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Committee Chair	
Clinical Reviewer(s)	Daniela Vanco, M.D.
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Bio Products Laboratory
Established Name	Immune Globulin Intravenous [Human], 5% Liquid
(Proposed) Trade Name	Gammaplex
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Liquid solution containing 5%IgG (50 mg/mL)
Dosing Regimen	300-800 mg/kg every 3-4 weeks
Indication(s) and Intended Population(s)	This supplement seeks to extend Gammaplex's indication in treating Primary Immunodeficiency Disease from adult patients to pediatric patients (>2 to 16 years of age).

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GLOSSARY

AE(s)	Adverse event(s)
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
AR	Adverse Reaction
AST	Aspartate aminotransferase
BLA	Biologics License Application
BUN	Blood urea nitrogen
CI	Confidence interval
CL	Confidence limit
CVID	Common variable immunodeficiency
HCG	Human chorionic gonadotrophin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV	Intravenous immunoglobulin
ISG	Immune serum globulin
ITP	Idiopathic Thrombocytopenic Purpura
IP	Investigated product
IV	Intravenously
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MHRA	Medicines and Healthcare products Regulatory Agency
PAS	Prior Approval Supplement
PID	Primary immunodeficiency disease
PIP	Pediatric Investigational Plan
PK	Pharmacokinetics
PLV	Product License Variation
PMR	Postmarketing Requirements
SABI	Serious, Acute, Bacterial Infections
SAE	Serious Adverse Event
sBLA	Supplementary Biologics License Application
SCIG	Subcutaneous immunoglobulin
SD	Standard deviation
ULN	Upper limit of normal

1. Executive Summary

This submission is an efficacy Prior Approval Supplement (PAS) to fulfill a deferred pediatric requirement for Gammaplex (BLA 125329, approved on September 19, 2009). The objective of this BLA supplement is to extend the age range of patients suitable for Gammaplex to include the pediatric population.

This submission includes the final report of a phase 4, multicenter, open-label study (GMX04) to evaluate the efficacy and safety of Gammaplex in primary immunodeficiency diseases (PID) in pediatric patients between 2 and 16 years of age.

This study enrolled 25 pediatric subjects. The primary efficacy endpoint is Serious, Acute, Bacterial Infection (SABI) rate. With a 0.085 infection rate per subject year, the one-sided 99% upper confidence limit was 0.358 per subject year, which is less than FDA's efficacy threshold value of 1. For the safety endpoint of the proportion of infusions associated with one or more Adverse Events (AEs) that begin during the infusion or within 72 hours after completion of the infusion, the upper one-sided 95% confidence limit for the proportion of infusions with at least one temporally associated AE (regardless of relationship) was 30.4%, less than the pre-specified criterion of 40%. The statistical report supports the indication of Gammaplex in pediatric patients with PID in both efficacy and safety.

Comparison of data from this pediatric study with those from the previous study of mostly adult subjects (GMX01) identified no clinically significant differences in the efficacy, safety and tolerability of Gammaplex between adults and children. There is no statistical issue in the submission.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition Studied

Primary immunodeficiency diseases are a heterogeneous group of disorders that involve an intrinsic defect in tissues, cells and/or proteins of the immune system that result in immune deficiency. Many of these disorders are characterized by hypogammaglobulinaemia and/or defective antibody production and, as a consequence, increased susceptibility to infection.

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

Replacement therapy with immunoglobulin G (IgG), purified from pools of plasma from multiple donors, has been used since the early 1950s. The initial products were administered intramuscularly but were of limited efficacy because of the relatively small quantities that could be administered by that route. Intravenous (IV) immunoglobulin (IGIV) became available in the US in the 1980s and, along with subcutaneous immunoglobulin (SCIG) therapy, has since become the current treatment of choice for patients with PID whose humoral immunity is impaired.

