Application Type	PAS-Efficacy Supplement
STN	125389/300
CBER Received Date	Feb 9, 2023
PDUFA Goal Date	Dec 8, 2023
Division / Office	DCEGM/OCE/OTP
Committee Chair	Hongloan La, MD
Clinical Reviewer(s)	Hongloan La, MD
Project Manager	Colleen Caldwell, MS, MPH
Priority Review	No
Reviewer Name(s)	Yakun Wang, Ph.D. Visiting Associate, TEB2/DB/OBPV
Supervisory Concurrence	Lin Huo, Ph.D., Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D., Branch Chief, TEB2/DB/OBPV
Applicant	ADMA Biologics
Established Name	Immune Globulin Intravenous (Human), 10% Liquid
(Proposed) Trade Name	BIVIGAM
Formulation(s), including Adjuvants, etc	Immune Globulin Intravenous (Human), 10% Liquid
Dosage Form(s) and Route(s) of Administration	Liquid, 300-800mg/kg via intravenous (IV) infusions
Dosing Regimen	• 300-800 mg/kg every 3-4 weeks • 0.5 mg/kg/min for first 10 minutes • Increase every 20 minutes (if tolerated) by 0.8 mg/kg/min up to 6 mg/kg/min
Indication(s) and Intended Population(s)	For treatment of adults and pediatric patients 2 years of age and older with primary humoral immunodeficiency (PI).

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GLOSSARY

AE	Adverse Event
AESI	Adverse Events of Special Interest
ASBI	Acute Serious Bacterial Infection
BLA	Biologics License Application
BIMO	Bioresearch and Monitoring
CBER	Center for Biologics Evaluation and Research
CRF	Case Report Form
CSR	Clinical Study Report
DRM	Data Review Meeting
DSMB	Drug Safety Monitoring Board
FDA	Food and Drug Administration
IAAE	Infusion-associated Adverse Event
IgG	Immunoglobulin G
IGIV	Intravenous Immune Globulin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IP	Investigational Product
IR	Information Request
ITT	Intent-to-treat (population)
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent-to-Treat
nTEAE	Non-treatment Emergent Adverse Event
PID	Primary Immunodeficiency
PK	Pharmacokinetic
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBI	Serious Bacterial Infection
SD	Standard Deviation
SOC	System Organ Class
TAAE	Temporally Associated Adverse Event
TEAE	Treatment-emergent Adverse Events
U.S. / USA	United States of America

1. Executive Summary

ADMA Biologics submitted a supplemental biologics license application (sBLA) STN 125389/300 for BIVIGAM to add pediatric population (subjects 2 through 16 years of age) in the indication of treatment for primary humoral immunodeficiency (PI). To support the application and also as part of the post-marketing requirement (PMR), a Phase IV, multicenter, open-label study (Study 994) was conducted to evaluate the safety, efficacy, and pharmacokinetics of BIVIGAM in subjects aged 2 through 16 years with primary immune deficiency disorders.

The primary efficacy endpoint of Study 994 was the incidence of acute serious bacterial infections (SBIs) during the 5-month study observation period. All 16 enrolled subjects completed the study. There were no acute SBIs occurred during the observation period (mean 152 days).

For secondary efficacy endpoints, there were no serious infections, or hospitalizations due to infections occurred, and none of the subjects required IV antibiotics during the study. A total of 17 non-serious infections occurred in 7 subjects (43.8%). Sixteen infections occurred in 6 subjects (75.0%) in the 3-week infusion schedule group, and a single infection occurred in 1 subject (12.5%) in the 4-week infection schedule group. A total of 6 of 16 subjects (37.5%) required antibiotic treatment for infections for a mean duration of 16.5 days (range from 1 to 35 days) during the study.

For safety, 7 of the 96 (7.3%) infusions administered among 16 subjects were temporally associated with at least one adverse event (AE). The one-sided 95% upper confidence limit of the probability that an infusion was associated with an AE was below the threshold of 40%. Most subjects (13 of 16, 81.3%) experienced at least one treatment-emergent adverse events (TEAE) during the study. There were no deaths and no treatment-related serious adverse events (SAEs) occurred during the study.

Conclusion and Recommendations:
There were no major statistical issues related to the submission. Primary results were confirmed by the reviewer's independent analyses. The efficacy results of Study 994 provide adequate statistical evidence for the proposed indication. I defer to the clinical reviewer on the acceptance of the safety profile of BIVIGAM.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiencies (PIDs) are a large heterogenous group of disorders resulting from inborn errors of immunity, characterized by absent or poor function in one or more components of the immune system.

