Application Type	Original BLA
STN	125810/0
CBER Received Date	06/30/2023
PDUFA Goal Date	06/29/2024
Division / Office	DCEGM/OCE/OTP
Committee Chair	Michael Kennedy, Ph.D.
Clinical Reviewer(s)	Afsah Amin, MD
Project Manager	Mona Badawy
Priority Review	No
Reviewer Name(s)	Hairong Shi, Ph.D., Mathematical Statistician, TEB2/DB/OBPV
Supervisory Concurrence	Lin Huo, Ph.D., Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D., Branch Chief, TEB2/DB/OBPV
	Shiowjen Lee, Ph.D., Deputy Division Director, DB/OBPV
Applicant	Biotest AG
Established Name	Immune globulin intravenous, human
(Proposed) Trade Name	YIMMUGO
Formulation(s), including Adjuvants, etc.	Contains not less than 96% IgG. The distribution of IgG subclasses is approximately (b) (4) IgG1,(b) (4) IgG2,(b) (4) IgG3, (b) (4) IgG4, which is similar to that of normal plasma, formulated in water for injection containing glycine with polysorbate 80.
Dosage Form(s) and Route(s) of Administration	A solution containing 10% IgG (100 mg/mL): 5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL for intravenous use only
Dosing Regimen	300–800 mg/kg body weight (3–8 mL/kg bw) every 3–4 weeks
Indication(s) and Intended Population(s)	Treatment of primary humoral immunodeficiency (PI) in patients 2 years of age or older.

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GLOSSARY

AE	adverse event
BLA	biologics license application
CI	confidence interval
CL	confidence limit
FAS	full analysis set
FDA	Food and Drug Administration
IgG	immunoglobulin
IMP	investigational medicinal product
IND	investigational new drug application
ITP	immune thrombocytopenia
IV	intravenous
IVIg	intravenous immunoglobulin
PI	primary humoral immunodeficiency
PK	pharmacokinetic
PPS	per-protocol set
Q3W	every-3-week dosing schedule
Q4W	every-4-week dosing schedule
SBI	serious bacterial infection

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1. EXECUTIVE SUMMARY

This biologics license application (BLA) is for approval of a new intravenous 10% human immunoglobulin (IVIg) Next Generation (YIMMUGO, also referred to as BT595 in this memo), for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age or older. The evidence to support the efficacy and safety of the product in the proposed indication was based on the results of Study 991.

Study 991 was a Phase 3, prospective, open-label, multicenter study investigating clinical efficacy, safety, and pharmacokinetic (PK) properties of the human normal IVIg BT595 as replacement therapy in patients with PI administered every 3 or 4 weeks for approximately 12 months. The primary efficacy endpoint was the incidence of acute serious bacterial infections (SBIs). To meet the success criterion for the primary endpoint, the upper one-sided 99% confidence limit (CL) for the rate of SBIs with BT595 must be less than 1.0 per person-year.

Of the 67 enrolled subjects, 5 SBIs were reported on 5 subjects (1 each in 3 adults and 2 children). This resulted in an annualized rate of SBIs of 0.074 per person-year with a 99% one-sided upper CL of 0.21, which met the efficacy success criterion.

No deaths occurred in the study. There were two serious adverse events (SAEs) related to YIMMUGO. One subject had anaphylactic reaction, and one subject had severe neutropenia. Both SAEs led to subjects discontinuing YIMMUGO. The adverse reactions observed in ≥5% of subjects included headache (19%), upper respiratory tract infections (12%), fatigue (8%), nausea (6%), and increased blood pressure (6%).

In summary, there were no major statistical issues related to the efficacy data submission. Primary efficacy was demonstrated based on the pre-specified criterion. There are no serious safety concerns based on the submitted data. Therefore, I recommend approval of YIMMUGO for treatment of PI in patients 2 years of age or older.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

PIs are a class of disorders in which there is an intrinsic defect in the human immune system. PIs result from largely inherited, diverse defects of the immune system, and affect approximately 1% to 2% of the population worldwide. PI affects men and women and occurs in both pediatric and adult patients. The major antibody deficiency syndromes of clinical significance include X-linked agammaglobulinemia and common variable immunodeficiency. These disorders are marked by hypogammaglobulinemia with or without defective antibody

production, which increases susceptibility to infections. Children and adults with PI are at increased risk for recurrent severe bacterial infections, especially respiratory tract infections.