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

Gammaplex® (immune globulin intravenous [human] 5% liquid) is a highly purified unmodified human IgG product intended for IV administration. Gammaplex is manufactured by Bio Products Laboratory Ltd. (BPL) (London, UK) using plasma from healthy US donors. It was licensed by the FDA on September 17, 2009 for use in PID in adults. Gammaplex is now licensed in the UK (approved on March 15, 2012), Israel (February 13, 2011), Brazil (July 16, 2012), and Lebanon (Feb 15, 2014).

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

The original BLA submission for Gammaplex was approved by FDA with a deferred pediatric study requirement as a post-marketing requirement (PMR) for ages ≥2 to 16 years; a pediatric study requirement for ages 0 to <2 years was waived. A deferral extension for the PMR was granted by the FDA on September 25, 2013 (125329/66) to extend the final report submissions to December 2014.

A supplemental biologics license application (sBLA) to extend the clinical use of Gammaplex to include chronic autoimmune (idiopathic) thrombocytopenic purpura (ITP) was approved for adults by the FDA on March 08, 2013 (125329/55). The pediatric requirement was exempt for the ITP indication because the biological product for ITP indication has an orphan drug designation. During the licensure for the product in ITP, the US Prescribing Information was changed to exclude children with PID in 2013.

The GMX04 study included in this BLA supplement is a phase 4 study in a pediatric population with PID conducted under IND 12569. This study was first presented to FDA as a phase 3 study in 2011, but the applicant was informed that GMX04 should be defined as a phase 4 study. BPL's rationale for conducting study GMX04 is to extend the age range for the Gammaplex license to include pediatric patients for the PID indication.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

This review memo focuses on both efficacy analyses and safety analyses of the pediatric study GMX04. GMX01 was the pivotal study for the adult PID indication and GMX02 for the ITP indication.

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

The following documents of 125329/112 formed the basis of this review.

- 2.5 Clinical Overview
- 2.7.2 Summary of Clinical Pharmacology Studies
- 2.7.3 Summary of Clinical Efficacy
- 2.7.4 Summary of Clinical Safety
- 5.3.5.2 – Study-report GMX04

This reviewer also used the original BLA 125329/0 as a reference.

5.3 Table of Studies/Clinical Trials

Table 1 summarizes all clinical studies for this product.

Table 1: Listing of clinical studies for Gammaplex

Study name	Study type	Study status	Number subjects treated	Indication	Main criteria for inclusion
GMX01	Single-arm, Open-label, Multi-center, Phase 3	complete	50	PID	≥16 years
GMX02	Single-arm, Open-label, Multi-center Phase 3	complete	35	ITP	≥6 years
GMX04	Single-arm, Open-label, Multi-center, Phase 4	complete	25	PID	≥2 years, <16 years

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: GMX04

6.1.1 Objectives

The primary objective of GMX04 is to determine the efficacy of Gammaplex by measuring the number of SABIs over a 12-month period in pediatric and adolescent subjects.

Secondary objectives include 1) to assess the safety and tolerability of Gammaplex in pediatric and adolescent subjects, and 2) to compare the efficacy and safety data from this study with that collected from adults in the GMX01 study.

6.1.2 Design Overview

This was a phase 4, multicenter, open-label, non-randomized study of Gammaplex. Subjects were to receive 13 to 17 infusions (i.e. 12 months of therapy on either a 21-day or 28-day treatment schedule) of Gammaplex.

The total planned duration of treatment for each subject was 12 months. The total duration of a given subject's participation in this study was up to 16 months, including screening (up to 30 days before enrolment), a 12-month treatment period and a 3-month follow-up period.

The design of this open-label study, including the primary objective, primary efficacy variable and analysis of the primary efficacy variable, was in accordance with the FDA Guidance *Safety, Efficacy, and Pharmacokinetics Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*, dated June 2008.

