Strategy (REMS) or a postmarketing requirement (PMR) or postmarketing commitment (PMC) study that is specifically designed to evaluate a particular safety issue as a primary endpoint. Please see the final version of the package insert submitted by the applicant for the final agreed-upon language for the label. OBPV/DPV recommends the following for postmarketing safety monitoring of YIMMUGO:

- Routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.
- Enhanced pharmacovigilance activities for AEs involving hemolysis for a period of 3 years post-licensure. Enhanced pharmacovigilance activities include:
 - Expedited reporting of all AEs involving hemolysis, regardless of label status or seriousness.
 - Submission of 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.
- The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement (PMR)

study at this time. There is no safety-related study as an agreed upon postmarketing commitment (PMC) at this time.

REFERENCES

1. Sullivan KE and Jyonouchi SC. Inborn errors of immunity (primary immunodeficiencies): classification. In *UpToDate*. Topic last updated 31 May 2023. Retrieved 06 July 2023 from https://www.uptodate.com/contents/inborn-errors-of-immunity-primary-immunodeficiencies-classification?search=primary%20humoral%20immunodeficiency&topicRef=3914&source=see_link.
2. Chinn IK. Primary humoral deficiencies: an overview. In *UpToDate*. Topic last updated 30 June 2022. Retrieved 06 July 2023 from https://www.uptodate.com/contents/primary-humoral-immunodeficiencies-an-overview?search=primary%20humoral%20immunodeficiency&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2048869491.
3. Perez EE and Shehata N. Intravenous immune globulin: adverse effects. In *UpToDate*. Topic last updated 14 November 2022. Retrieved 26 July 2023 from https://www.uptodate.com/contents/intravenous-immune-globulin-adverse-effects?search=igiv&source=search_result&selectedTitle=3~148&usage_type=default&display_rank=2#H25.
4. Krishnadasan R. Hemolytic anemias: autoimmune and beyond. *J Adv Pract Oncol*. 2021;12:337-340.
5. Padmore RF. Hemolysis upon intravenous immunoglobulin transfusion. *Transfusion and Apheresis Science* 2012;46:93-96.
6. Flegel WA. Pathogenesis and mechanisms of antibody-mediated hemolysis. *Transfusion* 2015;55:S47-58.
7. Hannon JL. Management of blood donors and blood donations from individuals found to have a positive direct antiglobulin test. *Transfusion Medicine Reviews* 2012;26:142-152.
8. Zarandona JM and Yazer MH. The role of the Coombs test in evaluating hemolysis in adults. *CMAJ* 2006;174:305-307.
9. Stiehm ER. Adverse effects of human immunoglobulin therapy. *Transfusion Medicine Reviews* 2013;27:171-178.
10. Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol*. 2012;2012:985646. doi:10.1155/2012/985646. Epub 2011 Oct 1.
11. Andreas NJ, Kampmann B, and Le-Doare KM. Human breast milk. *Early Human Development* 2015;91:629-635.
12. Atyeo C and Alter G. The multifaceted roles of breast milk antibodies. *Cell* 2021;184:1486-1499.

APPENDIX A
Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
30 June 2023	Biotest AG	STN 125810/0	Module 1.2, Cover Letter, Reviewers Guide
30 June 2023	Biotest AG	STN 125810/0	Module 1.14.1.3, Draft Labeling Text
30 June 2023	Biotest AG	STN 125810/0	Module 1.16.1, EU Risk Management Plan (version 0.2) for YIMMUGO
30 June 2023	Biotest AG	STN 125810/0	Module 2.2, Introduction
30 June 2023	Biotest AG	STN 125810/0	Module 2.5, Clinical Overview
30 June 2023	Biotest AG	STN 125810/0	Module 2.7.4, Summary of Clinical Safety
30 June 2023	Biotest AG	STN 125810/0	Module 2.7.6, Synopses of Individual Studies
30 June 2023	Biotest AG	STN 125810/0	Module 5.3.5.2, Clinical Study Report for Study-991-PID
30 June 2023	Biotest AG	STN 125810/0	Module 5.3.5.4, Clinical Study Report for Study-992-ITP
30 June 2023	Biotest AG	STN 125810/0	Module 5.3.5.3, Integrated Summary of Safety
18 August 2023	Biotest AG	STN 125810/0.7	Module 1.11.2, Response to Clinical Information Request #1, dated 16 August 2023
18 August 2023	Biotest AG	STN 125810/0.7	Module 1.11.2, Periodic Safety Update Report for YIMMUGO, dated 28 June 2023
20 September 2023	Biotest AG	STN 125810/0.13	Module 1.11.2, Response to Pharmacovigilance Information Request #1, dated 07 September 2023
20 September 2023	Biotest AG	STN 125810/0.13	Module 1.16.1, Description of the Routine Pharmacovigilance Activities
22 December 2023	Biotest AG	STN 125810/0.37	Module 1.11.2, Response to Pharmacovigilance Information Request #2, dated 12 December 2023
22 December 2023	Biotest AG	STN 125810/0.37	Module 1.16.1, Risk Management Plan (version 0.3) for YIMMUGO
03 January 2024	Biotest AG	STN 125810/0.39	Module 1.11.2, Response to Clinical Information Request #2, dated 21 December 2023
26 January 2024	Biotest AG	STN 125810/0.46	Module 1.11.2, Response to Clinical Information Request #3, dated 23 January 2024
28 March 2024	Biotest AG	STN 125810/0.69	Module 1.11.2, Response to Pharmacovigilance Information Request #3, dated 22 March 2024

Date	Source	Document Type	Document(s) Reviewed
16 April 2024	Biotest AG	STN 125810/0.74	Module 1.11.2, Response to Pharmacovigilance Information Request #4, dated 08 April 2024
16 April 2024	Biotest AG	STN 125810/0.74	Module 1.16.1, Risk Management Plan (version 0.4) for YIMMUGO
07 May 2024	Biotest AG	STN 125810/0.82	Module 1.11.2, Response to Pharmacovigilance Information Request #5, dated 30 April 2024
07 May 2024	Biotest AG	STN 125810/0.82	Module 1.16.1, Risk Management Plan (version 0.5) for YIMMUGO