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

Intravenous administration of immunoglobulins (IgGs) is a well-established therapy in patients with primary or secondary immune deficiencies and recurrent infections. Replacement therapy with IgGs, administered either intravenously or subcutaneously, provides antibodies to help not only reduce the severity and frequency of infections but also to prevent viral and bacterial diseases and is a mainstay of treatment in patients with primary or secondary immune deficiencies and recurrent infections.

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

The Applicant received marketing authorization for IgG Next Generation (BT595) (Brand name: YIMMUGO 100 mg/mL) in Germany on November 11, 2022, and in Austria on December 20, 2022, for all therapeutic indications listed in the European Medicines Agency guidelines on the core summary of product characteristics for human normal IVIg. Additionally, YIMMUGO 100 mg/mL has been marketed in Hungary on the basis of the German marketing authorization. A marketing authorization application was also submitted in the United Kingdom in March 2023. The authorization procedure in the United Kingdom is ongoing.

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

- On January 26, 2016, a Type B pre-investigational new drug application (IND) Meeting was held; the FDA agreed that in general, Study 991 would fulfill the expectations for a Phase 3 study to support licensure for BT595 for treatment of primary immune deficiency.

- On April 3, 2023, at a Type B, pre-BLA meeting, the FDA stated that it was premature to determine that the 18 pediatric subjects (3 subjects 2 to <6 years of age, 9 subjects 6 to <12 years of age, 6 subjects 12 to <17 years of age) treated for PI with IgG Next Generation (BT595) in Trial 991 have fulfilled the Pediatric Research Equity Act requirement according to the agreed-upon initial pediatric study plan on June 6, 2017, under IND 17046 without review of the BLA data.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Data Integrity

The study was conducted with good clinical practices. There were no issues with data integrity.

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

5.1 Review Strategy

Two clinical studies, Studies 991 and 992, were included in this submission. However, Study 992 was designed to assess the efficacy and safety of BT595 in adult subjects with chronic immune thrombocytopenia (ITP) that is not the sought indication in the current BLA. Study 991 was the only clinical trial that evaluated the safety and efficacy of BT595 in subjects with PI. This memo reviewed data in Study 991 only.

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

The following documents (and module number) in BLA 125810/0 were reviewed:

- Module 1.2 Cover Letter
- Module 1.6 Meetings
- Module 1.11 Information Not Covered Under Modules 2 -5
- Module 1.14 Labeling
- Module 2.2 Introduction
- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 5.2 Tabular Listing of all Clinical Studies
- Module 5.3.5 Reports of Efficacy and Safety Studies – Study 991 (Clinical Study Report, Statistical Analysis Plan, Protocol, datasets, etc.)

5.3 Table of Studies/Clinical Trials

The overview of the studies is provided in Table 1.

Table 1. Overview of Study 991 and Study 992

	Study 991	**Study 992**
Phase	Phase 3	Phase 3
Trial period, region	October 2016 to April 2020, United States, Europe (Hungary, Germany, Spain, and Russia), and Asia (Russia)	January 2017 to December 2018, Europe (Hungary, Serbia, Bulgaria, Germany, and Spain)
Therapeutic approach	Long-term, low-dose IVIg as replacement therapy to prevent infections	Short-term, high-dose IVIg to increase platelet counts and control or prevent bleeding
Trial design	Non-randomized, open-label, prospective, multicenter, multinational	Randomized, 2-arm, open label, prospective, multicenter, multinational
Assessed	Efficacy, PK, safety, HR-QoL	Efficacy, safety
Trial population	67 subjects with PID (2 to ≤75 years of age; 49 adults and 18 pediatric subjects) With dense PK data: 57 subjects	34 adults with chronic ITP (18 to ≤75 years of age)
Primary efficacy outcome	SBI rate (mean number of acute SBIs per person-year)	Responder rate: response (R) defined as per revised EMA response criteria

Source: Original BLA 125810/0; Module 2.5 Clinical Overview Table 2.5-1, p.12Abbreviations: EMA, European Medicines Agency; HR-QoL, health-related quality of life; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; PK, pharmacokinetics; PI, primary humoral immunodeficiency; SBI, serious bacterial infection.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study 991

This protocol was entitled “An open-label, prospective, multicenter study investigating clinical efficacy, safety, and PK properties of the human normal immunoglobulin for IV administration BT595 as replacement therapy in patients with primary immunodeficiency disease (PID).”

