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**BLA Clinical Review Memorandum**

|   |  |
|---|--|
| Application Type                              | Efficacy Supplement-BLA  |
| STN   | 125389/300   |
| CBER Received Date                            | February 9, 2023   |
| PDUFA Goal Date                               | December 8, 2023   |
| Division / Office                             | DCEGM/OCE  |
| Priority Review (Yes/No)                      | No   |
| Reviewer Name(s)                              | Hongloan La  |
| Review Completion Date / Stamped Date         | December 8, 2023   |
| Supervisory Concurrence                       |  |
| Team Lead                                     | Shelby Elenburg  |
| Branch Chief                                  | Elizabeth Hart   |
| Division Director                             | Tejashri Purohit-Sheth   |
| Applicant                                     | ADMA Biologics, Inc.   |
| Established Name                              | Immune Globulin Intravenous (human), (b) (4) Liquid  |
| Trade Name                                    | BIVIGAM  |
| Pharmacologic Class                           | Immune Globulin  |
| Formulation(s), including Adjuvants, etc.     | Liquid solution (using water for injection containing 0.100-0.140 M sodium chloride), the product also contains 0.20-0.29 M glycine, (b) (4) 0.25% (1.5 to 2.5 mg/mL) Polysorbate 80 and has a pH of 4.0 to 4.6. Contains ::200 ug/mL of IgA. No preservative. |
| Dosage Form(s) and Route(s) of Administration | 100 ± 10 mg/mL IgG for intravenous administration, supplied in single-use vials of 50 mL (5000 mg)   |
| Dosing Regimen                                | 300 to 800 mg/kg every 3 to 4 weeks  |
| Indication(s) and Intended Population(s)      | Primary Humoral Immunodeficiency in patients 2 years and older   |
| Orphan Designated (Yes/No)                    | No   |

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## GLOSSARY

|         |  |
|---------|--|
| AE      | adverse event                                |
| AR      | adverse reaction                             |
| (b) (4) |  |
| BLA     | biologics license application                |
| CL      | confidence limit                             |
| FDA     | Food and Drug Administration                 |
| IG      | immune globulin                              |
| IgG     | immunoglobulin G                             |
| IGIV    | immune globulin intravenous                  |
| iPSP    | initial pediatric study plan                 |
| MedDRA  | Medical Dictionary for Regulatory Activities |
| mITT    | modified intent-to-treat                     |
| PI      | primary humoral immunodeficiency             |
| PID     | primary immunodeficiency                     |
| PK      | pharmacokinetics                             |
| PMR     | postmarketing requirement                    |
| PREA    | Pediatric Research Equity Act                |
| PT      | preferred term                               |
| REMS    | risk evaluation and mitigation strategy      |
| SAE     | serious adverse event                        |
| SBI     | serious bacterial infection                  |
| SOC     | system organ class                           |
| STN     | submission tracking number                   |
| TEAE    | treatment-emergent adverse event             |

## 1. EXECUTIVE SUMMARY

On February 9, 2023, ADMA Biologics submitted an efficacy supplement for BIVIGAM, a liquid 10% immune globulin solution for intravenous (IGIV) infusion. The efficacy supplement contains the results of Study 994 in children, intended to fulfill the Pediatric Research Equity Act Post-Marketing Requirement (PREA PMR) and a proposal for revised pediatric labeling. BIVIGAM was first licensed for replacement therapy for primary humoral immunodeficiency (PI) in adults in 2012. In accordance with the provisions of section 505B of the Food Drug and Cosmetic Act [21 U.S.C. 355c, also referred to as the Pediatric Research Equity Act (PREA)], the approval of BIVIGAM included a post-marketing requirement (PMR) to complete a pediatric study in PI subjects aged 2 to 16 years of age. In this biologics licensing application (BLA) efficacy supplement 125389/300, the Applicant (ADMA Biologics, Inc.) seeks to obtain approval of BIVIGAM for pediatric patients 2 years of age and older with PI.

In this supplement, to fulfill the PREA PMR and support the pediatric PI indication in children 2 to 16 years of age, the Applicant submitted data from Study 994. Study 994 is a prospective, open-label, single arm, multicenter Phase 4 study wherein sixteen pediatric subjects 2 to 16 years of age with PI were administered BIVIGAM every 3 to 4 weeks at the same dose and regimen as their previous IGIV therapy prior to study enrollment. The subjects were followed over a mean period of approximately 5 months.

The primary efficacy endpoint was incidence of acute serious bacterial infections (SBIs) as defined in accordance with FDA's 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)," which will be referred to as the FDA IGIV Guidance throughout the clinical review memo. Study 994 planned to enroll 6 subjects in each age group: 2 to <6 years, 6 to <12 years and 12 to 16 years, as described in the agreed initial pediatric study plan (iPSP). However, due to challenges in enrollment, the study included only three subjects 2 to <6 years, five subjects 6 to <12 years and eight subjects 12 to 16 years. No acute SBIs occurred during the mean 5-month study period. All pediatric subjects with PK data had consistent immunoglobulin G (IgG) trough levels that remained above target therapeutic range (i.e., >500 mg/dL) throughout Study 994. No subject required dose adjustment due to low IgG levels or infection. Drug clearance was similar between each pediatric age group, and between adult and pediatric PI subjects, based on adult PK data from the previously completed pivotal study.

Additional efficacy data from children is from the pivotal study, Nabi-7101. This study enrolled four children 6 to <12 years old and five children 12 to 16 years old. None of the children had acute SBIs during the 12-month study period, which is consistent with efficacy considerations noted in the FDA IGIV Guidance defining effectiveness as <1 SBI per subject year.

The totality of pediatric clinical and clinical pharmacology data from Study 994 and Nabi-7101 support the indication for children who are at least 2 years of age, even though the Applicant did not follow all aspects of the FDA IGIV Guidance. Subjects were followed for less than a year in Study 994, but they were observed over an even distribution of seasons. Although there were only 3 subjects in the youngest pediatric age group, the lack of SBIs and similar PK assessments across all pediatric age groups allowed for extrapolation of efficacy to the youngest age group despite the short study duration of

Study 994. In conclusion, the cumulative pediatric findings in Study 994 and Nabi-7101 provide substantial evidence of efficacy of BIVIGAM for pediatric patients who are 2 years of age and older. The sponsor has provided substantial evidence of effectiveness from a single adequate and well controlled trial, Study 994, with confirmatory evidence from Study Nabi-7101 and meets the statutory requirements for approval.

All subjects in Study 994 completed all planned infusions and there were no deaths or dropouts due to an adverse event. The safety profile of BIVIGAM in pediatric subjects 2 years and older is consistent with other IGIV products and the safety profile of BIVIGAM in adults. The proportion of infusions temporally associated with an adverse event was below the upper one-sided 95 percent confidence limit of 40 percent, as outlined in the FDA IGIV Guidance.

Based on the review of the data submitted, the Division determined that the PREA post-marketing requirement was fulfilled. The clinical and clinical pharmacology data demonstrate efficacy of the proposed dose range. The benefit/risk is favorable in the pediatric population studied. It is recommended that the indication for PI be expanded to pediatric patients 2 years of age and older. The Pediatric Review Committee (PeRC) agreed with the Division's determination to expand labeling to the pediatric population.

The proposed pharmacovigilance plan (PVP) submitted as part of this post-approval supplement is adequate to monitor post-marketing safety of BIVIGAM with routine pharmacovigilance in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or safety-related post-marketing requirement or commitment (PMR/PMC) study.

### **1.1 Demographic Information: Subgroup Demographics and Analysis Summary**

Study 994 population was predominantly white (13 subjects, 81.3 percent) and non-Hispanic (13 subjects, 81.3 percent), and included 3 subjects (18.8 percent) 2 to <6 years, 5 subjects (31.3 percent) 6 to <12 years, and 8 subjects (50.0 percent) 12 to 16 years. The overall age range was between 3 to 16 years (mean of 10.3 years), and all enrolled subjects were males. [Table 1](#) shows the details of Study 994 demographics.

**Table 1. Demographics for Study 994**

| Category<br>Statistic/Response            | 3-Week Regimen<br>(N=8) | 4-Week Regimen<br>(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  |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-3

Percentages are calculated using N as the denominator.

Abbreviations: kg=kilogram, max=maximum, min=minimum, SD=standard deviation

## 1.2 Patient Experience Data

### Data Submitted in the Application

| Check if Submitted       | Type of Data                                     | Section Where Discussed, if Applicable |
|--------------------------|--|--|
| <input type="checkbox"/> | Patient-reported outcome                         |  |
| <input type="checkbox"/> | Observer-reported outcome                        |  |
| <input type="checkbox"/> | Clinician-reported outcome                       |  |
| <input type="checkbox"/> | Performance outcome                              |  |
| <input type="checkbox"/> | Patient-focused drug development meeting summary |  |
| <input type="checkbox"/> | FDA Patient Listening Session                    |  |



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

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiencies (PIDs) are a large heterogenous group of disorders resulting from inborn errors of immunity. They are characterized by absent or poor function in one or more components of the immune system. Consequently, affected patients are unable to mount an immune response to microorganisms and may experience recurrent protozoal, bacterial, fungal and viral infections. The estimated overall prevalence of PIDs in the United States is approximately 1 in 1200 live births, with the exception of immunoglobulin A (IgA) deficiency, which occurs in approximately 1 in 200 to 1 in 500 persons.

PIDs are broadly classified based on the component of the immune system that is primarily disrupted. Disorders of the adaptive immune system include B-cell (humoral) immune deficiencies (also referred to as antibody deficiencies), T-cell (cellular) immune deficiencies, and combined (B-cell and T-cell) immunodeficiencies. Primary humoral immunodeficiency (PI) is a form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked

agammaglobulinemia, Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, Severe Combined Immunodeficiency, and congenital agammaglobulinemia. Patients with PI present with recurrent, often severe bacterial and viral infections affecting the respiratory tract, gastrointestinal system, skin, as well as other organs.