6.1.3 Population

In order to qualify for the study, each subject had to satisfy all the criteria listed below:

1. The subject was between the age of, or was equal to, 2 and 16 years of age, of either sex, belonging to any ethnic group and above a minimum weight of 10 kg. At least four of the subjects enrolled were to be between 2 to 5 years of age, at least four were to be between 6 to 11 years of age and at least eight were to be between 12 to 16 years of age.
2. The subject had a PID, which had as a significant component hypogammaglobulinaemia and/or antibody deficiency (e.g. common variable immunodeficiency [CVID], X-linked and autosomal forms of agammaglobulinaemia, hyper-immunoglobulin M [IgM] syndrome, Wiskott-Aldrich Syndrome). Isolated deficiency of a single IgG subclass, or of specific antibodies without hypogammaglobulinaemia per se, did not qualify for inclusion.
3. The subject required the following before the first infusion of Gammaplex:
    - Documented IGIV dose(s) and treatment intervals for the last two consecutive routine IGIV treatments (one of which could be the screening visit result). The previous doses also should have met the following conditions before study entry:
        - Had not changed by ± 50% of the mean dose for at least 3 months.
        - Was between 300 and 800 mg/kg/infusion.
        - Was given every 21-28 days, inclusive.
        - Was a licensed or investigational product (IP) (phase 3 or 3b).
    - Documented previous IgG trough levels for the last two consecutive routine IGIV treatments:
        - Maintained at least 300 mg/dL above baseline serum IgG levels (defined as before initiation of any gamma globulin treatment for that subject).
        - Must have been ≥ 600 mg/dL.
4. If a subject was a female of child-bearing potential, she must have had a negative result on a human chorionic gonadotrophin (HCG)-based pregnancy test.
5. If a subject was a female who was or became sexually active, she must have practiced contraception by using a method of proven reliability for the duration of the study.
6. The subject was willing to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

7. The subject, if old enough (generally 6 to 16 years), had signed a Child Assent Form and the subject's parent or legal guardian had signed the Informed Consent Form, both approved by the IEC/IRB.

Subjects were excluded if any of the following exclusion criteria were met:

1. The subject had not been treated with IGIV (treatment-naïve subject).
2. The subject had a history of any severe anaphylactic reaction to blood or any blood-derived product.
3. The subject was known to be intolerant to any component of Gammaplex, such assorbitol (i.e. intolerance to fructose).
4. The subject had selective immunoglobulin A (IgA) deficiency, history of reaction to products containing IgA or had a history of antibodies to IgA.
5. Subjects who had completed the study and subjects who had withdrawn could not participate in the study for a second time.
6. The subject was currently receiving, or had received, any investigational agent, other than an immune serum globulin (ISG) preparation, that was being evaluated in a phase 3 or 3b study within the prior three months.
7. The subject had been exposed to blood or any blood product or derivative within the last six months, other than a commercially available IGIV or other forms of commercially available and licensed ISG. If an unlicensed ISG product that was in phase 3 or 3b had been given, the subject could not be infused with Gammaplex until 20 days after the last dose was given.
8. The subject was pregnant or nursing.
9. The subject, at Screening, had levels greater than 2.5 times the upper limit of normal (ULN) as defined at the central laboratory of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST) or lactate dehydrogenase (LDH).
10. The subject had a severe renal impairment (defined as serum creatinine greater than 2 times the ULN or blood urea nitrogen [BUN] greater than 2.5 times the ULN for the range of the laboratory doing the analysis); the subject was on dialysis; the subject had a history of acute renal failure.
11. The subject was known to abuse alcohol, opiates, psychotropic agents or other chemicals or drugs, or had done so within the past 12 months.
12. The subject had a history of deep vein thrombosis or thrombotic complications of IGIV therapy.
13. The subject suffered from any acute or chronic medical condition (e.g. renal disease or predisposing conditions for renal disease, coronary artery disease or protein-losing state) that, in the opinion of the investigator, may have interfered with the conduct of the study.
14. The subject had an acquired medical condition, such as chronic or recurrent neutropenia (absolute neutrophil count $< 1 \times 10^9$/L) or AIDS known to cause secondary immune deficiency or was post or recovering from haematopoietic stem cell transplantation.
15. The subject was receiving the following medication: systemic long-term corticosteroids (i.e. not intermittent or burst, daily, > 1 mg of prednisone equivalent/kg/day).