6.1.1 Objectives

The primary objective was to demonstrate that the rate of acute SBIs would be less than 1.0 per person-year to provide substantial evidence of efficacy for BT595 in the treatment of PI. The secondary objectives were to evaluate additional efficacy assessments as well as the safety and PK characteristics of BT595.

6.1.2 Design Overview

This was a non-randomized, open-label, prospective, uncontrolled, multicenter Phase 3 study to evaluate the efficacy, safety, and PK of the human normal IVIg

BT595 with a target enrollment of 70 subjects with PI. BT595 was to be administered at 3- or 4-week intervals for a treatment period of approximately 12 months. Efficacy and safety were assessed from baseline (Week 0) to the closing visit (Week 54 [3-week schedule]/Week 56 [4-week schedule]).

6.1.3 Population

Subjects enrolled were 2 to <76 years of age with PI and established replacement therapy.

6.1.4 Study Treatments or Agents Mandated by the Protocol

BT595 was administered at 3- or 4-week intervals for approximately 12 months. The initial dose and dosage intervals were required to be consistent with the subject's pre-study IVIg treatment, unless changed if medically indicated at the investigator's discretion. The planned dose of BT595 was 0.2 to 0.8 g/kg body weight administered as IV infusions. Subjects treated at 3-week intervals were to receive a total of 17 infusions, whereas subjects treated at 4-week intervals were to receive a total of 13 infusions during the 12-month treatment period. Concomitant medication (other than IgGs) were permitted as required.

6.1.6 Sites and Centers

There were 18 active sites: 9 in the United States, 3 in Hungary, 2 in Germany, 2 in the Russian Federation, and 2 in Spain.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy endpoint was the rate of acute SBIs per person-year. Acute SBIs included bacteremia or sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess.

Criterion for Study Success

The study would be considered a success if the upper limit of the one-sided 99% CL for the SBI rate is less than 1.0 per person-year according to the *Guidance for industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (June 2008).*

Secondary Efficacy Endpoints

- IgG trough levels (total IgG) before each infusion

- Rate of any infections (number per year)
- Rate of non-serious infections (number per year)
- Time to resolution of infections
- Antibiotic treatment
- Rate of time lost from school/work due to infections and their treatments
- Hospitalization
- Fever episodes

Reviewer's comments: Per clinical reviewer's preference, I revised my analysis strategy for the following two secondary endpoints:

- *Rate of non-serious infections was replaced by rate of non-SBI infections.*
- *Antibiotic treatment was restricted to only antibiotic use for therapeutic treatment (i.e., excluding prophylaxis antibiotic use)*

Safety Endpoint

- Number, severity, causality, and seriousness of adverse events (AEs) (including nonproduct related) temporally associated with the infusion (occurring during infusion or within 1, 24, and 72 hours after the end of infusion)
- Number of infusion-related 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 AEs
- Number, severity, causality, and seriousness of all AEs
- Number, severity, causality, and seriousness of all treatment-emergent AEs
- Number of non-infusion-related 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

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypotheses

Null: Acute SBI rate is greater than or equal to 1.0 per person-year

Alternative: Acute SBI rate is less than 1.0 per person-year

Sample Size Estimation

Assuming a true underlying rate of SBI is 0.5 per person-year, 50 evaluable person-years would ensure a power of at least 80% to reject the null hypothesis

of an acute SBI rate greater or equal to 1.0 by means of a 1-sided test and a significance level of 0.01. Accounting for dropouts, 70 subjects were to be enrolled, according to the following age categories:

- ≥2 to <17 years of age: at least 20 subjects
- ≥17 to <76 years of age: at least 20 subjects
- ≥2 to <76 years of age: at least 50 subjects

Analysis Populations

- Safety analysis set (SAF): all subjects who received at least one dose of study medication.
- Full analysis set (FAS): all subjects who received at least one dose of study medication (i.e., there is no difference between the FAS and the SAF sets in this study).
- Per-protocol set (PPS): all subjects who were compliant with the study protocol without any major protocol deviations. Classification of protocol deviations as major or minor were agreed upon at the Data Review Meeting prior to database lock.

Statistical Methods

Analysis of Primary Efficacy Endpoint: Annualized Rate of Acute SBI

The primary efficacy analysis was tested overall based on FAS, e.g., without separation by treatment schedule. The annualized acute SBI rate for BT595 and the upper 1-sided 99% CL were estimated by using a generalized linear model assuming the Poisson distribution for the number of acute SBIs with the logarithm link function. The Poisson model included the natural logarithm of the length of the observation period in years as an offset to account for the different lengths of the observation periods per subject.