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

Replacement therapy, comprised of polyclonal human normal immune globulin (IG) infusions, is standard treatment for PI. IG is manufactured through fractionation of plasma pooled from many plasmapheresis donors and contains immune antibodies. IG restores serum IgG to protective levels and provides the patients with specific antibodies to prevent or minimize the frequency or severity of severe bacterial and viral infections. For many patients, therapy is expected to be lifelong and increases life expectancy.

Additional infection prevention includes infection avoidance measures, vaccination, and prophylactic antibiotics. Treatment of infections often requires broad antimicrobial coverage and prolonged treatment courses. Bone marrow transplantation is a treatment option for some forms of PI (such as Severe Combined Immunodeficiency) but is limited by availability of appropriate donors and is associated with multiple risks including graft versus host disease, rejection of the graft, complications of conditioning agents, and death.

## **2.3 Safety and Efficacy of Pharmacologically Related Products**

All approved IGIV products have demonstrated substantial evidence of efficacy based on an SBI rate of less than 1.0 per person-year.

Currently marketed IGIV products, including BIVIGAM, carry the following class-label warnings and precautions (taken from BIVIGAM's label, Section 5 Warning and Precautions):

- Thrombosis
- Hypersensitivity
- Acute Renal Dysfunction and Acute Renal Failure
- Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia
- Aseptic Meningitis Syndrome
- Hemolysis
- Transfusion-Related Acute Lung Injury
- Transmissible Infectious Agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease agent)
- Interference with Laboratory Tests (e.g., passively transferred antibodies in the patient's blood may yield positive serological testing results and passive transmission of antibodies to erythrocyte antigens may cause a positive direct or indirect antiglobulin [Coombs'] test)

The following adverse reactions have been identified and reported during the postapproval use of IGIV products, including BIVIGAM. The following list of

postmarketing adverse events are taken from BIVIGAM's label, Section 6.2

Postmarketing Experience:

- Respiratory: Apnea, Acute Respiratory Distress Syndrome, Transfusion Associated Lung Injury, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- Cardiovascular: Cardiac arrest, thromboembolism, vascular collapse, hypotension
- Neurological: Coma, loss of consciousness, seizures, tremor
- Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- Hematologic: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- General/Body as a whole: Pyrexia, rigors
- Musculoskeletal: Back pain
- Gastrointestinal: Hepatic dysfunction, abdominal pain

#### **2.4 Previous Human Experience With the Product (Including Foreign Experience)**

BIVIGAM was approved in the United States in 2012 for treatment of PI in adults. The recommended dose is between 300 and 800 mg/kg every 3-4 weeks, administered at an initial infusion rate of 0.5 mg/kg/min for the first 10 minutes, with a maintenance infusion rate increased every 20 minutes (if tolerated) by 0.8 mg/kg/min up to a maximum rate of 6 mg/kg/min.

The initial approval of BIVIGAM was based on efficacy, safety and PK findings from a pivotal, multicenter, open-label, non-randomized trial (Study Nabi-7101) that included 54 adult subjects and nine pediatric subjects. The nine pediatric subjects included four children 6 to 11 years and five children 12 to 16 years. Study treatment was administered every 3 to 4 weeks at doses ranging from 254 to 1029 mg/kg/infusion for approximately 1 year. The mean age of subjects included in the study was 41 years.

The primary efficacy analysis included 58 subjects in the intent-to-treat population. During the 12-month study period, two confirmed acute SBIs occurred in two subjects, yielding an overall SBI rate of 0.037 per subject per year, with an upper 1-sided 99 percent confidence interval of 0.101. No SBIs occurred in any of the pediatric subjects. Based on a total of 197 non-SBI and SBI infections, the annualized infection rate was 3.7 infections per subject per year. Two subjects were hospitalized for a total of 122 days, resulting in a mean of 2.3 hospital days per subject year.

The following adverse reaction table ([Table 2](#)) was taken from BIVIGAM's label (Section 6.1 Clinical Trials Experience) and illustrates the most common (25% of subjects) adverse reactions that occurred in the pivotal study. Adverse reactions (ARs) reflected in the table are those that occurred during or within 72 hours after the end of an infusion. The most common ARs were headache, fatigue, infusion site reaction, nausea, sinusitis, and increased blood pressure.

**Table 2. Adverse Reactions (Within 72 hours After the End of a BIVIGAM Infusion) in 5% of Subjects**

| ARs                                | Number of Subjects Reporting ARs<br>(% of Subjects)<br>[n=63] | Number of Infusions With ARs<br>(% of Infusions)<br>[n=746] |
|------------------------------------|---|---|
| Headache                           | 27 (43%)  | 115 (15.4%)   |
| Fatigue                            | 15 (24%)  | 59 (7.9%)   |
| Infusion site reaction             | 5 (8%)  | 5 (0.7%)  |
| Nausea                             | 5 (8%)  | 8 (1.1%)  |
| Sinusitis                          | 5 (8%)  | 5 (0.7%)  |
| Blood pressure increased           | 4 (6%)  | 5 (0.7%)  |
| Diarrhea                           | 4 (6%)  | 4 (0.5%)  |
| Dizziness                          | 4 (6%)  | 4 (0.5%)  |
| Lethargy                           | 4 (6%)  | 4 (0.5%)  |
| Back pain                          | 3 (5%)  | 3 (0.4%)  |
| Blood pressure diastolic decreased | 3 (5%)  | 5 (0.7%)  |
| Fibromyalgia <sup>1</sup>          | 3 (5%)  | 17 (2.3%)   |
| Migraine                           | 3 (5%)  | 8 (1.1%)  |
| Myalgia                            | 3 (5%)  | 4 (0.5%)  |
| Pharyngolaryngeal pain             | 3 (5%)  | 3 (0.4%)  |

Source: BIVIGAM label

1. Symptoms occurring under pre-existing fibromyalgia

Abbreviations: AR=adverse reaction

For BIVIGAM's post-marketing experience, please refer to Section [2.3 Safety and Efficacy of Pharmacologically Related Products](#).

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

BIVIGAM was approved in the United States in 2012 for treatment of PI in adults. At the time of approval, a PMR was established under the Pediatric Research Equity Act to conduct a Phase IV study to evaluate the safety and pharmacokinetics of BIVIGAM in subjects aged 2 to 16 years with PI. The study, known as Study 994 and titled, "A Phase IV, Multicenter, Open-label Study to Evaluate the Safety and Pharmacokinetics (PK) of BIVIGAM in Primary Immune Deficiency Disorders in Subjects Aged 2 to 16", was submitted to FDA on January 14, 2016 and initiated by the previous manufacturer, Biotest Pharmaceuticals. The original PREA PMR completion was planned for October 2017.

In June 2017, ADMA Biologics acquired certain assets from Biotest Pharmaceuticals including BIVIGAM. Enrollment was on hold during the transition period and resumed in 2020. The PREA PMR study was to include evaluation of PK, safety, tolerability and efficacy in 6 subjects in each of the following pediatric categories: ages 2 to <6 years, 6 to <12 years, and 12 to <16 years, as described in the agreed iPSP. However, despite recruitment efforts, ADMA Biologics was not able to meet the enrollment targets in the younger age groups of 2 to <12 years old. A Type C Meeting Request and meeting materials were submitted to the FDA on February 4, 2022. The

purpose of the Type C meeting was to obtain FDA's feedback on whether a population pharmacokinetic (PK) analysis with dense PK data collected in 16 pediatric subjects enrolled in Study 994 and pediatric and adult PK data collected in Study Nabi-7101 (pivotal study) could sufficiently characterize the PK profile in children and support the approval of BIVIGAM for children 2 to 6 years. On April 20, 2022, FDA provided a Written Response that indicated the population PK data and analyses, if comprehensive, may be sufficient to support a revision to the Pediatric Use (8.4) section of the label with description of available data from the younger age group(s). However, without first evaluating the data and analyses, it was premature to opine on whether the data would be sufficient to support the addition of patients 2 to 6 years to <16 years to the approved indication.

The PREA PMR completion date was subsequently extended to December 31, 2022. Between December 26, 2016 and June 11, 2021, a total of 16 subjects: three subjects 2 to 6 years, five subjects 6 to 12 years, and eight subjects 12 to 16 years were enrolled, treated and completed the study. Since no additional subjects were able to be enrolled during the subsequent 12 months, ADMA made the decision to close the study on April 25, 2022.

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

#### 3.2 Compliance With Good Clinical Practices and Submission Integrity

The Division of Inspections and Surveillance conducted Biomedical Monitoring Inspections of three clinical investigator study sites that participated in Study 994. The data from these clinical sites account for approximately 75 percent of the total subjects enrolled in the trial. The inspections were conducted in accordance with FDA's Compliance Programs 7348.811, Inspection Program for Clinical Investigators, Sponsors, Monitor, Contract Research Organization. The Division of Inspections and Surveillance reported that the Biomedical Monitoring inspections did not reveal substantive issues that impacted the data submitted in this post-approval supplement.

#### 3.3 Financial Disclosures

**Covered clinical study** (name and/or number): 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 (Study 994)

Was a list of clinical investigators provided? Yes

Dr. Isaac Melamed (IMMUNOe Research Centers)

Dr. Amy Darter (Oklahoma Institute of Allergy & Asthma Clinical Research, LLC)

Dr. Oral Alpan (Lysosomal Rare Disorders Research and Treatment Center)

Dr. Devi Jhaveri (Ohio Clinical Research Associates)

|  |
|--|
| Dr. Jolan Walter (University of South Florida)<br>Dr. Alan Koterba (Allergy Associates of the Palm Beaches, PA)  |
| Total number of investigators identified: <u>6</u>   |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>   |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p> <p>Is an attachment provided with details of the disclosable financial interests/arrangements? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant)</p> <p>Is a description of the steps taken to minimize potential bias provided?<br/><input type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)</p> |
| <p>Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u></p> <p>Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)</p>  |

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

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

##### 4.1 Chemistry, Manufacturing, and Controls

BIVIGAM is a currently marketed product. No new chemistry, manufacturing, and controls information was provided in this supplement.