Children with antibody deficiencies present with recurrent, often severe bacterial infections affecting the respiratory tract, gastrointestinal system, skin, as well as other organs. Replacement therapy comprised of immune globulin for intravenous injection (IGIV) infusions administered every 3 or 4 weeks restores serum IgG to normal levels,

providing these patients with specific antibodies to prevent or minimize the occurrence of severe bacterial and viral infections and decrease the risk of hospitalizations.

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

Please refer to the clinical review.

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

The investigation medicinal product (IMP) in Study 994 was BIVIGAM (Immune Globulin Intravenous [Human], 10% Liquid). Originally approved by the U.S. food and drug administration (FDA) in 2012, BIVIGAM is indicated for the treatment of primary immunodeficiency (PID).

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

Please refer to the clinical review.

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

Please refer to the clinical and bioresearch and monitoring (BIMO) reviews.

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

5.1 Review Strategy

My review focuses on Study 994, the only clinical study submitted to this sBLA.

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

- STN 125389/300.0 Module 1.14. Labeling
- STN 125389/300.0 Module 2.7. Clinical Summary
- STN 125389/300.0 Module 5.3.5.2. Study 994
- STN 125389/300.2 Module 5.3.5.2. Clinical Information Amendment (Response to IR#1: Request for ADaM dataset and SDTM dataset)
- STN 125389/300.8 Module 5.3.5.2. Clinical Information Amendment (Response to IR#7: Request for statistical programs)

- STN 125389/300.10 Module 5.3.5.2. Clinical Information Amendment (Response to IR#8 follow up from IR#7: Request for statistical programs)
- STN 125389/300.11 Module 1.11.3. Clinical Information Amendment (Response to IR#9: Request for updating Table 12-8 results in CSR)

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the Study 994 in the clinical development program.

Table 1: Overview of Study 994

Protocol Number/Study number	994
Clinical Phase	Phase IV
Counties	USA
Subject age range	2 to 16 years (2 to <6 years, 6 to <12 years, and 12 to 16 years groups)
Number of subjects planned	18 (six subjects in each age group)
Number of subjects enrolled	18 (three in 2 to <6 years, six in 6 to <12 years, and nine in 12 to <16 years)
Number of subjects completed	16
Demographics	100% male, 80.3% white
Design	open-label, single-arm, multi-center
Dose level(s)	300-800 mg/kg every 3-4 weeks
Extent of exposure	5 months (7 infusions for 3-week regimen, 5 infusions for 4-week regimen)
Duration of follow-up	three weeks (3-week regimen) or four weeks (4-week regimen)
Whether the primary endpoint was met	Yes
Whether or not the study was conducted under IND	Yes

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study 994

This protocol is entitled "A Phase IV, Multicenter, Open-label Study to Evaluate the Safety and Pharmacokinetics of BIVIGAM in Primary Immune Deficiency Disorders in Subjects Aged 2 to 16."

6.1.1 Objectives

Primary: to evaluate the safety of BIVIGAM, including the incidence and profile of adverse events (AEs), serious adverse events (SAEs), and infusion-associated adverse events (IAAEs).

Secondary: to evaluate
a. The pharmacokinetic (PK) profile of total IgG in pediatric subjects with PID.

b. The efficacy of BIVIGAM, based on the rate of serious bacterial infections (SBIs), number of days missed from school/work, number of infections, and number of hospitalizations.

6.1.2 Design Overview

Study 994 was a Phase IV prospective, open-label, single-arm, multi-center clinical trial evaluating the safety, efficacy, and PK of BIVIGAM in pediatric subjects with confirmed and documented clinical diagnosis of PID, including hypogammaglobulinemia or agammaglobulinemia.

The study design required 18 evaluable male and female subjects (defined as completing PK sampling), including 6 subjects in each age group (2 to <6 years, 6 to <12 years and 12 to 16 years at time of signing the informed consent/assent).

The investigational product (IP) was given every 3 or 4 weeks (± 7 days) for approximately 5 months. Subjects treated according to the 3-week regimen were to receive a total of 7 infusions over 18 weeks (Day 0 through Day 126), whereas subjects treated according to the 4-week regimen were to receive a total of 5 infusions over 16 weeks (Day 0 through Day 112). Upon completion of study treatment, subjects underwent a Follow-up visit within three weeks (3-week regimen) or within four weeks (4-week regimen) after the last dose of study drug. Hence the total subject follow-up (after screening) was approximately 21 weeks (3-week regimen) or approximately 20 weeks (4-week regimen).