16. The subject was receiving immunosuppressive or immunomodulatory drugs.
17. The subject had non-controlled arterial hypertension.
18. The subject had anaemia (haemoglobin < 10 g/dL) at Screening.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Gammaplex was administered by intravenous infusion at a dosage of 300-800 mg/kg per infusion (at the same dose of IGIV that was previously used to establish steady state), once every 21 or 28 days.

6.1.6 Sites and Centers

There were nine sites in this study, with seven in the US, one in Chile and one in Israel.

6.1.7 Surveillance/Monitoring

No data monitoring committee was planned for this study.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was the number of SABI per subject per year. It was based on pre-specified events (i.e. bacterial pneumonia, bacteraemia or sepsis, osteomyelitis/septic arthritis, visceral abscess and bacterial meningitis) in accordance with definitions provided in the FDA guidance regarding use of IGIV as replacement therapy for primary humoral immunodeficiency. An estimate of the SABI rate for Gammaplex was calculated by dividing the total number of SABI events by the total number of subject years. The number of subject years was obtained by summing the total subject days and dividing by 365. The subject study duration (days) was calculated as (date of last visit) – (date of first infusion) +1. The one-sided 99% upper confidence limit for the annual SABI rate must be less than 1 to meet the efficacy recommendation in the FDA Guidance *Safety, Efficacy, and Pharmacokinetics Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency,* dated June 2008.

Secondary efficacy endpoints include the following variables:

- Number and proportion of subjects from Week 15 onwards who maintain trough IgG levels at least as high as the average of the two previous trough levels before the first Gammaplex infusion
- Number of days of school missed because of infection per subject year
- Number and days of hospitalizations because of infection per subject year
- Number of visits to physicians for acute problems and/or number of visits to hospital emergency rooms per subject year
- Other infections documented by fever or a positive result on a radiograph and/or culture per subject year
- Number of infectious episodes per subject per year
- Number of days on therapeutic and prophylactic antibiotics

Safety endpoints include assessment of:

- Adverse Events (AEs)

  - The number and percent of infusions associated with one or more AEs that begin during the infusion or within 72 hours after completion of the infusion will be calculated.
  - Nature, severity, and frequency of AEs (tolerability)
  - Suspected unexpected serious adverse reactions (SUSARs), if any
- Vital signs
- Clinical laboratory tests and Direct Coombs' Test
- Transmission of viruses
- Physical examination

An important safety endpoint of this study is the proportion of infusions with at least one AE that occurred during the infusion or within 72 hours after completion of the infusion. If the upper bound of the one-sided 95% confidence interval (CI) of this proportion is less than 40%, the incidence of infusion-related AEs associated with Gammaplex is considered acceptable.

6.1.9 Statistical Considerations & Statistical Analysis Plan

For the primary efficacy analysis, the SABI rate for Gammaplex and the upper bound of its one-sided 99% CI were estimated using the exact method for a one-sample Poisson rate.

Sensitivity analyses using Poisson regression and weighted Poisson regression were also planned. In the Poisson regression model, the upper one-sided 99% confidence bound was obtained by using the generalized linear model for Poisson regression with the log link. In the weighted Poisson regression, the weights was added in the Poisson regression model and defined as the length of study time of each subject, i.e., weight = min (1, number of days on study/365). Both models were performed with 4) in SAS.

Secondary efficacy variables were summarized descriptively.

For safety, the number and percent of infusions with at least one AE that occurred during the infusion or within 72 hours after completion of the infusion were calculated, and a one-sided 95% CI was derived. Other safety assessments were summarized descriptively by treatment group.