##### 4.2 Assay Validation

Not applicable.

### 4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical information was provided in this supplement.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

Ig replacement therapy restores serum IgG to protective levels and provides patients with specific antibodies to prevent or minimize the occurrence or severity of severe bacterial and viral infections.

#### 4.4.2 Human Pharmacodynamics

Not applicable.

#### 4.4.3 Human Pharmacokinetics

Ten out of sixteen subjects in Study 994 contributed sufficient samples for the noncompartmental analysis of serum concentrations of total IgG and IgG subclass after the fifth infusion (4-week regimen) or seventh infusion (3-week regimen). A population PK analysis was conducted using data pooled from Study 994 (PREA PMR study) and a prior pivotal study conducted in adult and pediatric subjects with PI (Study Nabi-7101). Based on the pooled population PK analysis in 79 subjects using evaluable total IgG PK concentrations, the clearance of BIVIGAM was similar across all age groups (2 to <6 years, 6 to <12 years, 12 to 16 years, and >16 years). [Table 3](#) below shows the clearance estimates by age group. Trough concentrations were maintained throughout the study and mean trough concentrations were well above the target trough concentration of 500 mg/dL for both treatment cycles (3-week regimen and 4-week regimen) in pediatric as well as adult subjects at all time points. Please refer to Clinical Pharmacology review memo for further details.

**Table 3. Total Immunoglobulin G Clearance Estimates by Age Group**

| Age Group (Years of Age) | Number of Patients | Clearance (dL/day/kg) Mean | Clearance (dL/day/kg) SD | Clearance (dL/day/kg) CV (%) |
|--------------------------|--------------------|----------------------------|--------------------------|------------------------------|
| 2 to <6                  | 3                  | 0.0149                     | 0.00103                  | 6.9                          |
| 6 to <12                 | 9                  | 0.0146                     | 0.00229                  | 15.7                         |
| 12 to ::16               | 13                 | 0.0137                     | 0.00291                  | 21.2                         |
| >16                      | 54                 | 0.0145                     | 0.00361                  | 24.9                         |

Source: Center for Drug Evaluation and Research's Division of Pharmacometrics consult memo

Abbreviations: CV=coefficient of variation, SD=standard deviation

### 4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. Please refer to the statistical review memo for further details.

#### 4.6 Pharmacovigilance

BIVIGAM has been approved in the United States for treatment of PI in adults for over 10 years. However, the initial indication did allow for use in children as no age minimum was specified on the labeling. Post-marketing surveillance has not shown any increased or unusual risks in the younger population compared to the adult population.

The proposed pharmacovigilance plan (PVP) submitted as part of this efficacy supplement is adequate to monitor post-marketing safety for BIVIGAM with routine pharmacovigilance in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related post-marketing requirement or commitment (PMR/PMC) study.

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

#### 5.1 Review Strategy

Data from one clinical trial, Study 994, were submitted to support approval of BIVIGAM for patients 2 to 16 years with PI. This clinical review memo provides a review of the safety, efficacy, and PK data from Study 994. However, because the previous pivotal study, Nabi-7101, included nine pediatric subjects, the clinical team assessed clinical data from these subjects and from Study 994 for a comprehensive evaluation of the safety and efficacy of BIVIGAM in pediatric PI patients. Additionally, due to the small number of pediatric subjects in Study 994, pooled population PK analysis was conducted by the Applicant, and confirmed by Clinical Pharmacology, using PK data from Study 994 and Nabi-7101. See [5.3](#) for a summary of Study 994 and Study Nabi-7101.

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

- Module 1
  - 1.2 Cover Letters
  - 1.3 Administrative Information
    - 1.3.4 Financial Certification and Disclosure
  - 1.11 Information Note Covered Under Modules 2 to 5
    - 1.11.3 Clinical Information Amendment
  - 1.14 Labeling
    - 1.14.1 Draft Labeling
- Module 2
  - 2.7 Clinical Summary
    - 2.7.6 Synopses of Individual Studies
- Module 5
  - 5.2 Tabular Listing of all Clinical Studies
  - 5.3 Clinical Study Reports
    - 5.3.5 Reports of Efficacy and Safety Studies
      - 5.3.5.3 Datasets



- BLA 125389/0 Clinical Review Memo for information regarding previous pivotal study, Study Nabi-7101

### 5.3 Table of Studies/Clinical Trials

**Table 4. Studies/Clinical Trials Reviewed for the BLA**

| Type of Study                 | Study Identifier           | Subject Ages     | Study Design                       | Number of Subjects               | Study Duration | Dose                          | Serious Bacterial Infections   |
|-------------------------------|----------------------------|------------------|------------------------------------|----------------------------------|----------------|-------------------------------|--------------------------------|
| Phase 3, Efficacy, PK, Safety | Nabi-7101 (pivotal study)  | 26 years         | Multi-center, open-label           | N=63 (54 adults and 9 pediatric) | 12 months      | 300-800 mg/kg every 3-4 weeks | 2 (none in pediatric subjects) |
| Phase 4, Efficacy, PK, Safety | Study 994 (PREA PMR study) | 22 to ::16 years | Multi-center, open-label (US only) | N=16 (all pediatric)             | 5 months       | 300-800 mg/kg every 3-4 weeks | 0                              |

Source: Clinical Reviewer

Abbreviations: PK=pharmacokinetics, PREA=Pediatric Research Equity Act, PMR: postmarketing requirement

**Reviewer's Comments:** Study 994 data were submitted and fully analyzed under this efficacy supplement. Study Nabi-7101 was the pivotal study that led to BIVIGAM's initial approval in 2012. Study Nabi-7101 data were fully analyzed under STN BLA 125389/0. Nabi-7101 study is included in this clinical review memo because the study included 9 pediatric subjects 6 to 16 years. The efficacy and PK data from Study Nabi-7101 combined with the efficacy and PK data from Study 994 provided substantial evidence of efficacy for BIVIGAM in treatment of PI in pediatric subjects who are at least 2 years old. For more details regarding Study Nabi-7101, please refer to Section [2.4 Previous Human Experience With the Product \(Including Foreign Experience\)](#) or STN BLA 125389/0 Clinical Review Memo. The details and analysis of Study 994 safety and efficacy data can be found in Section [6.1 Trial #1](#) of this clinical review memo.

## 5.4 Consultations

### 5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was held.

### 5.4.2 External Consults/Collaborations

The Center for Drug Evaluation and Research's Division of Pharmacometrics was consulted to analyze the population PK data. The pooled population PK analysis contained 79 evaluable subjects (Study 994 [n=16] and Study Nabi-7101 [n=63]) with 3, 9, 13, and 54 subjects in the age group of 2 to <6 years, 6 to <12 years, 12 to 16 years, and >16 years, respectively. The consultants concluded that the population PK model successfully described the PK of BIVIGAM. The model estimated clearance was similar across all age group categories and the model predicted that clinically acceptable IgG trough levels would be achieved in pediatric patients. The modeling and simulations for BIVIGAM supported the proposed body weight-based dosing regimen.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1

Study 994 was a Phase IV, multicenter, open-label study to evaluate the safety, pharmacokinetics and efficacy of BIVIGAM in subjects 2 to 16 years old with PID.

#### 6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to evaluate the safety of BIVIGAM in subjects 2 to 16 years with PID. The secondary objective is to evaluate the PK profile and efficacy of BIVIGAM in subjects aged 2 to 16 years with PID. This study was conducted to fulfill a PREA PMR as agreed upon during the initial approval of BIVIGAM in 2012.

#### 6.1.2 Design Overview

Study 994 was a prospective, open-label, single-arm study with a treatment and follow-up duration of 5 months.

**Reviewer's comment:** Based on the FDA IGIV Guidance, in evaluating the efficacy of an IGIV product, studies should "measure the rate of serious bacterial infections during regularly repeated administration of the investigational IGIV product in adult and

*pediatric subjects for 12 months (to avoid seasonal biases).” The study duration of 5-months in Study 994 is not consistent with the FDA IGIV Guidance to determine the incidence of serious bacterial infection. However, due to difficulties in conducting pediatric studies with IGIV products given the widely available number of approved IGIV products, it is reasonable to look at the totality of clinical and clinical pharmacology data in determining whether data that is less than 12 months is acceptable. In this case, we believe that the data are sufficient. Please refer to Section [6.1.11 Efficacy Analyses](#) for further details regarding the efficacy analyses of Study 994.*

### 6.1.3 Population

Subjects were eligible for study inclusion if they met all the following inclusion criteria:

- Are male or female 2 to 16 years at time of signing Informed Consent/Assent by subject or legal guardian
- Have confirmed and documented diagnosis of PID including hypogammaglobulinemia or agammaglobulinemia
- Have received IGIV therapy maintained at a steady dose ( $\pm 25$  percent of the mean dose) for at least 3 months prior to study entry and have maintained a trough IgG level of at least 500 mg/dL prior to receiving BIVIGAM

Subjects were excluded from study participation if they met any of the following exclusion criteria:

- Known intolerance to immunoglobulins or comparable substances (e.g., vaccination reaction)
- Known intolerance proteins of human origin; known allergic reaction to components of the study product
- Selective IgA deficiency or known antibodies to IgA
- Medical condition, laboratory finding, or physical exam finding (specify, e.g., vital signs outside of specific range that precludes participation)
- Confirmed screening visit laboratory results  $>2.5$  times upper limit of normal as defined at the local laboratory for pediatric populations for any of the following:
  - Alanine aminotransferase
  - Aspartate aminotransferase
  - Lactate dehydrogenase
  - Blood urea nitrogen
  - Serum creatinine
- Current use of daily corticosteroids ( $>10$  mg of prednisone equivalent/day); immunosuppressants or immunomodulators were prohibited, unless approved in advance by the medical monitoring. Intermittent use of corticosteroids during the study was allowed if medically necessary.
- Positive diagnosis of hepatitis B or hepatitis C
- Positive human immunodeficiency virus test
- SBI within the last 3 months
- Active infection and receiving antibiotic therapy for treatment of this infection at the time of screening

- History of thrombotic events (including deep vein thrombosis, myocardial infarction, cerebrovascular accident, and pulmonary embolism) within 6 months before first IGIV dose or has preexisting risk factors for thrombotic events
- Acquired medical condition known to cause secondary immune deficiency such as chronic lymphocytic leukemia, lymphoma, or multiple lymphoma
- Protein-losing enteropathies, hypoalbuminemia
- Females taking oral contraceptives
- Pregnancy or unreliable contraceptive measures or lactation period (females of childbearing potential). Males capable of reproduction must agree to a double-barrier method of contraception during their study participation.