6.1.3 Population

The study target population were male and female subjects aged 2 to 16 years, with a confirmed diagnosis of primary immune deficiency (PID) disorder.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The IP is a liquid IGIV that contains approximately 100 mg/mL of human IgG, and no preservative. The test product was supplied in single-use vials of 50 mL (containing 5 g of protein in total).

Eligible subjects received IV infusions of the study drug at the same weight-base dose (or higher if medically appropriate) and same regimen as used for their previous IGIV maintenance therapy. The study drug was administered at a dose of 300 to 800 mg/kg (of body weight) every 3 or 4 weeks (± 7 days; depending on their pre-study IGIV treatment schedule) for 5 months of study infusions. Dose adjustments were permitted during the study, to maintain trough total IgG concentrations at >500 mg/dL; however, dose increases above 800 mg/kg required approval by the Sponsor Medical Director (or designee).

In general, it was recommended that subjects beginning treatment with IGIV or switching from one product to another be started at a lower infusion rate (0.5 mg/kg/min) and then advanced to the maximal tolerated rate, with an increase by 0.8 mg/kg/min every 20

minutes, up to a maximum rate of 6 mg/kg/min if they have tolerated several infusions at intermediate rates of infusion.

6.1.6 Sites and Centers

The study was conducted in six centers in the United States of America (USA).

6.1.7 Surveillance/Monitoring

A third-party Drug Safety Monitoring Board (DSMB) monitored the safety of study subjects on a periodic basis.
Please refer to the clinical memo for more details on surveillance and monitoring.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint: the incidence of acute SBIs (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis). Acute SBI counts were analyzed by Poisson model with offset of log (subject's exposure time) and over-dispersion correction. A 99% one-sided (upper) confidence limit for the incidence rate of SBIs was derived. According to the FDA Guidance for industry: Safety, Efficacy, and Pharmacokinetic studies to support marketing of Immune Globulin Intravenous (Human) as replacement therapy for primary humoral immunodeficiency (2008), the upper one-sided 99% confidence limit should be less than 1.0.

Secondary efficacy endpoints:

1. Number of infections of any kind (serious or nonserious)
    - Derived from AEs coded to MedDRA SOC Infections and infestations
2. Number of nonserious infections
3. Time to first infection of any kind (serious or nonserious)
    - Calculated in days as follows: the [earliest AE start date] minus the [start date of the first infusion] +1 day
4. Time to resolution of infections (in days)
    - Calculated for each individual infection as follows: End Date of Infection - Start Date of Infection + 1, with N referring to the total number of infections.
5. Duration of infections (in days)
    - Represented the total number of days with infections per subject and was calculated as follows: End Date of Infection - Start Date of Infection + 1, with N referring to the number of subjects. If a subject had more than one infection, the sum of all infections was used.
6. Number of days of antibiotic treatment for infections
7. Number of days missed from school/work due to infections and treatment
8. Number of days of hospitalization and prolonged hospitalizations due to infection
9. Number of episodes of fever $\geqslant$38°C ($\geqslant$100.4°F) (per subject and overall).

Safety endpoints:

1. Incidence of TAAE (defined as AEs occurring during or within 1 hour, 24 hours, or 72 hours of completion of an infusion), and the mean number of TAAEs per infusion. According to the FDA Guidance for industry: Safety, Efficacy, and Pharmacokinetic studies to support marketing of Immune Globulin Intravenous (Human) as replacement therapy for primary humoral immunodeficiency (2008), the upper one-sided 95% confidence limit of the probability that an infusion was associated with an AE should below 40%.
2. Incidence of SAEs and related SAEs
3. Incidence of treatment-emergent adverse events (TEAEs) and related TEAEs
4. Incidence of non-treatment emergent adverse events (nTEAEs);
5. Total number and incidence of adverse reactions (including suspected adverse reactions)
6. Incidence of adverse infusion-related reactions (TAAEs deemed related to the study drug)
7. Incidence of infusion site reactions
8. Change in vital signs before and after administration of study drug

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Sample size

There was no sample size calculation. The applicant planned to enroll 18 subjects for this pediatric study per request from FDA, as part of the PMR.

