Application Type	Efficacy Supplement
STN	125329/112
CBER Received Date	September 29, 2014
PDUFA Goal Date	July 30, 2015
Division / Office	DHCR /OBRR
Priority Review	No
Reviewer Name(s)	Daniela J. Vanco, M.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Mitchell M. Frost, M.D.
Applicant	Bio Products Laboratory
Established Name	Immune Globulin Intravenous (Human), 5% Liquid
(Proposed) Trade Name	Gammaplex®
Pharmacologic Class	Class of Immune Sera and Immune Globulins
Formulation(s), including Adjuvants, etc.	Liquid Solution Containing 5% IgG
Dosage Form(s) and Route(s) of Administration	Liquid Solution for Intravenous Administration
Dosing Regimen	0.3g/kg—0.8 g/kg every 3—4 weeks
Indication(s) and Intended Population(s)	The treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older
Orphan Designated	No

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GLOSSARY

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve from time 0 to Day 28
BPL	Bio Products Laboratory Ltd. (Sponsor/manufacturer)
BUN	blood urea nitrogen
CI	confidence interval
Cmax	peak concentration in plasma
CRF	case report form
CVID	common variable immunodeficiency
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IgA	immunoglobulin A
IgG	immunoglobulin G
IGIV	intravenous immunoglobulin
IgM	immunoglobulin M
ITP	idiopathic thrombocytopoenic purpura
ITT	intent-to-treat
LDH	lactate dehydrogenase
MCH	mean corpuscular haemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
PID	primary immunodeficiency disease(s)
PK	pharmacokinetic(s)
SABI	serious, acute, bacterial infection
SAE	serious adverse event
SCIG	subcutaneous immunoglobulin

1. Executive Summary

On September 29, 2014, Bio Products Laboratory (hereafter Bio Products) submitted an efficacy supplement application to Biologics License Application (sBLA) STN 125329/112 for Gammaplex®, Immune Globulin Intravenous (Human), 5% Liquid (hereafter Gammaplex), to include revisions to the package insert that reflect the pediatric population studied in the postmarketing study GAM04.

Gammaplex 5% is an Immunoglobulin Globulin Intravenous (IGIV) (Human) manufactured from source plasma from healthy, accredited donors in the United States. The plasma is processed at Bio Products' facility in Elstree, Hertfordshire, UK. It is presented as a ready- prepared solution of human normal immunoglobulin G (IgG) at pH 4.9 for intravenous administration. The IgG is stabilized with sorbitol.

Gammaplex was licensed in the United States on September 17, 2009, for the indication treatment of primary humoral immunodeficiency (PI). At the time of approval, the pediatric study requirement for patients 0 to <2 years of age were waived because the necessary studies were impossible or highly impracticable. The pediatric study for patients >2 to 16 years of age was deferred because Gammaplex was ready for approval for use in adults, and the pediatric study had not yet been initiated.

The deferred pediatric postmarketing study under the Pediatric Research Equity Act (PREA), required under 505B(a) of the Federal Food, Drug, and Cosmetic Act, is the subject of this submission. The study is titled "A Phase 4, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Gammaplex® in Primary Immunodeficiency Diseases in Children and Adolescents," and includes a pharmacokinetic (PK) evaluation in children (>2 to <12 years) and adolescents (>12 to 16 years). The objectives of the study were to determine the efficacy of Gammaplex measured by the number of serious, acute, bacterial infections (SABIs) over a 12-month period, as well as the safety and tolerability of Gammaplex.

The study subjects were treated for 12 months at 21-day (14 subjects) or 28-day (11subjects) dosing intervals. 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. The median age of subjects was 11 years, and ranged from 3 to 16 years. Subjects were predominantly male (19 subjects, 76.0%). All of the subjects were Caucasian. Doses ranged from 300 mg/kg to 800 mg/kg. The mean dose (range) for the 21-day interval was 545 mg/kg (429 - 689 mg/kg); the mean dose (range) for the 28-day interval was 521 mg/kg (316- 800 mg/kg). Subjects received a total of 368 infusions of Gammaplex. The maximum infusion rate allowed during the clinical study was 0.08 mL/kg/min (4 mg/kg/min).