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

BIVIGAM is a liquid IGIV that contains approximately 100 mg/mL of human IgG and no preservatives. The test product was supplied in single-use vials of 50 mL (containing 5 g of protein in total). The following Lot Numbers of BIVIGAM were used during the study: 160024 and 2448-19. The investigational medicinal product was manufactured by ADMA Biologics and labelled and distributed to sites by (b) (4). It was stored at a temperature between 2 to 8°C (36 to 46°F).

All subjects were required to have received steady doses of an IGIV product for at least 3 months and maintained a trough IgG level of at least 500 mg/dL prior to study enrollment. After enrollment into the study, the subjects were treated with the same IGIV dose (300 to 800 mg/kg) and regimen (every 3 or 4 weeks) as their previous IGIV therapy prior to study enrollment. Subjects on the 3-week regimen received a total of seven IGIV infusions. Subjects on the 4-week regimen received a total of five IGIV infusions. Upon completion of the study treatment, subjects underwent a follow-up visit within 3 weeks (for those on the 3-week regimen) or within 4 weeks (for those on the 4-week regimen). This was a single-arm study, so no control product was administered to any study subjects.

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 ADMA Biologics Medical Director (or designee).

Use of daily corticosteroids (>10 mg of prednisone equivalent/day), immunosuppressants, or immunomodulators were not allowed unless approved in advance by the medical monitor. Intermittent use of corticosteroids during the study was allowed if medically necessary. The use of pre-medications was allowed if medically necessary. If subjects required premedication (e.g., Tylenol, Benadryl, etc.) for recurrent reactions to immune globulins, they were allowed to continue those medications for this study.

**Reviewer's comments:** *The BIVIGAM doses and dosing intervals used in the study are consistent with the approved doses of BIVIGAM for treatment of PI. Dose adjustment criteria, prohibition of daily corticosteroids, and allowance of pre-medications with Tylenol and Benadryl are appropriate.*

#### 6.1.5 Directions for Use

Not applicable.

### 6.1.6 Sites and Centers

[Table 5](#) below lists the six principal investigators and investigative sites with active recruitment of subjects during Study 994.

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

| Site ID | Investigator   | Location   | Number of Subjects Screened/Enrolled <sup>1</sup> | Number of Subjects Treated |
|---------|--|--|---|----------------------------|
| 01      | Dr. Isaac Melamed                                      | IMMUNOe International Research Centennial, CO 80112  | 5   | 4                          |
| 03      | Dr. Amy Darter   | Oklahoma Institute of Allergy and Asthma Clinical Research, LLC<br>Oklahoma City, OK 73131 | 4   | 4                          |
| 04      | Dr. Oral Alpan   | LDRTC (Lysosomal Rare Disorders Research and Treatment Center)<br>Fairfax, VA 22030        | 4   | 3                          |
| 05      | Dr. Devi Jhaveri                                       | Ohio Clinical Research Associates, Inc.<br>Mayfield Heights, OH 44124                      | 1   | 1                          |
| 07      | Dr. Jolan Walter<br>(previously: Dr. Jennifer Leiding) | University of South Florida<br>Tampa, FL 33701   | 3   | 3                          |
| 08      | Dr. Alan Koterba                                       | Allergy Associated of the Palm Beaches<br>Palm Beach, FL 33408                             | 1   | 1                          |
| Total   |  |  | 18 [1]  | 16                         |

Source: Adapted from sBLA 125389/300; Clinical Study Report, Table 6-2

Note: Two additional sites were active but did not screen/enroll or treat any subjects in Study ADMA 994: Site 06 (Allergy, Asthma & Immunology Relief, Charlotte, NC; PI Dr. Maeve O'Connor), and Site 09 (Duke University, Durham, NC; PI Dr. John Sleasman).

1. In this study, all subjects who had given informed consent/assent to participate in the study were considered "enrolled"; these subjects constitute the "All Subjects Enrolled Set."

### 6.1.7 Surveillance/Monitoring

Study visits for monitoring of safety and efficacy occurred during each infusion (five infusions for 3-week regimen cohort and seven infusions for 4-week regimen cohort) and 3 to 4 weeks after the last infusion. Assessments included adverse events (AE) and concomitant medication collection, physical exam, weight, vital signs, and IgG level, hematology, chemistry, and urinalysis testing. Table 6 details the study visits and assessments.

Table 6. Schedule of Study Assessments

| Period  | Screening  | Treatment                    |                             |                  |  |                       |                             |                                 | Follow-up       |
|---|------------|------------------------------|-----------------------------|------------------|--|-----------------------|-----------------------------|---------------------------------|-----------------|
| Infusion #  | -          | Infusion 1,2,3,4, (5*), (6*) |                             |                  | Infusion 5 or 7*   |                       |                             |                                 | -               |
| Study Visit #   |            | Visit 1 – 4 or Visit 1- 6    |                             |                  | Visit 5 or Visit 7   |                       |                             |                                 |                 |
| Visit Day   | D-30 to D0 | D0                           |                             |                  | 6h, 24h, D7, D14, and D21/EOT (for 3-week cycle ) or Day 28 ±1 day/EOT (for 4-week cycle). |                       |                             |                                 | Follow up visit |
|   |            | Pre <sup>4</sup>             | End of infusion + 10-30 min | Pre <sup>4</sup> | End of infusion + 10-30 min  | 6h, 24h post-infusion | Day 7, Day 14 post-infusion | Day 21 / 28 post-infusion (EOT) |                 |
| Informed Consent/Assent   | X          |                              |                             |                  |  |                       |                             |                                 |                 |
| Medical History <sup>1</sup>  | X          |                              |                             |                  |  |                       |                             |                                 |                 |
| AE Collection <sup>5</sup>  | X          | X                            |                             | X                |  | X                     | X                           | X                               | X               |
| Adverse Events <sup>3,7</sup>   | X          | X                            | X                           | X                | X  |                       | X                           |                                 | X               |
| Dispense/Collect AE Diary   | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Physical Exam   | X          | X                            |                             |                  | X  |                       |                             |                                 |                 |
| Weight (kg) <sup>2</sup>  | X          |                              |                             |                  |  |                       |                             |                                 |                 |
| Vital Signs: BP, heart rate, respiratory rate, temperature <sup>3,5</sup>       | X          | X                            | X                           | X                | X  |                       | ≤ 30 min                    |                                 |                 |
|   |            | ≤ 15 min                     |                             | ≤ 15 min         |  |                       |                             |                                 |                 |
| Total IgG Trough Sample   | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Baseline PK <sup>10</sup>   |            | X                            |                             | X                |  |                       |                             |                                 |                 |
| Dense PK <sup>11</sup>  |            |                              |                             | X                | X  | X                     | X                           | X                               |                 |
| IGIV Infusion   |            | X                            |                             | X                |  |                       |                             |                                 |                 |
| Concomitant Medications <sup>7</sup>  | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Serum Creatinine  | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| BUN   | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Serum Chemistry*  | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Hematology (Hemoglobin 2g/DL drop to below LLN [where applicable]) <sup>6</sup> | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Urinalysis  | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Serum haptoglobin <sup>6</sup>  | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Plasma-free haptoglobin <sup>6</sup>  | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| Urine hemosiderin <sup>6</sup>  | X          | X                            |                             | X                |  |                       |                             |                                 |                 |
| direct-anti-globulin (DAT/Coombs Testing) <sup>6</sup>                          | X          | X                            |                             |                  |  |                       |                             |                                 |                 |
| Viral Serology  | X          |                              |                             |                  |  |                       |                             | X                               |                 |
| Serum Pregnancy Test  | X          |                              |                             |                  |  |                       |                             |                                 |                 |
| Urine Pregnancy Test <sup>9</sup>   |            |                              |                             |                  |  |                       |                             | X                               |                 |

Source: Adapted from sBLA 125389/300; Clinical Study Report, Table 9-1

1. Medical history includes hypertension, hypotension, hepatitis, renal disease and liver injury.
2. CRO partners/facility, physical exam. Weight is measured in kg at Screening and prn, where appropriate.
3. Vital signs collected and measured up to approximately 15 minutes pre-infusion, prior to each infusion rate change, and approximately every 15 minutes for the first hour, every 30 minutes for the second hour, then at the onset of any AE and 30 minutes postinfusion. VS include blood pressure measurements with correct size pediatric/adult BP cuff.
4. Predose samples must be taken from few (5) minutes up to 2-4 hours before next dosing.
5. AE Collection queries (e.g.; IGIV infusion related AEs including IVIG infusion rate at time of AE onset, the time of onset of AEs, and the time AEs changed materially in intensity or resolve; review of subject diary ; number of infections (SBI and no-SBI, serious and nonserious), time to resolution of infections, antibiotic treatment of infections, number of days subject missed school/work due to infections or their treatment; any hospitalization and number of days hospitalized, incidence of fever  $\geq 38.0^\circ\text{C}$  (100.4°F) including the number of days with fever and if treated with antipyretic for fever record subject's body temperature.
6. Perform clinical evaluation for intravascular hemolysis during and post IGIV administration includes measurement of specific eluted antibodies in the event of positive Coombs test measurement and retesting. Indication of intravascular hemolysis is evaluated as: a drop in hemoglobin of 2 g/dL or greater, in conjunction with both a drop in serum haptoglobin to below the lower limit of normal (LLN ) and a rise in serum LDH from baseline.
7. Perform clinical and laboratory evaluation, including review of AEs for signs and symptoms of thrombosis.
8. This assessment is intended to be used for dosing adjustments- in order to maintain per protocol trough levels- only.