A sensitivity analysis of the primary efficacy endpoint was performed using the same statistical method as the primary analysis but based on the PPS dataset.

Analyses of Secondary Efficacy Endpoints

Rates of any infection and non-SBI infections were calculated as the mean number of all infections per person-year. Time to resolution of infections (days) was calculated as infection stop date – infection start date +1. The median and 95% CI of time to resolution of infection were estimated by Kaplan-Meier curve. Annualized rates of days on antibiotic treatment, time lost from school/work due to infections and their treatment, hospitalization, hospitalization due to infection, and episodes of fever were calculated by number of days of the event per person-year.

Subgroup Analyses

The analyses for efficacy endpoints were analyzed by subgroups: age groups, gender, race, and region.

Reviewer's comment: All analyses are also presented by the treatment schedule group (Q3W, Q4W) along with the overall group.

Handling of Missing Data

No missing data were imputed for the primary efficacy endpoint analysis. Incomplete/missing start and stop date/time for AEs/antibiotic treatments were imputed by predefined rules. Incomplete severity/ seriousness and/or relationship of AE were imputed by applying the worst-case scenario; that is, missing severities will be imputed as "severe," missing seriousness will be imputed as serious, while missing relationships will be imputed as "related."

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 81 subjects were screened. Of these, 67 subjects qualified for the study. Thirteen subjects who did not meet the eligibility criteria were screen failures and 1 subject withdrew his/her consent/assent prior to the first infusion and did not continue into the treatment phase.

All 67 eligible subjects received ≥1 dose of BT595 and were included in the SAF, FAS, and PK analysis sets. Twelve subjects received BT595 on the every-3-week dosing schedule (Q3W) and 55 subjects received BT595 on the every-4-week dosing schedule (Q4W). PPS included 57 subjects excluding the 10 subjects with major protocol deviations, including 3 subjects from the Q3W schedule group and 7 subjects from the Q4W schedule group.

6.1.10.1.1 Demographics

The study population was predominantly White (98.5%), with males representing 55.2% of the population. The age range was between 2 and 74 years, with a mean of 34.6 years (see Table 2). Of all 67 subjects in the FAS, 49 subjects (73.1%) were adults with ages ranging between 20 and 74 years, and 18 subjects (26.9%) were pediatric subjects between 2 and 16 years of age. Body mass indexes ranged from 13.3 to 45.3, with a mean of 23.3. Most subjects were treated in Europe (41 subjects [61.2%]), followed by the United States (21 subjects [31.3%]), and a single site in Asia (Russia) (5 subjects [7.5%]).

Table 2. Summary of Demographic Characteristics, Full Analysis Set

Criteria	3-Week Schedule (n=12)	4-Week Schedule (n=55)	Overall (n=67)
Age in years (screening)			
n	12	55	67
Mean (SD)	36.1(25.2)	34.3 (18.9)	34.6 (34.6)
Median	37	37	37
Min, Max	3, 69	2, 74	2, 74
BMI (screening)			
n	12	55	67
Mean (SD)	23.9 (7.5)	23.2 (6.2)	23.3 (6.4)
Median	23.5	22.3	22.3
Min, Max	14.9, 39.3	13.3, 45.3	13.3, 45.3
Age group, n (%)			
≥17	8 (66.7)	41 (74.5)	49 (73.1)
12 to <17	1 (8.3)	5 (9.1)	6 (9.0)
6 to <12	2 (16.7)	7 (12.7)	9 (13.4)
2 to <6	1 (8.3)	2 (3.6)	3 (4.5)
Sex, n (%)			
Male	5 (41.7)	32 (58.2)	37 (55.2)
Female	7 (58.3)	23 (41.8)	30 (44.8)
Race, n(%)			
White	12 (100)	54 (98.2)	66 (98.5)
Asian	0 (0)	1 (1.8)	1 (1.5)
Region			
United States	7 (58.3)	14 (25.5)	21 (31.3)
Europe	5 (41.7)	36 (65.5)	41 (61.2)
Asia	0 (0)	5 (9.1)	5 (7.5)

Source: Adapted from - BLA 125810/0; Clinical Study Report for Study 991 V1.0 Table 14.1.3.1.1, p.334
Abbreviations: BMI, body mass index; max, maximum; min, minimum; n, number of participants with the specified characteristic; SD, standard deviation.