- Definitions of analysis populations:
  - All Subjects Enrolled Set: all subjects who have given informed consent/assent to this study.
  - Efficacy Analysis Set / modified Intent-to-Treat (mITT): all subjects who received at least one dose of study drug and had at least one post-dosing follow-up visit.
  - Safety Set: all subjects who have received at least one dose of study medication.

- Key efficacy analysis:
  The rate of Acute Serious Bacterial Infections (SBIs) was the key efficacy parameter and will be analyzed using mITT set. Summary statistics for the number of SBI episodes per person-year will be based on:
  - The end of observation period was defined as the minimum of death date, SBI onset date, date of study follow-up visit, or last known visit if lost to follow-up. Each subject will have a time, and this would be considered as the length of observation (or length of "at-risk").
  - The cumulative length of observation would be the sum of each subject's value. The per person-year was obtained by calculating the days (End of Observation date First infusion date + 1 day), then converting years (365 days in 1 year, divide by 365).

- The rate of occurrence would be calculated for each subject as 365n/d where n is the number of reported infections and d was the number of days on study through end of observation.

SBI counts were to be analyzed by Poisson model with offset of log(subject's exposure time) and over-dispersion correction. A 99% one-sided (upper) confidence limit for the incidence rate of SBIs (scaled to represent 12 months exposure if necessary) would be derived.

- Analysis plan for safety endpoints

Descriptive statistics and analyses were provided for the study overall and by dosing regimen (4-week or 3-week cycle), and subgroup analysis by age group were performed for selective aspects e.g., treatment exposure, TEAEs, and TAAE etc. For quantitative data, the absolute values and differences from baseline, where appropriate, were summarized with number of observations (n), arithmetic mean, standard deviation, median, minimum, and maximum. Confidence intervals (95%, 2-sided) were added where applicable. The qualitative data were summarized using number of observations (n), frequency and percentages of subjects. Unless stated otherwise the counts of missing observations will be included in the denominator for the calculation of percentages and presented as a separate category.

- Subgroup analyses planned

  The following subgroup analyses of the primary efficacy and key safety endpoints were planned to be performed by pre-defined age brackets (2 to <6 years, 6 to <12 years, 12 to 16 years), and by sex (male or female).

- Missing data handling

No data imputation was used in the analysis of this study. Missing data were omitted from summary statistics. If a baseline value was missing, the last measurement prior to the first study drug administration was used as the baseline measurement. In case of partial dates for AEs or concomitant medications: for missing day portion of start dates, the 1st of the month was imputed, and for missing day portion of end dates the last day of the month was imputed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 18 subjects were enrolled, and 16 subjects received at least one dose of IMP in this study. These 16 subjects constitute the Safety Set and the mITT Set. The 16 subjects were equally distributed between the two infusion schedule cohorts (3-week and 4-week infusion regimens). Table 2 shows the population enrolled in this study.

Table 2: Population Enrolled for Study 994

Actual, n	3-Week Infusion Regimen, n	4-Week Infusion Regimen, n	Total
Screened	-	-	18
Enrolled	8	8	16*
mITT Set	8	8	16
Safety Set	8	8	16

* Two subjects were screen failures
Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-1

6.1.10.1.1 Demographics

The study population was predominantly white (13 subjects, 81.3%) and non-Hispanic (13 subjects, 81.3%), and included 3 subjects (18.8%) aged 2 to <6 years, 5 subjects (31.3%) aged 6 to <12 years, and 8 subjects (50.0%) aged 12 to 16 years. The overall age range was between 3 and 16 years (mean of 10.3 years), and all enrolled subjects were males. Table 3 shows the details of the demographics.

Table 3: Demographics for Study 994

Category Statistic/Response	3-week Regimen (N=8)	4-week Regimen (N=8)	Total (N=16)
Age (years)			
Mean (SD)	11.0 (5.2)	9.5 (3.1)	10.3 (4.2)
Median	13.5	10.5	11.5
Min, Max	3, 16	5, 13	3, 16
2 to <6 years, n (%)	2 (25.0)	1 (12.5)	3 (18.8)
6 to <12 years, n (%)	1 (12.5)	4 (50.0)	5 (31.3)
12 to 16 years, n (%)	5 (62.5)	3 (37.5)	8 (50.0)
Sex, n (%)			
Male	8 (100.0)	8 (100.0)	16 (100.0)
Female	0	0	0
Race, n (%)			
White	7 (87.5)	6 (75.0)	13 (81.3)
Black or African American	0	1 (12.5)	1 (6.3)
American Indian or Alaska Native	1 (12.5)	0	1 (6.3)
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	1 (12.5)	1 (6.3)
Ethnicity, n (%)			
Not Hispanic/Latino/Spanish Origin	6 (75.0)	7 (87.5)	13 (81.3)
Hispanic/Latino/Spanish Origin	2 (25.0)	1 (12.5)	3 (18.8)
Weight (kg)			
Mean (SD)	50.1 (32.7)	37.4 (17.2)	43.7 (26.1)
Median	45.9	31.7	39.5
Min, Max	16.3, 119.0	18.6, 67.1	16.3, 119.0