The clinical study achieved its primary efficacy endpoint of a 1-sided 99% upper bound confidence interval (CI) of less than one SABI per subject per year. The upper one sided 95% CI for the proportion of Gammaplex 5% infusions with at least one temporally associated adverse event (AE), regardless of causality, was 30.4%, which was less than

the established historical control of 40%, thus also meeting the primary safety criterion. There were no deaths, no thromboembolic, or hemolytic events in the clinical study. Gammaplex was shown to be safe and well-tolerated in the pediatric PI subjects. An impact of subject's gender and race could not be established, due to the small sample size.

The revised final label is acceptable, and approval of the efficacy supplement is recommended.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

PI is a spectrum of intrinsic defects in humoral and cellular immune function that can cause aberrations in immune globulins (IG), rendering subjects more susceptible to infections. Pathologies include, but are not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. IG replacement therapy has been the standard treatment for PI since the early 1950s.

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

Treatments for PI involve treating infections, generally with antibiotics, and preventing infections. Antibiotics may also be used to prevent infections in PI; however, the mainstay of prevention lies in correcting immunodeficiency. Bone marrow transplant (BMT) can be used, particularly in life-threatening immunodeficiency, and can be curative. BMT is not always successful and requires a donor who is a suitable tissue match to the recipient. Post-transplant BMT requires immunosuppressive therapy and runs the risk of graft vs. host disease. Enzyme replacement with adenosine deaminase is another option, but is only useful in patients who lack this enzyme.

2.3 Safety and Efficacy of Pharmacologically Related Products

Safety and effectiveness of intravenous human IG products for replacement therapy of PI in adults and pediatric patients have been well established. As per FDA's Guidance "*Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency"* and the cited literature references, IGIV administration to individuals with PI have observed SABI rates of 0.5 per year, as opposed to four or more SABIs in those without IGIV replacement therapy.

Currently available IGIV products carry warnings and precautions that include: thrombosis; hypersensitivity; renal dysfunction/failure; hyperproteinemia, increased serum viscosity, and hyponatremia; aseptic meningitis syndrome; hemolysis; transfusion-related acute lung injury; transmissible infectious agents; and interference with laboratory tests.

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

Gammaplex was licensed in the United States on September 17, 2009, for the indication treatment of PI. On March 8, 2013, Gammaplex received licensure for the indication treatment of chronic immune thrombocytopenic purpura (ITP), for which Orphan Drug Designation was granted. Gammaplex is currently licensed in the United States, United Kingdom, Israel, Brazil, and Lebanon.

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

- September 17, 2009, Gammaplex was licensed for the indication treatment of PI. The postmarketing requirement (PMR) pediatric study for the treatment of PI in pediatric patients >2 to 16 years of age was deferred with the following timelines:
    - **Protocol Submission:** November 2009
    - **Study Initiation:** January 2010
    - **Study Completion:** September 2012
    - **Final Report Submission:** December 2012
- March 8, 2013, ITP indication was approved (BLS 125329/55)
- April 9, 2013, Bio Products communicated to FDA that the ongoing GMX04 study had been significantly delayed due to very slow recruitment. The clinical study report would be delayed until December 2014. Deferral extension request was granted by FDA on July 9, 2013.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This supplement has been submitted electronically in compliance with *Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*. The submission is also compliant with ICH guideline M4E, *Common Technical Document for the Registration of Pharmaceuticals for Human Use*, using appropriate numbering within the Modules. The index provides links to the relevant sections.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Division of Inspections and Surveillance conducted Biomedical Monitoring (BIMO) inspections of two clinical sites, accounting for approximately 56% of the total subjects enrolled in the study (see Table 1). The data audit portion of the inspections focused on the verification of the safety and efficacy study data for 100% of the enrollees at the two sites.