Reviewer's comment: Age calculation was not precise and based on provided age at screening, rather than at the time of enrollment (i.e., date of informed consent) or at time of the first exposure. Subjects only provided months and years of birth during screening. Nevertheless, subjects are categorized in the correct age groups.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 3 provides the baseline subject characteristics by treatment schedule group and overall regarding the types of diagnoses, time since diagnosis (at screening,) and the mean of previous IVIg dose. Most subjects (53 subjects, 79.1%) were diagnosed with common variable immunodeficiency and 10 subjects (14.9%) were diagnosed with X-linked agammaglobulinemia.

Table 3. Relevant Disease Characteristics at Baseline, Full Analysis Set

Criteria	3-Week Schedule (N=12)	4-Week Schedule (N=55)	Overall (N=67)
Type of diagnosis, n (%)			
CVID	9 (75.0)	44 (80.0)	53 (79.1)
XLA	3 (25.0)	7 (12.7)	10 (14.9)
Congenital Agammaglobulinaemia	0 (0.0)	2 (3.6)	2 (3.0)
Congenital Hypogammaglobulinaemia	0 (0.0)	1 (1.8)	1 (1.5)
Other, Specify	0 (0.0)	1 (1.8)	1 (1.5)
Time since diagnosis, months			
Mean (SD)	83.0 (102.9)	94.1 (98.9)	92.1 (98.9)
Median	46.5	68.0	63.0
Min-max	4.0-315.0	6.0-492.0	4.0-492.0
Previous IVIg dose at baseline (g)			
Mean (SD)	29.4 (14.3)	27.1 (8.8)	27.6 (9.9)
Median	30.0	30.0	30.0
Min-max	8.0-60.0	5.0-45.0	5.0-60.0

Source: Adapted from - BLA 125810/0; Clinical Study Report 991 V1.0 Table 11-4, 14.1.3.1.1, 14.1.3.2.3, 14.1.3.2.2.
Abbreviations: CVID, common variable immunodeficiency; IVIg, intravenous immunoglobulin; max, maximum; min, minimum; n, number of participants with the specified characteristic; N, number of

participants in the specified group, or total sample; SD, standard deviation; XLA, X-linked agammaglobulinemia.

6.1.10.1.3 Subject Disposition

Of 67 enrolled subjects, 60 completed the study, and 7 discontinued the study. The reasons for early withdrawals are showed in Table 4: 3 due to AEs, 3 due to subject's decision, and 1 due to withdrawal of informed consent.

Table 4. Subject Disposition and Reasons for Early Termination

Criteria	3-week Schedule n(%)	4-week Schedule n(%)	Overall n(%)
Number of subjects eligible for the study (FAS/SAF)	12 (100.0)	55 (100.0)	67 (100.0)
Number of subjects treated with study medication	12 (100.0)	55 (100.0)	67 (100.0)
Number of subjects per protocol	9 (75.0)	48 (87.3)	57 (85.1)
Number of subjects completed the study	10 (83.3)	50 (90.9)	60 (89.6)
Number of subjects discontinued from study	2 (16.7)	5 (9.1)	7 (10.4)
Primary reason for study discontinuation:			
Adverse event	1 (8.3)	2 (3.6)	3 (4.5)
Subject‘s decision	0 (0.0)	3 (5.5)	3 (4.5)
Withdrawal of written informed consent/assent	1 (8.3)	0 (0.0)	1 (1.5)

Source: Adapted from - BLA 125810/0; Clinical Study Report 991 V1.0 Table 14.1.1.1, p.304.
Abbreviations: FAS, full analysis set; n, number of participants in the specified group; SAF, safety analysis set.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Among the 67 subjects in the FAS, 5 primary endpoint events of acute SBIs occurred during a cumulative total follow-up of 67.59 years, resulting in an annualized rate of acute SBIs of 0.074 per person-year with a 99% one-sided upper CL of 0.21 per person-year.

Sensitivity analysis of the primary endpoint in the PPS (N=57) yielded an overall rate of acute SBIs of 0.081 per person-year, with a 99% one-sided upper confidence limit of 0.23 per person-year. This result supported the conclusion of the primary analysis based on the FAS.

Reviewer's comment:

One SBI was initially reported in the study. FDA clinical reviewer identified four additional potential SBIs in two adults and two pediatric subjects who reported to

have lower respiratory infection/bronchitis of mild or moderate severity during the trial. In the applicant's response dated February 22, 2024, they stated that the investigator and the sponsor judged/considered that the bronchitis of those four subjects did not fulfill the FDA criteria of an SBI. However, since no imaging studies were performed to confirm one way or the other, the applicant agreed to consider those four additional infections as SBIs, with a total of five SBIs in the study.