Abbreviations: IgG=immune globulin G; kg=kilogram; Max=maximum; Min=minimum; SD=standard deviation. Percentages are calculated using N as the denominator.
Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-3

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline Disease Characteristics and Prior IGIV Treatment

The most common PID diagnosis was hypogammaglobulinemia (8 subjects, 50.0%), followed by common variable immunodeficiency (4 subjects, 25.0%), combined immunodeficiency (2 subjects, 12.5%), Bruton's agammaglobulinemia, and selective polysaccharide antibody deficiency (1 subject, 6.3% each. The mean disease duration since first PID diagnosis was approximately 4.3 years (range from 0.9 to 10.8 years. All subjects had been receiving IGIV infusions at regular 3- or 4-week intervals prior to enrollment. Overall, the most commonly prescribed prior IGIV products were Gammagard 10% (7 subjects, 43.8%), followed by Octagam 5% (6 subjects, 37.5% [including 1 subject who was switched from Gammagard to Octagam for their last pre-study infusion]), BIVIGAM 10%, and Privigen 10% (2 subjects, 12.5% each). The last IGIV doses prior to the first IMP administration ranged from 300 mg to 1043 mg/kg in the 3-week infusion cohort, and between 313 mg/kg and 622 mg/kg in the 4-week infusion regimen cohort. One subject in the 4-week infusion cohort (Subject (b) (6) (b) (6), 459 mg/dL) IgG levels measured prior to the first IMP infusion below 500 mg/dL. The 3-week (compared to the 4-week) infusion regimen was associated with higher baseline trough IgG levels (Table 4)

Table 4: Relevant Disease Characteristics at Baseline, Safety Set

Category Statistic/Response	3-week Regimen (N=8)	4-week Regimen (N=8)	Total (N=16)
Years since PID Diagnosis (years)[1]	N=7	N=7	N=14
Mean (SD)	3.88 (2.23)	4.69 (4.21)	4.29 (3.26)
Median	3.34	3.18	3.26
Min, Max	1.6, 7.1	0.9, 10.8	0.9, 10.8
IgG Trough Level (mg/dL) at Screening	N=8	N=8	N=16
Mean (SD)	1016.4 (181.29)	821.4 (183.08)	918.9 (202.78)
Median	992.0	819.0	910.0
Min, Max	799, 1390	557, 1096	557, 1390
IgG Trough Level (mg/dL) at Pre-infusion 1	N=8	N=8	N=16
Mean (SD)	964.3 (127.56)	760.3 (182.70)	862.3 (185.12)
Median	1013.5	809.5	873.5
Min, Max	761, 1112	459, 1022	459, 1112

Abbreviations: IgG=immune globulin G; kg=kilogram; Max=maximum; Min=minimum; PID=primary immunodeficiency; SD=standard deviation
Percentages are calculated using N as the denominator.
[1] Years since PID Diagnosis = (date of informed consent – PID Diagnosis date + 1)/365.25
Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-4.

Relevant General Medical History

All subjects in the Safety Set had a history of at least one prior medical condition apart from the underlying disease. The most commonly reported (frequency ⩾50%) prior medical conditions/disorders by MedDRA System Organ Class (SOC) were infections and infestations (13 subjects, 81.3%), followed by respiratory, thoracic and mediastinal disorders (11 subjects, 68.8%), immune system disorders, surgical and medical procedures (9 subjects, 56.3% each), gastrointestinal disorders, and nervous

system disorders (8 subjects, 50.0% each). The most commonly reported (frequency ⩾20%) prior medical conditions/disorders by MedDRA PT were rhinitis allergic (10 subjects, 62.5%), asthma (8 subjects, 50.0%), chronic sinusitis, gastrooesophageal reflux disease (5 subjects, 31.3% each), sinusitis, and tonsillectomy (4 subjects, 25.0% each).