Abbreviations: AE=adverse event, BP=blood pressure, BUN=blood urea nitrogen, D=day, DAT=Direct Antiglobulin Test, EOT=end of treatment, h=hours, IgG=immunoglobulin G, min=minutes, LLN=lower limit of normal, PHI=Private Health Information, PK=pharmacokinetic, Pre=pre-infusion



A third-party Data Safety Monitoring Board monitored the safety of study subjects on a periodic basis. Members of the Data Safety Monitoring Board were independent of the study teams and ADMA Biologics. The two voting members were clinicians experienced in management of pediatric patients with PID and the third, a nonvoting member, was the reporting statistician.

Site management and clinical monitoring responsibilities were delegated to (b) (4) as the responsible clinical research organization (b) (4) also provided safety reporting, data management, and statistical services including the design and implementation of the Statistical Analysis Plan for the study. An independent statistician (b) (4) consulted on the statistical analysis plan and the statistical analyses. Medical monitoring was delegated to (b) (4) for all sites.

Case Report Forms were used for data collection. Entries in the case report forms were made by the investigator or persons authorized by the investigator.

#### 6.1.8 Endpoints and Criteria for Study Success

Prespecified safety endpoints included the following:

- Incidence of temporally associated adverse events (defined as AEs occurring during or within 1 hour, 24 hours, or 72 hours of completion of an infusion)
- Mean number of temporally associated AEs per infusion
- Incidence of SAEs and related SAEs
- Incidence of treatment-emergent adverse events (TEAEs) and related TEAEs
- Incidence of nontreatment-emergent adverse events
- Incidence of adverse infusion-related reactions
- Incidence of infusion site reactions
- Change in vital signs before and after administration of study drug.

Prespecified PK endpoints include the following:

- Trough levels of Total IgG prior to each administration and IgG subclasses 1 to 4 prior to the fifth and seventh administration
- End of infusion level of Total IgG
- Total IgG PK parameters after the fifth and seventh infusion including maximum serum concentration ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), minimum serum concentration ( $C_{min}$ ), elimination rate constant (AZ), elimination half-life ( $t_{1/2}$ ), area under the curve (AUC), total serum clearance and volume of distribution ( $V_z$ )
- Levels of specific antibody (anti-pneumococcal capsular polysaccharide, anti-haemophilus influenza B)

After the fifth infusion (4-week cycle regimen) and seventh infusion (3-week cycle regimen), IgG serum concentration samples are drawn at the following timepoints: pre-dose, 10 to 30 minutes after end of the infusion, 6 and 24 hours, 7 days, 14 days, 21 days, and 28 days (for the 4-week schedule only) postinfusion.

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Prespecified clinical efficacy endpoints included the following:

- Primary efficacy endpoint:
  - Incidence of acute serious bacterial infections, including bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis
- Secondary efficacy endpoints:
  - Incidence of infections of any kind (serious versus nonserious)
  - Time to first infection (serious and nonserious)
  - Time to resolution of infections/duration of infection
  - Number of days of antibiotics treatments
  - Number of school/workdays missed due to infections and their treatment
  - Episodes of fever (2 38°C or 2100.4°F)
  - Number of days of hospitalizations due to infections.

**Reviewer's comments:** *Study endpoints were not modified during or after completion of the study. Safety, PK, and efficacy endpoints are consistent with FDA IGIV Guidance. Serious bacterial infection (i.e., bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) definitions were also consistent with the FDA IGIV Guidance.*

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review memo.

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

Definition of analysis populations:

- All Subjects Enrolled Set: all subjects who have given informed consent/assent to the study.
- Safety Analysis Set: all subjects who received at least one dose of study medication.
- 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.

A total of 18 subjects were screened and enrolled, and 16 subjects received at least one dose of BIVIGAM. These 16 subjects constituted the Safety set and the mITT set. There was an equal distribution of subjects between the 3-week regimen and 4-week regimen cohorts. [Table 7](#) shows the population enrolled in the study.

**Table 7. Population Enrolled for Study 994**

| Population Sets | 3-Week Infusion Regimen, | 4-Week Infusion Regimen, | Total           |
|-----------------|--------------------------|--------------------------|-----------------|
|                 | n                        | n                        |                 |
| Screened        | -                        | -                        | 18              |
| Enrolled        | 8                        | 8                        | 16 <sup>1</sup> |
| mITT set        | 8                        | 8                        | 16              |
| Safety set      | 8                        | 8                        | 16              |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-1

1. Two subjects were screen failures

Abbreviation: mITT=modified intent-to-treat

#### 6.1.10.1.1 Demographics

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

**Table 8. Demographics for Study 994**

| Category<br>Statistic/Response            | 3-Week Regimen<br>(N=8) | 4-Week Regimen<br>(N=8) | Total<br>(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     |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-3

Percentages are calculated using N as the denominator.

Abbreviations: kg=kilogram, max=maximum, min=minimum; SD=standard deviation

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**Reviewer's Comments:** Study 994 planned to enroll six subjects in each age group: 2 to <6 years, 6 to <12 years, and 12 to '516 years, as described in the agreed iPSP. However, due to challenges in enrollment, the study included only three subjects 2 to <16 years, 5 subjects 6 to <12 years, and 8 subjects 12 to '516 years. Despite the suboptimal number of subjects in the 2 to <6-year and 6 to <12-year age groups, there were safety, PK, and efficacy data for analysis and approval determination. Please refer to Sections [4.4.3 Human Pharmacokinetics](#), [6.1.11 Efficacy Analyses](#), and [6.1.12 Safety Analyses](#) for further details.

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

##### **PID Diagnosis**

The most common PID diagnoses were hypogammaglobulinemia (8 subjects, 50 percent), followed by common variable immunodeficiency (4 subjects, 25 percent), combined immunodeficiency (2 subjects, 12.5 percent), Bruton's agammaglobulinemia (1 subject, 6.3 percent), and selective polysaccharide antibody deficiency (1 subject, 6.3 percent). 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 with stable doses for at least 3 months prior to study enrollment. The last IGIV doses prior to first BIVIGAM administration ranged from 300 mg/kg to 1,043 mg/kg in the 3-week regimen cohort, and between 313 mg/kg and 622 mg/kg in the 4-week regimen cohort. One subject in the 4-week regimen (Subject (b) (6)) had an IgG trough level that was below 500 mg/dL prior to the first BIVIGAM infusion but had an IgG trough level above 500 mg/dL at screening. All other subjects had IgG trough levels above 500 mg/dL at screening and prior to the first BIVIGAM infusion. The 3-week regimen cohort had higher baseline trough IgG levels compared to the 4-week regimen cohort. [Table 9](#) shows the details of the years since PID diagnosis and IgG trough levels at screening and prior to the first BIVIGAM infusion.

**Table 9. Disease Characteristics at Baseline, Safety Set**

| Category<br>Statistic/Response                    | 3-Week Regimen<br>(N=8) | 4-Week Regimen<br>(N=8) | Total (N=16)   |
|---|-------------------------|-------------------------|----------------|
| Years since PID<br>diagnosis (years) <sup>1</sup> | 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)<br>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)<br>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      |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-4.

1. Years since PID Diagnosis = (date of informed consent – PID diagnosis date + 1)/365.25

Abbreviations: IgG=immunoglobulin G, kg=kilogram, max=maximum, Min=minimum, PID=primary immunodeficiency, SD=standard deviation

**Reviewer's comment:** *The most common PIDs included in the study represent the most common forms of PID within the general population.*

### Medical History

All subjects had a history of at least one prior medical condition apart from PID. The most commonly reported (frequency 250 percent) prior to medical conditions/disorders by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) were infections and infestations (13 subjects, 81.3 percent), followed by respiratory thoracic and mediastinal disorders (11 subjects, 68.8 percent), immune system disorders, surgical and medical procedures (99 subjects, 56.3 percent), gastrointestinal disorders, and nervous system disorders (88 subjects, 50.0 percent each) The most commonly reported (frequency 2 20 percent) prior medical conditions/disorders by MedDRA Preferred Terms (PT) were rhinitis allergic (10 subjects, 62.5 percent), asthma (88 subjects 50.0 percent), chronic sinusitis, gastroesophageal reflux disease (55 subjects, 31.3 percent), sinusitis, and tonsillectomy (4 subjects, 25.0 percent each).

**Reviewer's comments:** *The most common medical conditions affecting subjects in the study represent common medical conditions that may affect the general population with PID.*

### Prior and Concomitant Medications

Apart from prior IVIG Infusions, prior medication use consisting of ibuprofen was reported for one subject in the 4-week regimen cohort (Subject (b) (6)). The majority of the subjects (15 subjects, 93.8 percent) took at least one concomitant medication (prescription or nonprescription) during the study. The most used (frequency 250 percent) concomitant medications by class were non-steroidal anti-inflammatory and antirheumatic products (9 subjects, 56.3 percent), inhalant adrenergic, systemic antihistamines and decongestants and other nasal preparations for topical use (8

subjects, 50 percent each). The most commonly used (frequency 2 20 percent) concomitant medications by preferred term were ibuprofen (9 subjects, 56.2 percent), followed by salbutamol sulfate (6 subjects, 37.5 percent), cetirizine, epinephrine, fluticasone, propionate, and salbutamol (4 subjects, 25.0 percent each).