6.1.11.2 Analyses of Secondary Endpoints

Rate of Any Infections and non-SBI Infections

Among all 67 subjects (FAS), 48 subjects (71.6%) experienced a total of 189 infections. The corresponding annualized rate for any infections was 2.80 per person-year (Table 5). The annualized rates of any infections were 2.10 and 2.93 per person-year, in the Q3W and Q4W schedule groups, respectively.

Excluding the 5 SBIs, the annualized rates of other infections per person-year were 2.72 overall, 2.00 and 2.86 for the Q3W and Q4W schedule groups, respectively. The proportions of subjects with ≥1 infection were 70.1% overall, 67.0% and 70.9% for the Q3W and Q4W schedule groups, respectively.

Time to Resolution of Infections

Of all 189 treatment-emergent infections, 187 had resolved by the end of the study. Two infections had not resolved at the end of study and events were censored at the last visit. The median times to resolution as per Kaplan-Meier analysis were 7 days overall, 7 and 8 days for the Q4W and Q3W schedule groups, respectively.

Antibiotic Treatment

Among all 67 subjects (FAS), 35 subjects (52.2%) received a total of 115 antibiotic treatment episodes. Duration for three antibiotic treatment episodes with either missing start date or missing end date were imputed. Based on clinical reviewer's decision, the imputed antibiotic treatment days were excluded since the imputed durations unrealistically overestimated the treatment time. The proportions of subjects who required ≥1 antibiotic treatment were 58.3% (7 of 12) and 50.9% (28 of 55) in the Q3W and Q4W schedule groups, respectively. For subjects who required ≥1 antibiotic treatment, the medians (ranges) of antibiotic treatment days were 9.5 (3, 35) overall, 11 (9, 35) in the Q3W schedule group and 7.5 (3, 21) in the Q4W schedule group. The annualized rates of therapeutic antibiotics use durations were 13.9 days per person-year, 32.5 and 10.3 days per person-year in the Q3W and Q4W schedule groups, respectively.

Time Lost from School/Work Due to Infections and Their Treatment

Twenty-six subjects (38.8%) lost a total of 292 days from school/work due to infections and their treatment. For subjects who had time lost, the median (range) numbers of days lost were 6 (1, 85) overall, 1 (1, 8) in the Q3W schedule group and 6 (1, 85) in the Q4W schedule group. The annualized rates of days lost was 4.3 days per person-year overall. The annualized rates of days lost were 1.1 and 4.9 days per person-year in the Q3W and Q4W schedule groups, respectively.

Hospitalizations and Hospitalizations Due to Infections

Of 67 subjects, 6 (9.0%) required a total of 8 hospitalizations with 47 hospitalization days overall. For subjects who had hospitalizations, the medians (ranges) of hospitalization days were 4 (1, 19) days overall, 6 days in the Q3W schedule group, and 2 (1, 19) days in the Q4W schedule group. The annualized rates of hospitalization days were 0.70 per person-year overall, 0.55 in the Q3W schedule group, and 0.72 in the Q4W schedule group.

There were three subjects with four hospitalizations due to infections. For subjects who had hospitalizations due to infections, the median (range) of hospitalization days was 2 (2, 20) days.

Fever Episodes

Fourteen subjects (20.9%) had 27 fever episodes with a total of 114 fever days, with fever defined as body temperature ≥38°C (≥100.4°F). For subjects who had fever episodes, the median (range) of fever days was 6 (2, 19) days, 4 (4, 4) days in the Q3W schedule group and 6 (2, 19) days in the Q4W schedule group. The annualized rates of fever days were 1.69 per person-year overall, 0.37 in the Q3W schedule group, and 1.94 in the Q4W schedule group.