Prior and Concomitant Medications

Apart from prior IGIV infusions, prior medication use was reported for one subject in the 4-week, infusion regimen cohort (Subject (b) (6), ibuprofen). The majority of subjects in the ITT population (15 subjects, 93.8%) took at least one concomitant medication (prescription or non-prescription) during the study. The most commonly used (frequency ⩾50%) concomitant medications by ATC class were non-steroidal anti-inflammatory and antirheumatic products (9 subjects, 56.3%), inhalant adrenergics, antihistamines for systemic use, and decongestants and other nasal preparations for topical use (8 subjects, 50.0% each). The most commonly used (frequency ⩾20%) concomitant medications by preferred term were ibuprofen (9 subjects, 56.3%), followed by salbutamol sulfate (6 subjects, 37.5%), cetirizine, epinephrine, fluticasone propionate, and salbutamol (4 subjects, 25.0% each).

6.1.10.1.3 Subject Disposition

A total of 18 subjects were enrolled into the study. Two enrolled subjects did not proceed to the administration of the IP due to screening failure. For the rest of 16 subjects, eight were in 3-week infusion regimen, another 8 subjects were in 4-week infusion regimen. No withdrawn during the study. All 16 subjects completed the study.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the incidence of acute SBIs. There were no acute SBIs occurred during the observation period (mean 152 days). As a result, the planned Poisson model was not employed. The descriptive primary efficacy results are provided in Table 5.

Table 5: Incidence of Acute Serious Bacterial Infections, mITT Set

Category Statistic/Response	3-week Regimen (N=8)	4-week Regimen (N=8)	Total (N=16)
Number of ASBI episodes (per person-years)[1]			
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
Median	0.0	0.0	0.0
Min, Max	0, 0	0, 0	0, 0
Length of observation (days)			
Mean (SD)	158.1 (18.59)	145.9 (13.05)	152.0 (16.76)
Median	156.0	141.5	147.0
Min, Max	134, 196	136, 177	134, 196

Abbreviations: ASBI=acute serious bacterial infection; Max=maximum; Min=minimum; NA=not applicable; SD=standard deviation
Percentages are calculated using N as the denominator.
[1] The rate of ASBI episodes per person-year was calculated for each person as 365n/d, where n is the number of episodes and d is the length of observation in days. The length of observation is the time from first infusion until ASBI onset, death, or date of last study visit.
Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-6

6.1.11.2 Analyses of Secondary Endpoints

Number of infections of any kind (serious or nonserious)
A total of 17 infections occurred in 7 subjects (43.8%) in the mITT Set; 16 infections occurred in 6 subjects (75.0%) in the 3-week infusion schedule group, and a single infection occurred in 1 subject (12.5%) in the 4-week infection schedule group.

Number of nonserious infections
All 17 infections were non-serious; no serious infections were reported during the study. The mean number of infections (and nonserious infections) per subject was 2.0 in the 3-week infusion schedule group, 0.1 in the 4-week infusion schedule group, and 1.1 overall.

Time to first infection of any kind
The mean time to first infection during the study was 69.3 days in the 3-week infusion schedule group, 75.0 days in the 4-week infusion schedule group, and 70.1 days overall.

Time to resolution of infections (including duration of infections)
The mean duration of infections per subject were 21.5 days in the 3-week infusion schedule group, 0.4 days in the 4-week infusion schedule group, and 10.9 days overall.

Number of days of antibiotic treatment for infections
A total of 6 of 16 subjects (37.5%) required antibiotic treatment for infections for a mean duration of 16.5 days (range from 1 to 35 days) during the study; 5 subjects (62.5%) required antibiotic treatment for a mean duration of 12.8 days (range from 1 to 31 days) in the 3-week infusion schedule group, and 1 subject (12.5%) required antibiotic treatment for 35 days in the 4-week infusion schedule group. None of the subjects required IV antibiotics during the study.

Number of days missed off school/work due to infections and treatment
One subject in the 3-week infusion schedule group missed a total of 9 days from school due to infection; there were no days missed from school in the 4-week infusion schedule group.

Number of days of hospitalization and prolonged hospitalizations due to infection
There were no hospitalizations due to infection during the study.

Number of episodes of fever ⩾38°C (⩾100.4°F) (per subject and overall)
The reported number of days with fever defined as a body temperature ≥ 38°C does not take into consideration two TEAEs of fever for which no body temperature measurements were provided. The two fever episodes resolved in 7 and 3 days, respectively.

The detailed secondary efficacy results can be found in Table 6.