**Reviewer's comments:** *The most common concomitant medications used by subjects in the study represent common concomitant medications that may be used in the general population with PID.*

#### 6.1.10.1.3 Subject Disposition

A total of 18 subjects were screened and enrolled. Two enrolled subjects did not proceed to the administration of BIVIGAM due to screening failure. For the other 16 subjects, 8 were treated in the 3-week regimen cohort and 8 were treated in the 4-week regimen cohort. No subjects withdrew from 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 incidence of SBIs in the mITT set (n=16). No acute SBIs occurred during the study observation period (mean 152 days). The descriptive primary efficacy results are provided in [Table 10](#).

**Table 10. Incidence of Acute Serious Bacterial Infections, mITT Set**

| Category<br>Statistic/Response                             | 3-Week<br>Regimen (N=8) | 4-Week Regimen<br>(N=8) | Total (N=16)  |
|--|-------------------------|-------------------------|---------------|
| Number of ASBI episodes<br>(per person-years) <sup>1</sup> |                         |                         |               |
| 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      |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-6

<sup>1</sup> 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.

Abbreviations: ASBI=acute serious bacterial infection, max=maximum, min=minimum, mITT=modified intent-to-treat, NA=not applicable, SD=standard deviation

**Reviewer's comments:** *The FDA IGIV Guidance considers the demonstration of SBI rate per person-year less than 1.0 as adequate to provide substantial evidence of efficacy and that the rate of SBI is measured during regularly repeated administration of the IGIV product for 12 months to avoid seasonal bias. The SBI rate in Study 994 was 0 per person over a 5-month study period. Evaluation of the treatment months showed the seasons in which the subjects were treated and observed during the study were evenly distributed between the four seasons. [Table 11](#) below shows the treatment months for each subject. In addition, PK data demonstrated that clearance of BIVIGAM was similar*

across all pediatric age groups and between pediatric and adult subjects. Consistent IgG trough levels were maintained throughout the study and were above the target therapeutic range of 500 mg/dL for both 3-week and 4-week regimens. Furthermore, results from the previous pivotal study, Nabi-7101, which included 4 children 6 to <12 years and 5 children 12 to <16 years, showed no SBIs occurred during the 12-month study period. The cumulative data from Study 994 and Nabi-7101 provide substantial evidence of efficacy of BIVIGAM for pediatric patients who are at least 2 years old.

**Table 11. Subjects' Treatment Months**

| Age Group (Years) | Subject | Treatment Months      |
|-------------------|---------|-----------------------|
| 2 to <6           | (b) (6) | December to June      |
| 2 to <6           | (b) (6) | May to October        |
| 2 to <6           | (b) (6) | September to January  |
| 6 to <12          | (b) (6) | May to October        |
| 6 to <12          | (b) (6) | May to October        |
| 6 to <12          | (b) (6) | December to June      |
| 6 to <12          | (b) (6) | January to June       |
| 6 to <12          | (b) (6) | September to January  |
| 12 to <16         | (b) (6) | September to January  |
| 12 to <16         | (b) (6) | January to July       |
| 12 to <16         | (b) (6) | April to September    |
| 12 to <16         | (b) (6) | June to November      |
| 12 to <16         | (b) (6) | February to July      |
| 12 to <16         | (b) (6) | September to February |
| 12 to <16         | (b) (6) | August to January     |
| 12 to <16         | (b) (6) | September to March    |

Source: Clinical Reviewer

#### 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 percent) in the mITT set. Sixteen infections occurred in 6 subjects (75 percent) in the 3-week infusion schedule group, and a single infection occurred in 1 subject (12.5 percent) in the 4-week infection schedule group.

##### **Number of Nonserious Infections**

All 17 infections were nonserious. No serious infections were reported during the study. The mean number of 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.

### Duration of Infections

The mean duration of infections per subject was 21.5 days in the 3-week regimen group, 0.4 days in the 4-week regimen group, and 10.9 days overall.

### Number of Days of Antibiotic Treatment for Infections

A total of 6 out of 16 subjects (37.5 percent) required antibiotic treatment for infections for a mean duration of 1.65 days (ranging from 1 to 35 days) during the study. Five subjects (62.5 percent) required antibiotic treatment for a mean duration of 12.8 days (ranging from 1 to 31 days) in the 3-week infusion schedule group, and 1 subject (12.5 percent) required antibiotic treatment for 35 days in the 4-week infusion schedule group. None of the subjects required intravenous antibiotics during the study.

### Number Days Missed From School/Work Due to Infections

One subject in the 3-week regimen group missed a total of 9 days of school due to infection. There were no days missed of school in the 4-week regimen 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 $\geq 38^{\circ}\text{C}$ ( $\geq 100.4^{\circ}\text{F}$ ) (Per Subject and Overall)

The Applicant reported that the number of episodes of fever (defined as a body temperature  $\geq 38^{\circ}\text{C}$ ) was zero. However, the reported number of episodes of fever did 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 12](#).

**Table 12. Summary of Other Secondary Efficacy Endpoints, mITT Set**

| Category<br>Statistic/Response                                  | 3-Week<br>Regimen (N=8) | 4-Week<br>Regimen (N=8) | Total<br>(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 nonserious infections on study                  | 16                      | 1                       | 17              |
| Total number of nonserious 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) <sup>1</sup>         | 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         |



| Category<br>Statistic/Response  | 3-Week<br>Regimen (N=8) | 4-Week<br>Regimen (N=8) | Total<br>(N=16) |
|---|-------------------------|-------------------------|-----------------|
| Time to resolution of infection (days) <sup>2</sup>                   | 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) <sup>3</sup>                | 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                      | 9                       | 0                       | 9               |
| Number of days missed school/work per subject                         | 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 238° C on study <sup>4</sup>          | 0                       | 0                       | 0               |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 11-7

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 238° C on study."

Abbreviations: max=maximum, MedDRA=Medical Dictionary for Regulatory Activities, min=minimum, mITT=modified intent-to-treat, SD=standard deviation, TEAE=treatment-emergent adverse event

**Reviewer's comments:** *The above findings are similar to other U.S.-licensed IGIV products in pediatric patients with PI and BIVIGAM in adults.*

#### 6.1.11.3 Subpopulation Analyses

Subpopulation analysis was not performed because there were no acute SBI events that occurred during the study.

#### 6.1.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

## 6.1.12 Safety Analyses

### 6.1.12.1 Methods

The safety population consisted of all subjects who received any amount of BIVIGAM (N=16). Adverse events were obtained by the investigator through observation of the subject, from any information volunteered by the subject, and through active questioning during infusion visits and last follow-up visit. Also, a subject diary was provided to each subject to record adverse events daily between visits. The adverse events datasets contain safety data obtained actively and passively.

### 6.1.12.2 Overview of Adverse Events

The most common treatment-emergent adverse events by MedDRA SOC (frequency 220 percent) were infections and infestations (7 subjects, 43.8 percent), respiratory, thoracic, and mediastinal disorders (7 subjects, 43.8 percent), nervous system disorders (6 subjects, 37.5 percent), general disorders and administration site conditions (4 subjects, 25 percent), and gastrointestinal disorders (4 subjects, 25.0 percent). The most common TEAEs by MedORA PT (frequency 210 percent) were headache (31.3 percent), upper respiratory infection (18.8 percent), bronchitis, cough, fatigue, influenza, nasal congestion, oropharyngeal pain, pyrexia, and sinus congestion (12.5 percent each). [Table 13](#) provides details regarding common TEAEs by MedDRA SOC and PT. There was one SAE that was considered by the Applicant and the clinical reviewer to not be related to BIVIGAM. Please refer to Section [6.1.12.4 Nonfatal Serious Adverse Events](#) for further details. All other TEAEs were mild to moderate in severity. There were no TEAEs that lead to treatment interruption or withdrawal, study withdrawal, or death.

Table 13. Common Adverse Events, by MedDRA System Organ Class and Preferred Term

| System Organ Class/Preferred Term                | 3-Week Regimen (N=8) Total Events | 3-Week Regimen (N=8) Subjects (n) | 3-Week Regimen (N=8) n (%) | 4-Week Regimen (N=8) Total Events | 4-Week Regimen (N=8) Subjects (n) | 4-Week Regimen (N=8) n (%) | Total (N=16) Total Events | Total (N=16) Subjects (n) | Total (N=16) n (%) |
|--|-----------------------------------|-----------------------------------|----------------------------|-----------------------------------|-----------------------------------|----------------------------|---------------------------|---------------------------|--------------------|
| Subjects with at least one TEAE                  | 62                                | 8                                 | 100                        | 12                                | 5                                 | 62.5                       | 74                        | 13                        | 81.3               |
| Infections and infestations                      | 16                                | 6                                 | 75                         | 1                                 | 1                                 | 12.5                       | 17                        | 7                         | 43.8               |
| Upper respiratory tract infection                | 2                                 | 2                                 | 25                         | 1                                 | 1                                 | 12.5                       | 3                         | 3                         | 18.8               |
| Bronchitis                                       | 3                                 | 2                                 | 25                         | 0                                 | 0                                 | 0                          | 3                         | 2                         | 12.5               |
| Influenza  | 2                                 | 2                                 | 25                         | 0                                 | 0                                 | 0                          | 2                         | 2                         | 12.5               |
| Respiratory, thoracic, and mediastinal disorders | 12                                | 4                                 | 50                         | 3                                 | 3                                 | 37.5                       | 15                        | 7                         | 43.8               |
| Sinus congestion                                 | 3                                 | 1                                 | 12.5                       | 1                                 | 1                                 | 12.5                       | 4                         | 2                         | 12.5               |
| Nasal congestion                                 | 2                                 | 1                                 | 12.5                       | 1                                 | 1                                 | 12.5                       | 3                         | 2                         | 12.5               |
| Oropharyngeal pain                               | 3                                 | 2                                 | 25                         | 0                                 | 0                                 | 0                          | 3                         | 2                         | 12.5               |
| Cough  | 1                                 | 1                                 | 12.5                       | 1                                 | 1                                 | 12.5                       | 2                         | 2                         | 12.5               |
| Nervous system disorders                         | 12                                | 4                                 | 50                         | 4                                 | 2                                 | 25                         | 16                        | 6                         | 37.5               |
| Headache   | 5                                 | 3                                 | 37.5                       | 3                                 | 2                                 | 25                         | 8                         | 5                         | 31.3               |
| General disorders/administration site conditions | 5                                 | 2                                 | 25                         | 3                                 | 2                                 | 25                         | 8                         | 4                         | 25                 |
| Fatigue  | 4                                 | 1                                 | 12.5                       | 1                                 | 1                                 | 12.5                       | 5                         | 2                         | 12.5               |
| Pyrexia  | 1                                 | 1                                 | 12.5                       | 1                                 | 1                                 | 12.5                       | 2                         | 2                         | 12.5               |
| Gastrointestinal disorders                       | 6                                 | 4                                 | 50                         | 0                                 | 0                                 | 0                          | 6                         | 4                         | 25                 |