Table 5. Primary and Secondary Outcomes Analyses, Full Analysis Set

Outcome Category	3-Week Schedule (N=12)	4-Week Schedule (N=55)	Overall (N=67)
Total follow-up time, person-years	10.95	56.65	67.59
Infections			
Number (%) of subjects with ≥1 acute SBI	1 (8.3)	4 (7.3)	5 (7.5)
Annualized rate of acute SBIs, events per person-year [upper limit of the 1-sided 99% CI]	0.091 [0.94]	0.071 [0.23]	0.074 [0.21]
Number (%) of subjects with ≥1 any infections	9 (75.0)	39 (70.9)	48 (71.6)
Annualized rate of any infections (events per person-year)	2.10	2.93	2.80
Number (%) of subjects with ≥1 non-SBI infections	8 (67.0)	39 (70.9)	47 (70.1)
Annualized rate of non-SBI infections (events per person-year)	2.00	2.86	2.72

Outcome Category	**3-Week Schedule (N=12)**	**4-Week Schedule (N=55)**	**Overall (N=67)**
Time to resolution of any infections, Kaplan-Meier analysis			
Days, median [95% CI]	8 [7, 14]	7 [6, 8]	7 [7, 8]
Range (min, max)[#]	2, 61	1, 172[#]	1, 172[#]
Antibiotics for therapeutic treatment			
Number of subjects who received antibiotics (%)	7 (58.3)	28 (50.9)	35 (52.2)
Number of days on antibiotics*, median (min, max)[##]	11 (9, 35)	7.5 (3, 21)	9.5 (3, 35)
Annualized rate, event days per person-year[##]	32.5	10.3	13.9
Missed school/work due to infections and treatment			
Number of subjects (%)	5 (41.7)	21 (38.2)	26 (38.8)
Number of days*, median (min, max)	1 (1, 8)	6 (1, 85)	6 (1, 85)
Annualized rate, event days per person-year	1.1	4.9	4.3
Hospitalizations			
Number of subjects (%)	1 (8.3)	5 (9.1)	6 (9.0)
Number of hospitalizations	1	7	8
Number of days*, median (min, max)	6 (6, 6)	2 (1, 19)	4 (1, 19)
Annualized rate, event days per person-year	0.55	0.72	0.70
Hospitalizations due to infection			
Number of subjects (%)	0	3 (5.5)	3 (4.5)
Number of hospitalizations	0	4	4
Number of days*, median (min, max)	NA	2 (2, 20)	2 (2, 20)
Annualized rate, event days per person-year	0.00	0.42	0.36
Fever episodes			
Number of subjects (%)	1 (8.3)	13 (23.6)	14 (20.9)
Number of days*, median (min, max)	4 (4, 4)	6 (2, 19)	6 (2, 19)
Annualized rate, event days per person-year	0.37	1.94	1.69

Source: Adapted from - BLA 125810/0; Clinical Study Report 991 V1.0 Table 14.2.1.1.1, p.1138; Table 14.2.2.2.1, p. 1678; Table 14.2.2.3.1, p. 1573; Table 14.2.2.4.1, p. 1837; Table 14.2.2.5.1, p. 1945; Table 14.2.2.6.1, p. 2052; Table 14.2.2.7.1, p. 2118; Table 14.2.2.8.1, p. 2316.
*Statistics are based on the subjects experiencing underlying events with a duration of ≥ 1 day, maximum duration is used if there were multiple events.
[#]This includes two subjects with unresolved infections, and excludes two infections from 0115-001 since duration were imputed given missing end date (imputed times to resolution of any infection were 335 and 342).
[##] Three antibiotic treatment episodes with missing either start or end dates were excluded. The imputed duration for those three episodes were 12, 22, 342.
Abbreviations: CI, confidence interval; max, maximum; min, minimum; N, number of participants in the specified group, or total sample; SBI, serious bacterial infection.

6.1.11.3 Subpopulation Analyses

Table 6 presents subgroup analyses for the primary and selected key secondary efficacy endpoints by age, sex, and region. The selected key secondary endpoints include any infections, antibiotic treatments, missed school/work days, hospitalizations, and fever episodes. Since almost all (66) of the 67 subjects were white, subgroup analyses by race are not presented. While the results across the sex and region subgroups appear to be generally comparable, notable numerical differences were observed across age groups for all of the primary and selected secondary endpoints, with numerically higher observed rates in the 2-<6 years group. However, because of the small sample sizes, no firm statistical conclusions can be drawn.