Table 1: Inspection of Clinical Sites and Outcomes

Study site / Site #	Location	Number of subjects enrolled	Form FDA 483 issued	Final classification
Family Allergy & Asthma Center, P.C. / 402	Atlanta, Georgia	6	No	NAI
IMMUNOe International Research Centers / 401	Centennial, Colorado	8	No	NAI

NAI-No Action Indicated

In summary:
The BIMO inspections of two clinical investigators did not reveal substantive problems that would impact integrity of the data submitted in the sBLA.

3.3 Financial Disclosures

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when he/she disclosed information about his/her financial interests to the sponsor, and/or interests of any sub-investigators, spouse(s) and dependent children, and if and when the information was updated. The information submitted to the sBLA was verified for the investigator and sub-investigators.

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

4.1 Chemistry, Manufacturing, and Controls (CMC)

Gammaplex contains sorbitol, glycine and polysorbate 80 as stabilizers. Specifically, Gammaplex contains approximately 5 g normal human immunoglobulin and 5 g D-sorbitol in 100 mL of buffer solution containing: 0.6 g glycine, 0.2 g sodium acetate, 0.3 g sodium chloride and ~5 mg polysorbate 80. Immunoglobulin G purity is > 95%, the pH is in the range of 4.8 to 5.1, and osmolality is not less than 240 mOsmol/kg (typically 420 to 500 mOsmol/kg). The distribution of the four IgG subclasses is approximately 64% IgG1, 30% IgG2, 5% IgG3, and 1% IgG4. The batches used in GMX04 conform to the BLA-approved specifications.

No new CMC data were included in the submission.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data were included in the submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Gammaplex acts through a broad spectrum of opsonic and neutralizing IgG antibodies against pathogens and their toxins involving antigen binding and effector functions. However, the mechanism of action in PI has not been fully elucidated.

4.4.3 Human Pharmacokinetics (PK)

The clinical PK of Gammaplex 5% has been evaluated in a pediatric population in GMX04. Data from 23 of 25 (92%) recruited subjects were used for PK analysis. One subject (Subject (b) (6)) discontinued early, and a second subject (Subject (b) (6)) had limited PK samples taken because of school commitments; therefore, these two subjects were excluded from the PK analysis. There were 17 males and 6 females with an age range of 3-16 years inclusive. The numbers of subjects in each age range was:

- n = 3 actual ages 3 to 5 years inclusive
- n = 11 actual ages 6 to 11 years inclusive
- n = 9 actual ages 12 to <17 years

PK parameters were estimated by non-compartmental analysis using both baseline adjusted and baseline unadjusted total IgG concentrations. The results of the study are summarized in Table 2 below.

Table 2: Effect of Age on Absolute and Baseline-adjusted PK Parameters of IgG Following Intravenous Infusion of Doses of 304 to 813 mg/kg Gammaplex