| System Organ Class/Preferred Term               | 3-Week Regimen (N=8) Total Events | 3-Week Regimen (N=8) Subjects (n) | 3-Week Regimen (N=8) n (%) | 4-Week Regimen (N=8) Total Events | 4-Week Regimen (N=8) Subjects (n) | 4-Week Regimen (N=8) n (%) | Total (N=16) Total Events | Total (N=16) Subjects (n) | Total (N=16) n (%) |
|---|-----------------------------------|-----------------------------------|----------------------------|-----------------------------------|-----------------------------------|----------------------------|---------------------------|---------------------------|--------------------|
| Injury, poisoning and procedural complications  | 4                                 | 3                                 | 37.5                       | 0                                 | 0                                 | 0                          | 4                         | 3                         | 18.8               |
| Metabolism and nutrition disorders              | 2                                 | 2                                 | 25                         | 0                                 | 0                                 | 0                          | 2                         | 2                         | 12.5               |
| Blood and lymphatic system disorders            | 1                                 | 1                                 | 12.5                       | 0                                 | 0                                 | 0                          | 1                         | 1                         | 6.3                |
| Immune system disorder                          | 1                                 | 1                                 | 12.5                       | 0                                 | 0                                 | 0                          | 1                         | 1                         | 6.3                |
| Musculoskeletal and connective tissue disorders | 1                                 | 1                                 | 12.5                       | 0                                 | 0                                 | 0                          | 1                         | 1                         | 6.3                |
| Psychiatric disorders                           | 1                                 | 1                                 | 12.5                       | 0                                 | 0                                 | 0                          | 1                         | 1                         | 6.3                |
| Skin and subcutaneous tissue disorders          | 1                                 | 1                                 | 12.5                       | 0                                 | 0                                 | 0                          | 1                         | 1                         | 6.3                |
| Vascular disorders                              | 0                                 | 0                                 | 0                          | 1                                 | 1                                 | 12.5                       | 1                         | 1                         | 6.3                |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 12-4

Adverse events were coded using MedDRA, Version 22.1. All events are included in events columns.

System Organ Class and Preferred Term were sorted by total number of incidences. A subject was only counted once within each Preferred Term and System Organ Class.

\* All SOC's with at least one event are listed in this table; Preferred Terms are listed if the event occurred in 210 percent of subjects in the intent-to-treat (ITT) population.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, TEAE=treatment-emergent adverse event

**Reviewer's comments:** *The most common TEAEs are common symptoms and conditions that occur in children irrespective of IGIV therapy.*

Four subjects (25 percent) experienced a total of 9 temporally associated adverse events (occurring during or within 72 hours after the end of an infusion) and all were considered to be adverse reactions (AR). All ARs were nonserious. No infusion site reactions occurred during the study. Seven of the 96 (7.3 percent) infusions were temporally associated with an adverse event. Two infusions were associated with more than one AR. The mean proportion of infusions temporally associated with an AE per subject was 6.95 (one-sided 95 percent confidence limit [CL] of the mean, 1.1 to 12.8) for the total safety set, 8.93 percent (one-sided 95 percent CL, 0.2 to 17.7) for the 3-week regimen group, and 5.00 (one-sided 95 percent CL, -4.5 to 14.5) for the 4-week infusion regimen group. [Table 14](#) shows the adverse reactions that occurred within 72 hours after the end of a BIVIGAM infusion. [Table 15](#) shows the details regarding the infusions temporally associated with adverse events.

**Table 14. Adverse Reactions Within 72 Hours After the End of a BIVIGAM Infusion**

| Adverse Reaction (AR) | Number of Subjects Reporting AR (n=16) | Percent of Subjects Reporting AR (n=16) | Number of Infusions With AR (n=96) | Percent of Infusions With AR (n=96) |
|-----------------------|--|---|------------------------------------|-------------------------------------|
| Fatigue               | 1                                      | 6                                       | 2                                  | 2                                   |
| Headache              | 3                                      | 19                                      | 5                                  | 5                                   |
| Nausea                | 1                                      | 6                                       | 1                                  | 1                                   |
| Rash                  | 1                                      | 6                                       | 1                                  | 1                                   |

Source: Clinical reviewer from analysis of safety database

Abbreviation: AR=adverse reaction

**Reviewer's comments:** *ADMA Biologics initially coded the AEs nausea and rash as not related to BIVIGAM. However, the AEs occurred within 72 hours and therefore may be related to BIVIGAM. The AEs of nausea and rash were re-coded as adverse reactions by the FDA and ADMA Biologics. In addition, ADMA Biologics initially coded "procedural headache" and "headache" separately. However, both terms describe the same symptoms of headache, and therefore should be coded as "headache." FDA and ADMA Biologics re-coded procedural headache as headache. The above table was included in the labeling for clarity.*

**Table 15. Infusions Temporally Associated With Adverse Events, Safety Set**

| Category<br>Statistic/Response                                | 3-Week<br>Regimen<br>(N=8) | 4-Week<br>Regimen<br>(N=8) | Total (N=16) |
|---|----------------------------|----------------------------|--------------|
| Study <sup>1</sup>  |                            |                            |              |
| Total infusions   | 56                         | 40                         | 96           |
| Total infusions with 21 TAAE                                  | 5                          | 2                          | 7            |
| Proportion of infusions with 21 TAAE, m/n (%)                 | 5/56 (8.9)                 | 2/40 (5.0)                 | 7/96 (7.3)   |
| Upper one-sided 95% CL based on binomial distribution (exact) | 17.9                       | 14.9                       | 13.3         |
| Proportion of subjects with 21 TAAE, m/n (%)                  | 3/8 (37.5)                 | 1/8 (12.5)                 | 4/16 (25.0)  |

| Category<br>Statistic/Response | 3-Week<br>Regimen<br>(N=8) | 4-Week<br>Regimen<br>(N=8) | Total (N=16) |
|--------------------------------|----------------------------|----------------------------|--------------|
| Per subject <sup>2</sup>       |                            |                            |              |
| 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 one-sided 95% CL of mean | 17.7                       | 14.5                       | 12.8         |

Source: Adapted from sBLA 125389/300, Clinical Study Report, Table 12-8.

1. The calculation is the percentage of affected infusions. m is the number of infusions with 21 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 percent (one-sided) confidence limit for the mean. m is the number of subjects with 21 TAAE. n is the total number of subjects.

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)

**Reviewer's comments:** *The upper one-sided 95 percent CL of the probability that an infusion was associated with an AE was below the threshold of 40 percent as outlined in the FDA IGIV Guidance.*

#### 6.1.12.3 Deaths

No deaths occurred during the study.

#### 6.1.12.4 Nonfatal Serious Adverse Events

One subject experienced a single SAE of 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 BIVIGAM. The subject required hospitalization and symptoms resolved the following day. The SAE was assessed to not be related to BIVIGAM but possibly due to conversion disorder or underlying disease of common variable immunodeficiency.

**Reviewer's comments:** *Hemiparesis is not a known side effect of immune globulin products, nor has it been described in BIVIGAM's previous pre-marketing and post-marketing experiences. However, autoimmune conditions involving the central nervous system have been described with common variable immune deficiency. Therefore, the SAE is most likely not related to BIVIGAM and may be related to the underlying disease of common variable immune deficiency.*

#### 6.1.12.5 Adverse Events of Special Interest

No adverse events of special interest, defined as hemolysis or thrombosis, occurred during the study.

#### 6.1.12.6 Clinical Test Results

One subject was found to have a positive Direct Antiglobulin Test/Coombs test result prior to the sixth infusion. However, there were no changes in hemoglobin levels compared to baseline (127 g/L prior to the sixth infusion versus 126 g/L at screening), and lactate dehydrogenase levels remained within normal limits. Haptoglobin levels were

below normal levels at most assessment timepoints in this subject including at screening and prior to the sixth infusion (<0.2 g/L).

**Reviewer's comments:** *The significance and cause of the positive Direct Antiglobulin Test/Coombs test and intermittently low haptoglobin levels are unclear; however, hemoglobin levels remained stable throughout the study, which was reassuring and indicated that hemolysis did not occur.*

#### 6.1.12.7 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

#### 6.1.13 Study Summary and Conclusions

Study 994 was a prospective, open-label, single arm, multicenter Phase 4 study wherein 16 pediatric subjects 2 to 16 years of age with PI were administered BIVIGAM every 3-4 weeks at the same dose and regimen as their previous IGIV therapy prior to study enrollment. The subjects were followed over a mean period of approximately 5 months. The primary efficacy endpoint was incidence of acute SBIs as defined in accordance with FDA IGIV Guidance, <1.0 SBIs per annualized subject-year.