All subjects who received at least one infusion of Gammaplex were included in the intent-to-treat (ITT) population. The ITT population was used for both efficacy and safety analyses.

Age (years) was calculated as (date-of informed consent - date of birth)/365.25, rounded down to the nearest whole number. Three categories in age were defined: 2-5 years, 6-11 years, and 12-16 years.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 25 subjects were enrolled in the study and treated with Gammaplex.

All of the 25 subjects were included in the ITT population.

The PK population included 23 subjects. One subject (Subject) discontinued early and a second subject (Subject) had limited PK samples taken because of school commitments; therefore, these two subjects were excluded from the PK analysis.

6.1.10.1.1 Demographics

Table 2 summarizes the demographic and baseline characteristics for the ITT population.

Table 2: Demographic and Baseline Characteristics (ITT)

	21-Day Infusion Schedule (N=14)	28-Day Infusion Schedule (N=11)	Total (N=25)
Age (years)			
Mean (SD)	11.8 (3.47)	8.5 (3.64)	10.4 (3.84)
Median	12.5	7.0	11.0
Min, Max	4, 16	3, 16	3, 16
Age group, n (%)			
2-5 years	1 (7.1)	2 (18.2)	3 (12.0)
6-11 years	5 (35.7)	7 (63.6)	12 (48.0)
12-16 years	8 (57.1)	2 (18.2)	10 (40.0)
Gender, n (%)			
Male	9 (64.3)	10 (90.9)	19 (76.0)
Female	5 (35.7)	1 (9.1)	6 (24.0)
Race, n (%)			
Caucasian	14 (100)	11 (100)	25 (100)
Diagnosis, n (%)			
Common variable immunodeficiency (CVID)	13 (92.9)	9 (81.8)	22 (88.0)
X-linked and autosomal forms of agammaglobulinaemia	1 (7.1)	2(18.2)	3 (12.0)
Hyper-IgM syndrome	0	0	0
Wiskott-Aldrich syndrome	0	0	0
Baseline chest X-ray, n (%)			

Normal	12 (85.7)	11 (100)	23 (92.0)
Abnormal	2 (14.3)	0	2 (8.0)
Any planned elective procedures scheduled, n (%)			
Yes	1 (7.1)	0	1 (4.0)
No	13 (92.9)	11 (100)	24 (96.0)

Source: Original sBLA 125329/112; study report gamx04.report, Table 11-1, p.60.

The median age of subjects was 11.0 years and ranged from 3 to 16 years. Three subjects were between the ages of 2 to 5 years, 12 subjects between the ages of 6 to 11 years and 10 subjects were between the ages of 12 to 16 years. Subjects were predominantly male (19 subjects, 76.0%). All of the subjects were Caucasian. Twenty-two subjects (88.0%) entered the study with a diagnosis of CVID, and the remaining 3 subjects had a diagnosis of X-linked agammaglobulinaemia. The baseline chest X-ray was interpreted as normal for 23 subjects (92.0%); one subject (Subject (b) (6)) had a baseline chest X-ray finding of mild blunting of the costophrenic angles, and one subject (Subject) had a finding of slight scoliosis and dextroscoliosis. Only one subject had a planned elective procedure.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All 25 subjects had at least one pre-existing medical condition other than PID (Table 3). The most common systems affected were ear, nose and throat disorders (22 subjects, 88.0%) and respiratory disorders (20 subjects, 80.0%).

Table 3: Medical conditions for ITT population

Medical condition	Number of subjects (N=25)	Percentage
Ear, nose, and throat disorders	22	88%
Respiratory disorders	20	80%
Immune/allergy history	16	64%
Chronic sinusitis	15	60%
Allergic rhinitis	11	44%
Gastrooesophageal reflux disease	10	40%

Source: Adapted from sBLA 125329/112, study-report gmx04.pdf, Section 11.2.2, page 61.