PK Parameter	Baseline-Adjusted?	Age Category	Least Squares Geometric Mean	Ratio (Child Category/Adult) Estimate	90% CI	p-value
C_{max} (mg/dl)	No	2-5	1600	0.73	(0.62, 0.86)	0.002
		6-11	1800	0.82	(0.75, 0.90)	0.001
		12-15	1870	0.85	(0.76, 0.96)	0.034
		>16	2190			
	Yes	2-5	719	0.61	(0.47, 0.79)	0.002
		6-11	871	0.74	(0.63, 0.86)	0.001
		12-15	909	0.77	(0.64, 0.93)	0.024
		>16	1180			
C_{max}/Dose (kg.mg/dL/mg)	No	2-5	3.25	0.73	(0.62, 0.86)	0.002
		6-11	3.65	0.82	(0.75, 0.90)	0.001
		12-15	3.80	0.85	(0.76, 0.96)	0.034
		>16	4.44			
	Yes	2-5	1.46	0.61	(0.47, 0.79)	0.002
		6-11	1.76	0.74	(0.63, 0.86)	0.001
		12-15	1.84	0.77	(0.64, 0.93)	0.024
		>16	2.39			
$AUC_{0-\tau}$ (days.mg/dL)	No	2-5	28400	0.87	(0.75, 1.01)	0.125
		6-11	28600	0.88	(0.80, 0.96)#	0.018
		12-15	27600	0.85	(0.75, 0.95)	0.022
		>16	32500			
	Yes	2-5	5390	0.67	(0.50, 0.90)	0.025
		6-11	6140	0.76	(0.64, 0.91)	0.013
		12-15	6550	0.81	(0.65, 1.03)	0.142
		>16	8060			
CL (dL/days/kg)	No	2-5	0.0174	1.15	(0.99, 1.33)	0.125
		6-11	0.0173	1.14	(1.04, 1.24)#	0.018
		12-15	0.0180	1.18	(1.05, 1.33)	0.022
		>16	0.0152			
	Yes	2-5	0.0918	1.49	(1.12, 2.00)	0.025
		6-11	0.0806	1.31	(1.10, 1.56)	0.013
		12-15	0.0755	1.23	(0.97, 1.55)	0.142
		>16	0.0614			
V_{ss} (dL/kg)	No	2-5	1.13	1.72	(1.39, 2.13)	<.001
		6-11	0.903	1.38	(1.21, 1.57)	<.001
		12-15	0.940	1.43	(1.21, 1.70)	0.001
		>16	0.656			
	Yes	2-5	0.729	1.50	(1.02, 2.19)	0.081
		6-11	0.628	1.29	(1.03, 1.62)	0.069
		12-15	0.556	1.14	(0.84, 1.55)	0.466
		>16	0.487			
$t_{½}$ (days)	No	2-5	44.6	1.51	(1.26, 1.80)	<.001
		6-11	36.4	1.23	(1.10, 1.37)	0.002
		12-15	37.1	1.25	(1.08, 1.44)	0.012
		>16	29.6			
	Yes	2-5	5.32	0.92	(0.71, 1.20)	0.594
		6-11	5.20	0.90	(0.77, 1.05)	0.259
		12-15	5.20	0.90	(0.73, 1.11)	0.393
		>16	5.79			

90% CI contained within bioequivalence limits of (0.80, 1.25)
Source Pharmacokinetic Report GMX01 and GMX04, [redacted] *Ref. No. BPL109, Table 18, Pg 51 of 111.*

Reviewer Comment: *The PK of IgG shows difference in the 2-5 years of age group of children compared to adults. Interpreting the clinical significance of these differences is difficult, given the small sample size (N=3). For more details, please refer to the clinical pharmacology review.*

4.5 Statistical

Both efficacy analyses and safety analyses in the submission were verified to support the claim for the use of Gammaplex in pediatric subjects with PI, and no statistical issues were identified.

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

5.1 Review Strategy

All documents submitted in the supplement were reviewed. Information requests (IR) and labeling revisions were sent to the applicant as necessary, until the subjects of the IR were clarified and agreement was reached on the labeling.

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

- BLA 125329/0
- BLS 125329/55
- BLS 125329/112
- IND 12569

    - Adverse event listings
    - Audit certificates
    - Demographic data listing
    - IRBs and Consent Forms
    - Efficacy data
    - Sites and investigators
    - Protocol/amendments
    - Full study report
    - Individual Case Study Report Forms

5.4 Consultations

No consultations were obtained during the review.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 "A Phase 4, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Gammaplex® in Primary Immunodeficiency Diseases in Children and Adolescents"

6.1.1 Objectives (Primary, Secondary)

The primary objective of the study was to determine efficacy, measured by the number of SABIs over a 12-month period. The secondary objectives were to assess the safety and tolerability of Gammaplex in pediatric subjects with PI, as compared to adults with PI.

6.1.2 Design Overview

Protocol GMX04:
This was a phase 4, multicenter (nine sites), open-label, non-randomized study of Gammaplex. A total of 25 subjects between the ages 2 through 16 were enrolled in the study, and administered the study drug by intravenous (IV) 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.