Study 994 planned to enroll 6 subjects in each age group: 2 to <6 years, 6 to <12 years and 12 to 16 years, as described in the agreed iPSP. However, due to challenges in enrollment, the study included only three subjects 2 to <6 years, five subjects 6 to <12 years and eight subjects 12 to 16 years.

No acute SBIs occurred during the mean 5-month study period, and subjects were observed over an even distribution of seasons.

The efficacy of BIVIGAM in the pediatric PI population was further supported by PK assessments for all pediatric age groups. IgG trough levels remained consistent and above target therapeutic range (i.e., >500mg/dL) throughout Study 994. No subject required dose adjustment due to low IgG levels or infection. Drug clearance was similar between each pediatric age group and between adult and pediatric PI subjects when compared to adult data from the previous pivotal study, Nabi-7101. Although there were only 3 subjects in the youngest pediatric age group, the lack of SBIs and similar PK assessments across all pediatric age groups allowed us to feel comfortable in extrapolating efficacy to the youngest age group despite the short study duration of Study 994. In conclusion, the cumulative pediatric findings in Study 994 and Nabi-7101 provide substantial evidence of effectiveness of BIVIGAM for pediatric patients who are 2 years of age and older.

All subjects in Study 994 completed all planned infusions and there were no deaths or dropouts due to an adverse event. The safety profile of BIVIGAM in pediatric subjects 2 years of age and older is consistent with other IGIV products and the safety profile of BIVIGAM in adults. The proportion of infusions temporally associated with an adverse event was below the upper one-sided 95 percent confidence limit of 40 percent, as outlined in the FDA IGIV Guidance.

## 6.2 Trial #2

Study Nabi-7101 was a pivotal Phase 3, multicenter, open-label study to evaluate the safety, efficacy, and PK of BIVIGAM in Subjects 6 years to 75 years old with Primary Immune Deficiency Disorders (PID). All subjects were required to have received steady doses of a IGIV product for at least 3 months and maintained a trough IgG level of at least 500 mg/dL prior to study enrollment. After enrollment into the study, the subjects were treated with the same IGIV dose (300 to 800 mg/kg) and regimen (every 3 or 4 weeks) as their previous IGIV therapy prior to study enrollment, for approximately 1 year. Sixty-three subjects were enrolled into the study. Of the 63 subjects, 54 were adult subjects and nine were pediatric subjects 6 to 16 years old. Nabi-7101 data was submitted under STN BLA 125389/0. Please refer to the clinical review memo under the original BLA submission for further details regarding Study Nab-7101.

### 6.2.11 Efficacy Analyses

The primary efficacy endpoint was rate of SBIs per person-year. The primary efficacy analysis included 58 subjects in the intent-to-treat population. Two SBIs (bacterial pneumonia) occurred in a 21-year-old male and a 49-year-old female. No SBIs occurred in any of the pediatric subjects.

### 6.2.12 Safety Analyses

Most common adverse reactions (2 5% of subjects) included headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increased, diarrhea, dizziness, lethargy, back pain, blood pressure diastolic decreased, fibromyalgia, migraine, myalgia, and pharyngolaryngeal pain. No deaths were reported in the study. Based on the original clinical review memo, the safety profile of BIVIGAM was considered similar between adults and pediatric subjects, as well as other immune globulin products.

### 6.2.13 Study Summary and Conclusions

The safety and efficacy data from children treated in Nabi-7101 support the pediatric data from Study 994. Study 994 provides important supplemental efficacy information as children were treated for 12 months.

## 7. INTEGRATED OVERVIEW OF EFFICACY

### 7.1 Indication #1

Not applicable as the primary basis for review of this application was the single adequate and well controlled trial submitted for the pediatric population expansion.

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

No new safety signals were identified in this clinical trial and were consistent with previously submitted data. As such, an integrated safety evaluation was not done.



## 9. ADDITIONAL CLINICAL ISSUES

### 9.1 Special Populations

#### 9.1.1 Human Reproduction and Pregnancy Data

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproductive studies have not been conducted with BIVIGAM. It is not known whether BIVIGAM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. BIVIGAM should be given to pregnant women only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

#### 9.1.2 Use During Lactation

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

#### 9.1.3 Pediatric Use and PREA Considerations

The pediatric study, Study 994, was conducted to fulfill PREA requirements and PMR as agreed upon during the initial approval of BIVIGAM in 2012. This study fulfills the PMR. The Applicant has received a PREA waiver for pediatric studies in patients 0 to less than 2 years old because such studies are impossible and highly impracticable due to the rarity of PI in this age group.

#### 9.1.4 Immunocompromised Patients

Not applicable as subjects have immunodeficiency.

#### 9.1.5 Geriatric Use

Not applicable as this supplement is for approval in pediatric subjects.

## 10. CONCLUSIONS

The cumulative pediatric evidence from Study 994 and previous pivotal study, Nabi-7101, provides substantial evidence of effectiveness of BIVIGAM for pediatric patients who 2 years of age and older. The safety profile of BIVIGAM is consistent with the IGIV class of products and is similar between children and adults.

## 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

### 11.1 Risk-Benefit Considerations

Table 16. Risk-Benefit Considerations

| Decision Factor       | Evidence and Uncertainties  | Conclusions and Reasons  |
|-----------------------|---|--|
| Analysis of Condition | <ul style="list-style-type: none"> <li>PI represents a heterogeneous group of disorders resulting from inherited defects of the immune system.</li> <li>Patients with PI are at increased risk for recurrent, severe infections</li> </ul>  | <ul style="list-style-type: none"> <li>PI diseases are serious, chronic conditions associated with considerable morbidity and mortality.</li> <li>IgG replacement therapy (administered either intravenously or subcutaneously) has been shown to reduce the incidence of serious infections through provision of passive immunity and prolong life span.</li> </ul> |
| Unmet Medical Need    | <ul style="list-style-type: none"> <li>Numerous marketed IgG products (both intravenous and subcutaneous forms) have demonstrated efficacy with serious bacterial infection rates less than 1.0 per subject-year.</li> </ul>  | <ul style="list-style-type: none"> <li>Currently, there is not an unmet medical need.</li> <li>However, given potential for supply chain disruptions and shortages, there is a public health benefit for having additional immunoglobulin replacement products on the market.</li> </ul>   |
| Clinical Benefit      | <ul style="list-style-type: none"> <li>No SBI occurred in 16 children (age 2 to 16 years) during a mean observation period of approximately 5 months in Study 994.</li> <li>No SBI occurred in the 9 pediatric subjects (age 6 to 16 years) over a study period of 12-month in pivotal study, Study Nabi-7101.</li> <li>All pediatric subjects had consistent IgG trough levels that remained above target therapeutic range (i.e., &gt;500 mg/dL) throughout Study 994. No subject required dose adjustment due to low IgG levels or infection. Drug clearance was similar between each pediatric age group, and between adult and pediatric PI subjects.</li> </ul> | <ul style="list-style-type: none"> <li>The product is effective at preventing acute SBIs in children 2 to 16 years based on clinical and clinical pharmacology data.</li> </ul>  |
| Risk                  | <ul style="list-style-type: none"> <li>Most common adverse reactions in children with PI included fatigue, headache, nausea, and rash.</li> <li>There were no infusion site reactions or deaths reported in children in the clinical studies.</li> </ul>  | <ul style="list-style-type: none"> <li>The safety profile of BIVIGAM in pediatric subjects 2 years to 16 years is consistent with other IgG products and the safety profile of BIVIGAM in adults.</li> </ul>   |
| Risk Management       | <ul style="list-style-type: none"> <li>IgG products carry an obligate boxed warning for thrombosis and renal dysfunction.</li> <li>Warnings and Precautions for this class of products include hypersensitivity, aseptic meningitis, hemolytic anemia, TRALI, and transmissible infectious agents.</li> </ul>   | <ul style="list-style-type: none"> <li>Labeling and routine pharmacovigilance are appropriate.</li> <li>Patients should be monitored for signs and symptoms of thrombosis, renal dysfunction, hypersensitivity, aseptic meningitis, hemolytic anemia, TRALI and transmissible infectious agents.</li> </ul>  |

Abbreviations: IgG=immunoglobulin G, PI=primary immunodeficiency, SBI=serious bacterial infection, TRALI=transfusion-related acute lung injury

### **11.2 Risk-Benefit Summary and Assessment**

Data submitted to the BLA supplement establish a benefit in pediatric patients 2 years of age and older with PI. The risks associated with BIVIGAM for the treatment of PI are small and are outweighed by the benefits. Compared indirectly against other IGIV products, the safety profile appears similar. The overall benefit-risk profile is favorable.

### **11.3 Discussion of Regulatory Options**

The regulatory options for this application are approval for the entire pediatric population 2 years of age and older with PI, approval for a subset of the pediatric population with PI, or a complete response letter. The clinical review team supports approval for the entire pediatric population 2 years of age and older with PI.

### **11.4 Recommendations on Regulatory Actions**

The Applicant has provided substantial evidence of effectiveness and safety for the proposed pediatric population based on a single adequate and well controlled trial with confirmatory evidence from a previously conducted clinical trial. On a clinical basis, I recommend that BIVIGAM be approved for pediatric patients 2 years of age and older with PI.

### **11.5 Labeling Review and Recommendations**

The Applicant satisfactorily addressed the labeling revisions requested by FDA prior to the action date and was reviewed and cleared by the Advertising and Promotional Labeling Branch. The clinical team finds the revised labeling acceptable.

### **11.6 Recommendations on Postmarketing Actions**

No postmarketing studies or REMS are recommended. Routine surveillance appropriate for the product class is recommended.