All 25 subjects had prior IGIV therapy. Prior IGIV therapy included Gamunex (9 subjects, 36.0%), Gammagard (4 subjects, 16.0%), Flebogamma (7 subjects, 26.0%), Gammaplex liquid 5% (3 subjects, 12.0%) and Carimune, Omrigam, Privigen and Sandoglobulin (1 subject each, 4.0%). Two subjects (8.0%) received NewGam (Octagam 10%).

The mean baseline trough IgG (prior IGIV treatment) was 973.8 mg/dl (SD 160.82 mg/dl).

6.1.10.1.3 Subject Disposition

A summary of subject disposition is reported in Table 4.

Table 4: Subject Disposition

	21-Day Infusion Schedule (N=14) n (%)	28-Day Infusion Schedule (N=11) n (%)	Total (N=25) n (%)
Enrolled	14 (100)	11 (100)	25 (100)
ITT population	14 (100)	11 (100)	25 (100)
PK population	13 (92.9)	11 (100)	24 (96.0)
Completed treatment	13 (92.9)	11 (100)	24 (96.0)
Discontinued treatment	1 (7.1)	0	1 (4.0)
Subject withdrew consent	1 (7.1)	0	1 (4.0)

Source: Adapted from sBLA 125329/112, study-report gmx04.pdf, Section 10.1, Table10-1, page 58.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The estimate of SABI rate was obtained by dividing the total number of SABI events by the total number of subject years. The total number of subject years was 23.44 (8557 days). Table 5 lists the study duration for all 25 subjects.

Table5: Subject duration (days)

Subject	Duration	Subject	Duration	Subject	Duration
(b) (6)	88	(b) (6)	345		369
	342		356		350
	355		343		352
	355		347		350
	364		340		352
	351		341		351
	348		361		344
	376		350		
	369		358		

Two events of pneumonia in two subjects were reported as SABIs. One is subject (b) (6) (male, 7 years old) and the other is subject (male, 17 years old). No SABI events of bacteraemia, sepsis, osteomyelitis/septic arthritis, visceral abscess or bacterial meningitis occurred in any subject.

There were two additional events of pneumonia that were not classed as SABIs. Both subject (male, 12 years old) and subject (male, 8 years old) were diagnosed with mild pneumonia.

The primary endpoint was calculated using the two SABIs in the 23.44 subject years. This led to a mean SABI event rate per subject year of 0.085 and a one-sided 99% upper confidence bound of 0.358, which meets the efficacy requirement.

The sponsor performed a worst-case estimate of four possible SABIs in 25 subjects in this study, and also combined data from this study with data from the earlier study GMX01. The mean SABI event rate for all four scenarios is reported in Table 6.

Table 6: Sensitivity analysis SABI Mean Event Rate and the CI

	Mean Event Rate per year	One-sided 99% Upper Confidence Bound
Two SABIs in 25 subjects (GMX04 only; primary analysis)	0.085	0.358
Four SABIs in 25 subjects (GMX04 only)	0.171	0.495
Two SABIs in 75 subjects (GMX01 and GMX04)	0.03	0.12
Four SABIs in 75 subjects (GMX01 and GMX04)	0.06	0.17

Source: Adapted from sBLA 125329/112; study-report gamx04.pdf, p.68.

The applicant also performed sensitivity analyses using Poisson regression and weighted Poisson regression (Table 7).

Table 7: Sensitivity Analysis of SABI Mean Event Rate and the CI

	Mean Event Rate per year	One-sided 99% Upper Confidence Bound
All subjects		
Poisson regression	0.09	0.44
Weighted Poisson regression	0.08	0.46
Subjects receiving all infusions and attending the first follow-up		
Poisson regression	0.09	0.45
Exact method for one-sample Poisson rate	0.09	0.36

Source: Adapted from sBLA 125329/112; study-report gamx04.pdf, p. 280.