6.1.3 Population

Subjects eligible for inclusion in the study:

1. The subject was between the age of, or equal to, 2 and 16 years of age, of either sex, belonging to any ethnic group, and above a minimum weight of 10 kg. This weight was based on the amount of blood required for testing. At least four of the subjects enrolled were to be 2 to 5 years of age, at least four were to be 6 to 11 years of age, and at least eight were to be12 to 16 years of age.
2. The subject had a PI, which had as a significant component: hypogammaglobulinaemia and/or antibody deficiency (e.g. common variable immunodeficiency; X-linked and autosomal forms of agammaglobulinaemia; hyper-immunoglobulin M [IgM] syndrome; or Wiskott-Aidrich Syndrome). Isolated deficiency of a single gG sub-class 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 should also 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 (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 gonadotropin (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 Independent Ethics Committee/Institutional Review Board.

Subjects excluded from the study participation:

1. Had not been treated with IGIV (treatment-naive 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 as sorbitol (i.e., intolerance to fructose).

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study drug, Gammaplex, was administered by IV 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. The ready-prepared solution for IV administration contained 5 g human normal immunoglobulin, and 5 g D sorbitol (as stabilizer), in 100 mL of buffer solution. The infusion rates were initially at 0.01 mL/kg/min for the first 15 minutes and then, if tolerated, increased stepwise (i.e. to 0.02, 0.04, 0.06 and 0.08, maximum, mL/kg/min) every 15 minutes.

The total 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. Subjects received 13 to 17 infusions (i.e., 12 months of therapy on either a 21-day or 28-day treatment schedule) of Gammaplex at a dose of 300 to 800 mg/kg. Safety assessment was done during each infusion visit, plus 7 days after first infusion, and at 14 days, and three months after the last infusion. See the schema:

Figure 3: Schematic Representation of 21-day and 28-day Infusion Cycles

		Diary		Diary		Diary		
Screening Visit 1	**Visit 2**	→	**Visit 3**	→	**Visit 4 to 15/19**	→	**F1**	**F2**
Eligibility assessed	Eligibility confirmed First infusion		Safety visit		Infusion visits 13/17		Follow-up	Follow-up
Up to 30 days before enrolment			6-7 days after first infusion (+ 1 day)		Every 21 or 28 days		10-14 days after last infusion	3 months after last infusion (- 2 weeks to + 4 weeks)

Source: GMX04 Clinical Study Report/Version: 22 August 2014, page 29

All subjects underwent a PK profile of Gammaplex at the seventh infusion for subjects assigned to the 28-day schedule and at the ninth infusion for subjects on the 21-day schedule. PK samples were drawn before infusion and at 60 min, 24 hours, 2, 4, 7, 14, 21, and 28 days after the infusion.

6.1.6 Sites and Centers

Table 4: Sites and Investigators

Principal Investigator	Site #	Site Address	Sub-Investigators	No. Subjects
Isaac R. Melamed, MD	401	IMMUNOe International Research Centers 6801 S. Yosemite St. Centennial, CO 80112 United States	Angela R. McDonald, PA-C Alessandro Testori, MD, PhD Brandon Freson Kevin O'Brien, MD Scott Kaiser, MD Joe Williams, Jr.,MD James Doody, PA-C Maninderphal S. Sethi	8
Robyn J. Levy, MD	402	Family Allergy & Asthma Center, PA 5555 Peachtree Dunwoody Road, NE Suite 340 Atlanta, GA 30342 United States	Steven D. Goodman	6
Todd Green, MD	404	Children's Hospital of Pittsburgh of UPMC One Children's Hospital Drive 4401 Penn Avenue Pittsburgh, PA 15224 United States	David Nash, MD Allyson Larken, MD Hey Chong, MD Shayna Burke, MD Russell Traister, MD Marc Ikeda, MD Nina Ahuja, MD	1
James Moy, MD	405	Rush University Medical Center 1725 West Harrison, #117 Chicago, IL 60612 United States	Byung Ho Yu, MD Susan Fox, PA-C, MMS Christopher Codispoti, MD R. Joseph Mittel, MD	2