Table 6: Summary of Other Secondary Efficacy Endpoints, mITT Set

Category Statistic/Response	3-week Regimen (N=8)	4-week Regimen (N=8)	Total (N=16)
Total number of infections (serious and nonserious) on study	16	1	17
Total number of infections (serious and nonserious) per subject	N=8	N=8	N=16
Mean (SD)	2.0 (2.14)	0.1 (0.35)	1.1 (1.77)
Median	1.0	0.0	0.0
Min, Max	0, 6	0, 1	0, 6
Total number of serious infections on study	0	0	0
Total number of non-serious infections on study	16	1	17
Total number of non-serious infections per subject	N=8	N=8	N=16
Mean (SD)	2.0 (2.14)	0.1 (0.35)	1.1 (1.77)
Median	1.0	0.0	0.0
Min, Max	0, 6	0, 1	0, 6
Time to first infection per subject (days) [1]	N=6	N=1	N=7
Mean (SD)	69.3 (48.93)	75.0 (-)	70.1 (44.72)
Median	72.0	75.0	75.0
Min, Max	14, 123	75, 75	14, 123
Time to resolution of infection (days) [2]	N*=16	N*=1	N*=17
Mean (SD)	15.3 (11.83)	3.0 (-)	14.5 (11.83)
Median	12.0	3.0	11.0
Min, Max	2, 48	3, 3	2, 48
Duration of infections on study (days)	172	3	175
Duration of infections per subject (days) [3]	N=8	N=8	N=16
Mean (SD)	21.5 (29.58)	0.4 (1.06)	10.9 (22.97)
Median	9.0	0.0	0.0
Min, Max	0, 78	0, 3	0, 78
Total duration of antibiotic treatments for infection on study(days)	64	35	99
Duration of antibiotic treatments for infection per subject(days)	N=5	N=1	N=6
Mean (SD)	12.8 (11.28)	35.0 (-)	16.5 (13.56)
Median	11.0	35.0	12.5
Min, Max	1, 31	35, 35	1, 35
Total number of days missed school/work on study(days)	9	0	9
Number of days missed school/work per subject(days)	N=1	N=0	N=1
Mean (SD)	9.0 (-)		9.0 (-)
Median	9.0		9.0
Min, Max	9, 9		9, 9
Total number of days hospitalized on study	0	0	0
Total number of days with fever >=38 C on study [4]	0	0	0

Abbreviations: Max=maximum; MedDRA=Medical Dictionary for Regulatory Activities; Min=minimum; SD=standard deviation; TEAE=treatment-emergent adverse event
Percentages are calculated using N as the denominator.
Infections were defined as TEAEs coded to MedDRA System Organ Class 'Infections and infestations'.
[1] Time to first infection (in days) was calculated as follows: the [earliest AE start date] minus the [date of the first infusion] +1 day.
[2] Time to resolution of infections (in days) was calculated for each individual infection as follows: End Date of Infection Start Date of Infection + 1, with N* referring to the total number of infections.

[3] Duration of infections (in days) represents the total number of days with infections per subject, and was calculated as follows: End Date of Infection - Start Date of Infection + 1, with N referring to the number of subjects. If a subject had more than one infection, the sum of all infections was used to calculate duration.
[4] Two TEAEs of fever occurred during the study (Subjects (b) (6) ; as described in Section 12.3.1.4.3); however, given that the associated body temperature levels were not reported, these cases were not included in the analysis of the secondary endpoint of "Total number of days with fever ≥38° C on study".
Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-7.

6.1.11.3 Subpopulation Analyses

Given that no acute SBI events occurred during this study, no subgroup analyses were performed for this endpoint.

6.1.11.4 Dropouts and/or Discontinuations

No dropouts or discontinuations in this study.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please refer to the clinical review.

6.1.12.3 Deaths

No death occurred during this study.

6.1.12.4 Nonfatal Serious Adverse Events

No treatment-related SAEs occurred during the study.

One subject (6.3%) experienced a single SAE (hemiparesis, reported as left side weakness) during the study. The event occurred in a 15-year-old male 7 days after the second infusion of study drug, required hospitalization, and resolved the following day. There were no changes made to the study drug dose or regimen as a result of this SAE. The investigator assessed the event of hemiparesis as severe, and not related to the IMP.

6.1.12.5 Adverse Events of Special Interest (AESI)

No AESI (defined as hemolysis or thrombosis) occurred during the study.