Results of the sensitivity analyses demonstrate the robustness of the primary analysis to changes in assumptions.

6.1.11.2 Analyses of Secondary Endpoints

Trough IgG levels

All trough IgG levels were maintained above 600 mg/dL from Week 15 onwards. While a high proportion of subjects had trough levels below the mean of the pre-study values (18 subjects, 72.0%), there is no evidence of a systematic decline in IgG values over time during Gammaplex treatment. Trough levels of total IgG were summarized overall and

by infusion schedule by the applicant (Section 14.5, Table 42.1 and Table 42.2 in study-report gmx04.pdf).

Number of days of school missed because of infection
Sixteen subjects (64.0%) missed at least one day from school or nursery because of an infection or other problem. The mean (SD) number of days off from school or nursery was 4.2 (8.28) per subject per year, and the maximum number of days missed was 32. No subjects in the 2 to 5 year age group had days off from school or nursery. Seven of the 12 subjects (58.3%) in the 6 to 11 year age group missed days from school or nursery; mean (SD) days missed for this age group was 2.3 (3.22). In the 12 to 16 year age group, nine of the 10 subjects (90.0%) missed days from school or nursery. The mean (SD) for this age group was 7.8 (12.06) days missed.

Number of days of hospitalization because of infection
The majority of subjects (22 subjects, 88.0%) did not require hospitalization because of an infection or a medical problem during the study. The overall mean (SD) number of days of hospitalization was 0.3 (0.87) per subject per year.

Number of visits to physician/emergency room for acute problems
The majority of subjects (18 subjects, 72.0%) visited a physician or hospital emergency room because of an infection or other medical problem. Eighteen subjects (72.0%) visited a physician and eight subjects (32.0%) visited the emergency room. Overall, the mean (SD) number of visits to a physician or hospital emergency room was 4.0 (4.67).

Other infections documented by fever, positive result on radiograph and/or culture or clinical examination
Twenty-one subjects (84.0%) experienced at least one infection during the study. Overall upper respiratory tract infections were reported by more subjects than any other infection (Table 8).

Table 8: Number of subjects with infections by type of infection

Type of infection	Subjects with non-serious infections (N=25)	Subjects with serious infections (N=25)	Total subjects with infections (N=25) n (%)
Subjects with at least one infection	19	2	21 (84.0)
Sinus infections	10	0	10 (40.0)
Overall upper respiratory tract infections	16	0	16 (64.)
Lower respiratory tract infections	5	2	7 (28.0)
Urinary tract infections	1	0	1 (4.0)
Gastrointestinal infections	4	0	4 (16.0)
Other infections	8	0	8 (32.0)

Source: Adapted from sBLA 125329/112; study-report gamx04.pdf, Table11-6, p.74.

Number of infectious episodes per subject per year
Twenty-one subjects (84.0%) experienced at least one infection during the study (Table 9). The mean (SD) number of infections per subject per year was 3.20 (2.713).

Table 9: Number of infections episodes per subject per year

Number of infections	Number of subjects (N=25)
Subjects with any infection during study, n (%)	21 (84.0)
Number of infections per subject per year	
Mean (SD)	3.20 (2.713)
Median	3.08
Minimum, Maximum	0, 10.4
Number of infections per subject per year, n (%)	
None	4 (16.0)
>0 to <3	7 (28.0)
3 to <5	9 (36.0)
5 to <10	4 (16.0)
≥10	1 (4.0)

Source: Adapted from sBLA 125329/112; study-report gamx04.pdf, Table 11-7p.75.

Number of days on therapeutic and prophylactic antibiotics
Twenty-one subjects (84.0%) took systemic antibiotic medications during the study. Therapeutic systemic antibiotic medications were taken by the same number of subjects (21 subjects, 84.0%), and prophylactic systemic antibiotic medications were taken by six subjects (24.0%).