Principal Investigator	Site #	Site Address	Sub-Investigators	No. Subjects
Daniel Suez, MD	407	Allergy, Asthma & Immunology Clinic, PA 1115 Kinwest Parkway Suite 100 Irving, TX 75063 United States	Tran Ly, MD Florence Iyamu, FNP	1
Anne-Marie Irani, MD	408	Children's Hospital of Richmond VCU Health System 1001 East Marshall Street Richmond, VA 23219 United States	Lawrence Schwartz, MD Wei Zhao, MD Santhosh Kumar, MD Brant Ward, MD Manar Abdalgani, MD Donna Mitchell, CPNP Diane Sun, MD Joud Hajjar, MD Jessica Miles, CRC Michelle Rhea, CCRC	2
Sudhir Gupta, MD, PhD	411	University of California, Irvine Medical Sciences I C-240 Irvine, CA 92697 United States	Ravi Chandra Gutta, MD Thu Michelle Tran, NP Maritza Clawges, ACRC	2
Carmen Luz Navarrete Súare, MD	602	Hospital Roverto del Rio Profesor Zañartú 1085 Independencia Santiago, Chile 8390418	María Cecilia Berta Poli Harlowe, MD	1
Dr. Raz Somech, MD, PhD	804	Pediatric Department B North Pediatric Immunology Service Pediatric Immunology Laboratory Edmond and Lily Safra Children's Hospital Sheba Medical Center Tel Hashomer, Israel 52621	Arie Augarten, MD Shulamit Katz, MD	2

Source: GMX04 Clinical Study Report/Version: 22 August 2014, 16.1.3 *Page 1-2*

6.1.7 Surveillance/Monitoring

Table 5: Study Scheme

Evaluation (volume of blood)	Visit Number/Definition										
	1/S[a]	2/I-1	3[b]	4/I-2	5/I-3	6/I-4	7/I-5	8/I-6	9/I-7	10/I-8	11/I-9
	Screening	Infusion 1	Safety	Infusion 2	Infusion 3	Infusion 4	Infusion 5	Infusion 6	Infusion 7	Infusion 8	Infusion 9
Eligibility	X	X									
Consent	X										
HCG urine test	X										
Complete medical history	X										
Interval medical history		X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	(X)[c]										
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[e]		X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Diary Cards		X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X		X		X		X		X
Pharmacokinetics[f,g] **(only to be conducted once)**									X[f]		X[g]
ALT, AST, Bilirubin, Creatinine, BUN, LDH and CBC with differential	X	X	X	X		X		X		X	
HCV and HIV NAT and serological tests for HBsAg, HCV, and HIV 1 & 2 and Parvovirus B19 at V2 and V3L/laboratory visit [h]		X[h]	X[h]								
Trough IgG	X	X		X		X		X	X	X	X
IgG Subclasses[i]	X	X				X		X	X	X	X
Specific antibody levels[j]	X								X	X	X
IgA, IgM	X[a]										
Direct Coombs' Test[k]	X	X	X	X	k	k	k	k	k	k	k
C-reactive Protein	X					X				X	
Reserve Sample	X	X	X	X		X		X	X	X	X
Retention Sample[p]		X									
(28 day infusion cycle) Estimated maximum Total Blood Volume Required in mL	12	18	9	8	0	7	0	6	6+PK	9	6
(21 day infusion cycle) Estimated maximum Total Blood Volume Required in mL	12	18	9	8	0	7	0	6	6	9	6+PK