6.1.12.6 Clinical Test Results

Temporally Associated Adverse Events

In the total Safety Set, total of 16 subjects, 7 of the 96 (7.3%) IMP infusions administered was temporally associated with an AE. The applicant stated that the mean proportion of infusions temporally associated with an AE per subject was 6.96 (95% one-sided Confidence Limit [CL] of Mean, 1.1 to 12.8) for the total Safety Set, 8.93 (95% on-sided CL, 0.2 to 17.7) for the 3-week infusion regimen group, and 5.00 (95% one-side CL, -4.5 to 14.5) for the 4-week infusion regimen group. Table 7 shows the detail results of the infusions temporally associated with adverse events.

Table 7: Infusions Temporally Associated with Adverse Events, Safety Set

Category Statistic/Response	3-week Regimen (N=8)	4-week Regimen (N=8)	Total (N=16)
Study [1]			
Total infusions	56	40	96
Total infusions with >=1 TAAE	5	2	7
Proportion of infusions with >=1 TAAE, m/n (%)	5/56 (8.9)	2/40 (5.0)	7/96 (7.3)
Upper 95% one-sided CL based on binomial distribution (exact)	17.9	14.9	13.3
Proportion of patients with >=1 TAAE, m/n (%)	3/8 (37.5)	1/8 (12.5)	4/16 (25.0)
Per Subject [2]			
N	8	8	16
Mean (SD)	8.93 (13.09)	5.00 (14.14)	6.96 (13.32)
Median	0.0	0.0	0.0
Min, Max	0.0, 28.6	0.0, 40.0	0.0, 40.0
Upper 95% one-sided CL of Mean	17.7	14.5	12.8

Abbreviations: CL=Confidence Limit; Max=maximum; Min=minimum; SD=standard deviation; TAAE=temporally associated adverse event (defined as adverse events occurring during or within 1 hour, 24 hours, or 72 hours following an infusion of the study drug).
[1] The calculation is the percentage of affected infusions. m is the number of infusions with >=1 TAAE. n is the number of infusions.
[2] The calculation is the percentage of affected infusions for each subject, then calculating the mean of these percentages, with a 95% (one-sided) confidence limit for the mean. m is the number of subjects with >=1 TAAE. n is the total number of subjects.
Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 12-8.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The Study 994 was a Phase IV, multicenter, open-label study to evaluate the safety, efficacy, and pharmacokinetics of BIVIGAM in primary immune deficiency disorders in subjects aged 2 to 16. Eighteen subjects were enrolled and 16 were included into the mITT set and safety dataset. Two subjects failed the screening.

The primary efficacy endpoint of Study 994 was the incidence of acute serious bacterial infections (SBIs) during the 5-month study observation period. There were no acute SBIs occurred during the observation period (mean 152 days). The mean number of acute SBI episodes per person-year was 0.0.

For the secondary efficacy results, there were no serious infections, or hospitalizations due to infections occurred, and none of the subjects required IV antibiotics during the study. All 17 non-serious infections occurred in 7 subjects (43.8%) in the mITT Set. The mean number of infections (and non Serious infections) per subject was 2.0 in the 3-week infusion schedule group, 0.1 in the 4-week infusion schedule group, and 1.1 overall. The mean time to first infection during the study was 69.3 days in the 3-week infusion schedule group, 75.0 days in the 4-week infusion schedule group, and 70.1 days overall. The mean time to first infection during the study was 69.3 days in the 3-week infusion schedule group, 75.0 days in the 4-week infusion schedule group, and 70.1 days overall. A total of 6 of 16 subjects (37.5%) required antibiotic treatment for infections for a mean duration of 16.5 days (range from 1 to 35 days) during the study. One subject in the 3-

week infusion schedule group missed a total of 9 days from school due to infection; there were no days missed from school in the 4-week infusion schedule group. There were no hospitalizations due to infection during the study.

For safety, 7 of the 96 (7.3%) infusions administered among 16 subjects were temporally associated with at least one adverse event (AE). The one-sided 95% upper confidence limit of the probability that an infusion was associated with an AE was below the threshold of 40%. Most subjects (13 of 16, 81.3%) experienced at least one treatment-emergent adverse events (TEAE) during the study. There were no deaths and no treatment-related serious adverse events (SAEs) occurred during the study.

10.2 Conclusions and Recommendations

In conclusion, there were no major statistical issues related to the submission. Primary results were confirmed by the reviewer's independent analyses. The efficacy results of Study 994 provide adequate statistical evidence for the proposed indication. I defer to the clinical reviewer on the acceptance of the safety profile of BIVIGAM.