Comparison of secondary efficacy variables between GMX01 and GMX04 was provided by the applicant. No significant differences were detected between these two studies.

6.1.11.3 Subpopulation Analyses

The primary analysis was repeated for the age categories and sex subgroups (Table 10). All SABIs occurred in male subjects. One subject in the 6 to 11 year age group (Subject (b) (6)) experienced a SABI of lobar pneumonia, and one subject in the 12 to 16 year age group (Subject (b) (6)) also experienced a SABI of lobar pneumonia. No SABIs occurred in the 2 to 5 year age group. With the exception of this age group (due to its small size), the subgroup results are consistent with the primary efficacy result.

Table 10: Subgroup Analysis of SABI Mean Event Rate and the CI by age and sex

	Number of subjects	Number of SABIs	Mean event rate per year	One-sided 99% upper confidence bound
Age group				
2-5 years	3	0	0	1.59

6-11 years	12	1	0.09	0.57
12-16 years	10	1	0.11	0.74
Sex				
Male	19	2	0.105	0.442
Female	6	0	0	0.768

Source: Adapted from sBLA 125329/112; study-report gamx04.pdf, Table 11-4, p.68.

6.1.11.4 Dropouts and/or Discontinuations

Data from subjects who withdrew were included, where possible, in all summaries and analyses. All summaries and analyses were based on observed data. No imputation was performed for missing data.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No death occurred during this study.

6.1.12.4 Nonfatal Serious Adverse Events

Two subjects had a total of two SAEs onset between first infusion date and 30 days after the last infusion. Subject [redacted] experienced an SAE of lobar pneumonia (left lower lobe pneumonia) of moderate intensity. Subject [redacted] experienced an SAE of lobar pneumonia (left lower lobe pneumonia) of severe intensity. Neither of the SAEs was considered related to study drug.

Subject [redacted] experienced an SAE of gastroenteritis with onset and resolution before the first infusion of study treatment, which is not included in the summary tables.

6.1.12.5 Adverse Events of Special Interest (AESI)

Among 368 infusions, there were 97 infusions associated with temporally associated AEs within 72 hours after infusion (26.4%). The upper one-sided 95% confidence limit for the proportion of infusions with at least one temporally associated AE (regardless of relationship) was 30.4% as calculated by the applicant using SAS. This reviewer calculated the upper one-sided 95% confidence limit as 30.1% with R. This result met the pre-specified criterion. This safety endpoint was also tested in GMX01. The upper one-sided 95% confidence limit was 22.1% by 48 hours after the infusion and 23.9% by 72 hours after the infusion in GMX01.

6.1.12.6 Clinical Test Results

The applicant submitted laboratory results for blood biochemistry, hematology, urinalysis, direct Coombs and CRP analysis in the study report.

6.1.12.7 Dropouts and/or Discontinuations

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Study GMX04 was the first pediatric study of Gammaplex. There were 25 pediatric subjects enrolled in this study, with 3 subjects aged 2 to 5 years, 12 subjects aged 6 to 11 years, and 12 subjects aged 12 to 16 years.

The study results show that Gammaplex meets FDA's efficacy and safety guidelines. Two SABI events occurred for 25 subjects during the study period. With a 0.085 mean infection rate per subject year, the one-sided 99% upper confidence limit was 0.358 per subject year. This one-sided 99% upper confidence limit is less than FDA's efficacy threshold value of 1. For safety, the upper one-sided 95% confidence limit of the proportion of infusions with at least one associated AEs (regardless of relationship) was 30.4%, less than the pre-specified criterion of 40%.

Secondary efficacy endpoints and other safety analyses were also reviewed in this memo. No statistical issues were detected.

10.2 Conclusions and Recommendations

Both efficacy analyses and safety analyses in this supplemental biologics license application were verified to support the claim for the use of Gammaplex in pediatric subjects with PID. There were no statistical issues in this submission.