Evaluation (volume of blood)	12/I-10	13/I-11	14/I-12	15/I-13[l]	16/I-14[m]	17/I-15[m]	18/I-16[m]	19/I-17[m]	F1[n]	F2[o]
	Infusion 10	Infusion 11	Infusion 12	Infusion 13	Infusion 14	Infusion 15	Infusion 16	Infusion 17	Follow-up	Follow-up
Eligibility										
Consent										
HCG urine test										
Complete medical history										
Interval medical history	X	X	X	X	X	X	X	X	X	X[r]
Physical examination	X	X	X	X	X	X	X	X	X	(If required)
Chest X-ray										
Vital Signs[d]	X	X	X	X	X	X	X	X		
Adverse Events[e]	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Diary Cards	X	X	X	X	X	X	X	X		
Urinalysis		X		X		X		X	X	
Pharmacokinetics										
Biochemistry & CBC ALT, AST, Bilirubin, Creatinine, BUN, LDH and CBC with differential	X		X		X		X		X	
HCV and HIV NAT and serological tests for HBsAg, HCV, and HIV 1 & 2 and Parvovirus B19 at V2 and V3L/laboratory visit [h]										X
Trough IgG	X		X		X		X		X	
IgG Subclasses[i]	X		X		X		X		X	
Specific antibody levels[j]	X		X		X		X		X	
IgA, IgM										
Direct Coombs' Test[k]	k	k	k	k	k	k	k	k	X	
C-reactive Protein			X				X			
Reserve Sample	X		X		X		X		X	X
Retention Sample[p]									X	
(28 day infusion cycle) Estimated maximum Blood Volume Required in mL	8	0	9	0					12	10
(21 day infusion cycle) Estimated maximum Blood Volume Required in mL	8	0	9	0	8	0	9	0	12	10

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; HBsAg, hepatitis B surface antigen; HCG, human chorionic gonadotrophin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; I, Infusion; Ig, immunoglobulin; IGIV, intravenous immunoglobulin; LDH, lactate dehydrogenase; NAT, nucleic acid amplification test; PK, pharmacokinetic; S, Screening.

[a] Screening visit could have coincided with subject's scheduled infusion of a licensed IGIV product or could have been scheduled separately. If scheduled with an infusion, required blood samples were drawn before the infusion was started. After the Screening Visit, the subject should not have received any blood or blood products (other IGIV product) until receiving GAMMAPLEX at Infusion 1. Two trough IgG levels (one of which could have been the screening visit result) and 2 trough levels of IgG subclasses (one of which could have been the screening visit result), determined from blood samples drawn just before routine IGIV infusions, were obtained for each subject before the first study infusion was given.

[b] The physical examination, interval medical history, checking of vital signs and the collection of laboratory samples at this visit could have been conducted by a qualified member of staff making a home visit. The sample was taken 6 to 7 days ± 1 day after Infusion 1.

[c] A chest X-ray was done if there had been no chest X-ray in the previous 12 months.

[d] Vital signs were recorded 10 minutes before and at the start of each infusion, 10 minutes after the start of the infusion and 10 minutes after each rate increase; 10 minutes and 30 minutes after the maximum rate was achieved and every 60 minutes thereafter until the infusion was stopped; at the time that the infusion was stopped and 15 and 30 minutes after stopping the infusion. At Visit 3 resting vital signs were recorded.

[e] Adverse events were reviewed monthly and during the infusion by direct observation. The study coordinator interviewed the subject weekly between the first and second infusions and collected the diaries at each subsequent infusion.

[f] Only for those subjects on the 28-day infusion cycle.

[g] Only for those subjects on the 21-day infusion cycle.

[h] At Visit 2 (immediately before the 1st infusion), the sample was also tested for parvovirus B19. At Visit 3, a sample was drawn for parvovirus B19 testing only.

[i] IgG subclasses were measured before infusion.

[j] A specific antibody test on Streptococcus pneumoniae, Haemophilus influenzae type b and Cytomegalovirus was performed.

[k] Testing for IgA and IgM was to have only occurred in those subjects where results were not available for the previous 12 months.

[l] All subjects had samples taken for a direct Coombs test and tests of haemolysis (haptoglobin and urine haemosiderin) at Visit 2, Visit 3 and at Visit 4. Subjects with a positive result had a direct Coombs test on blood drawn before every subsequent IGIV infusion and at all follow-up visits. For these subjects, approximately 2 mL of additional blood was added to the estimated blood volume (per visit) from Visit 5 onwards.

[m] Before infusion.

[n] Last infusion for subjects on the 28-day schedule.

[o] Only for those subjects on the 21-day schedule.

[p] This visit occurred 10 to 14 days after the last study infusion.

[q] This visit occurred 3 months after the last study infusion. This could have been done when the subject came for regular infusion of a licensed IGIV product.