Table 6. Subgroup Analyses for Primary and Selected Secondary Outcomes

Subgroup	SBIs* n (Rate)	Any Infection n (Rate)	Antibiotic Treatment* n (Rate)	Missed school/work days* Median	Hospitalization n (Rate)	Fever n (Rate)
Age						
≥17 (N=49)	3 (0.062)	33 (2.43)	25 (11.3)	5	4 (0.43)	6 (1.15)
12 to <17 (N=6)	1 (0.15)	6 (3.08)	4 (28.8)	12	0	3 (3.85)
6 to <12 (N=9)	0 (0)	6 (3.15)	4 (14.7)	7	0	4 (1.42)
2 to <6 (N=3)	1 (0.38)	3 (7.67)	2 (22.2)	44	2 (9.96)	1 (7.28)
Sex						
Male (N=37)	3 (0.078)	24 (2.58)	16 (13.9)	8	4 (0.75)	9 (1.98)
Female (N=30)	2 (0.069)	24 (3.09)	19 (14.0)	6	2 (0.62)	5 (1.30)
Region						
U.S. (N=21)	2 (0.089)	19 (2.76)	15 (20.8)	5	0	5 (1.29)
Europe (N=41)	3 (0.074)	28 (3.07)	19 (11.5)	8	6 (1.15)	9 (2.09)
Asia (N=5)	0 (0)	1 (0.46)	1 (1.1)	NE	0	0

Source: Adapted from - BLA 125810/0; Clinical Study Report 991 V1.0 Table 11-8, p.101, Table 14.2.2.2.4 - 14.2.2.2.6, 14.2.2.4.4 -14.2.2.4.6, 14.2.2.5.4 -14.2.2.5.6, 14.2.2.7.4 -14.2.2.7.6, and 14.2.2.8.4 -14.2.2.8.6.
Notes: rate = number of events per person-year for SBIs and any infections, number of event days per person-year for antibiotic treatment, hospitalization, and fever episodes.
*reviewer's analysis
Abbreviations: NE, not evaluable; U.S., United States; N=number of subjects in a specified subgroup category; n= number of subjects experiencing at least one event.

6.1.11.4 Dropouts and/or Discontinuations

Of the 67 enrolled subjects, 7 (10.4%) withdrew from the study. All withdrawals occurred after the first dose of IMP. Missing data after early termination were not imputed. While the missing mechanism is unknown, I consider that it's reasonable to assume the missing data were missing completely at random therefore the primary analysis is appropriate. In an unlikely scenario where each subject terminated early had an event (SBI), the overall SBI rate would be approximately 0.17 with one-sided 99% upper confidence limit remaining below the 1.0 threshold. Therefore, I conclude that missing data in this study would unlikely impact the primary efficacy conclusion.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

There were two serious adverse events (SAEs) related to YIMMUGO. One subject had anaphylactic reaction, and one subject had severe neutropenia. Both SAEs led to subjects discontinuing YIMMUGO.

6.1.12.5 Adverse Reactions

Table 7 summarizes the adverse reactions (ARs) and ARs related to infusions. The ARs observed in ≥5% of subjects included headache (19%), upper respiratory tract infections (12%), fatigue (8%), nausea (6%), and increased blood pressure (6%).

Table 7. Adverse Reactions* in ≥5% of PI Subjects

Adverse Reaction **MedDRA Preferred Term**	**Number (%) of Subjects With AR N=67**	**Number (%) of Infusions With AR N =923**
≥1 AR, n (%)	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: Created by FDA clinical reviewer based on dataset ADAE submitted in BLA 123810/0, Module 5.3.5.2 16. Appendices

Abbreviations: AR, adverse reaction; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in the specified group, or the total sample; PI, primary humoral immunodeficiency.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Two Phase 3 clinical studies (991 and 992) are included in this submission. As the targeted indication is the treatment of PI in patients 2 years of age or older, Study 991, in which 67 subjects 2 to 74 years of age with PI were treated, is the only trial to provide data for efficacy evaluation and therefore is the focus of this review memo.

Of the 67 enrolled subjects, 5 SBIs were reported on 5 subjects (1 each in 3 adults and 2 children). That resulted in an annualized rate of acute SBIs of 0.074 per person-year with a 99% one-sided upper CL of 0.21, which met the efficacy success criterion of less than 1.0 per person-year.

No deaths occurred in the study. There were two serious adverse events (SAEs) related to YIMMUGO. One subject had anaphylactic reaction, and one subject had severe neutropenia. Both SAEs led to subjects discontinuing YIMMUGO. The adverse reactions observed in ≥5% of subjects included headache (19%), upper respiratory tract infections (12%), fatigue (8%), nausea (6%), and increased blood pressure (6%).

10.2 Conclusions and Recommendations

In conclusion, there were no major statistical issues related to the efficacy data submission. Primary efficacy was demonstrated based on the pre-specified criterion. There are no serious safety concerns based on the submitted data. Therefore, I recommend approval of YIMMUGO for treatment of PI in patients 2 years of age or older.