[r] If any concerns were raised by the principal investigator, a physical examination could also have been conducted.

Source: GMX04 Clinical Study Report/Version: 22 August 2014, page 26-28

6.1.8 Endpoints and Criteria for Study Success

Efficacy:

Primary:

The primary efficacy endpoint was the number of SABIs per subject per year, pre-defined by FDA as:

- Bacterial pneumonia
- Bacteraemia or sepsis
- Osteomyelitis/septic arthritis
- Visceral abscess
- Bacterial meningitis

Treatment success was defined as a mean SABI event rate of< 0.5 per patient per year.

Secondary:

- Number and proportion of subjects from Week 15 onwards who maintained 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:

- Number and percentage of adverse events (AEs) and adverse reactions (AR),
- Significant changes in vital signs, clinical laboratory tests (including kidney and liver function), direct Coombs test, transmission of viruses and physical examination during the study

PK Endpoints:

- C_{max} peak concentration in plasma;
- t_{max} time to reach the peak concentration in plasma;
- $t_{1/2}$ terminal half-life;
- CL systemic clearance;
- V_{ss} volume of distribution at steady state;
- $AUC_{(0\text{-}tau)}$ area under the plasma concentration-time curve from 0 (infusion start time) to the end of the dosing interval (21 or 28 days, depending on the assigned schedule)
- Trough levels IgG, IgG subclasses and antibodies against three specific antigens (Streptococcus pneumoniae, Haemophilus influenzae type b and cytomegalovirus) were measured before certain infusions)

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 by using the exact method for a one-sample Poisson rate. Treatment success was defined as a mean SABI event rate of < 0.5 per patient per year.

Secondary efficacy variables and PK variables were summarized descriptively.

For the primary safety criterion, the upper one sided 95% CI for the proportion of Gammaplex infusions with at least one temporally associated AE (regardless of relationship) was compared with the historical control.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The intent-to-treat (ITT) population was used for safety and efficacy analyses. All subjects who receive at least one infusion of Gammaplex were included in the ITT population. A total of 25 subjects were enrolled; of these, all 25 were treated with Gammaplex and were included in the ITT population.

6.1.10.1.1 Demographics

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.

Table 6: Demographics

Category Statistic/Response	21-Day Infusion Schedule (N = 14)	28-Day Infusion Schedule (N = 11)	Total (N = 25)
Age (years)			
n	14	11	25
Mean	11.8	8.5	10.4
Std Dev	3.47	3.64	3.84
Median	12.5	7.0	11.0
Min	4	3	3
Max	16	16	16
Age			
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			
Male	9 (64.3)	10 (90.9)	19 (76.0)
Female	5 (35.7)	1 (9.1)	6 (24.0)

Category Statistic/Response	21-Day Infusion Schedule (N = 14)	28-Day Infusion Schedule (N = 11)	Total (N = 25)
Race			
White or Caucasian	14 (100)	11 (100)	25 (100)
Black or African American	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Ethnicity			
Hispanic or Latino	1 (7.1)	1 (9.1)	2 (8.0)
Not Hispanic or Latino	13 (92.9)	10 (90.9)	23 (92.0)
Diagnosis			
Common Variable Immunodeficiency	13 (92.9)	9 (81.8)	22 (88.0)
X-linked and Autosomal Forms of Agammaglobulinemia	1 (7.1)	2 (18.2)	3 (12.0)
Hyper-IgM Syndrome	0	0	0
Wiskott-Aldrich Syndrome	0	0	0

Source: GMX04 Clinical Study Report/Version: 22 August 2014, page 140-141.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects were PI patients with history of recurrent infections. The most common medical history conditions were chronic sinusitis (15 subjects, 60.0%), allergic rhinitis (11 subjects, 44.0%) and gastroesophageal reflux disease (10 subjects, 40.0%).

All 25 subjects had prior IGIV therapy; 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

Table 7: Subject Disposition

No. of Subjects, n (%)	21-Day Infusion Schedule (N = 14)	28-Day Infusion Schedule (N = 11)	Total (N = 25)
Enrolled	14 (100)	11 (100)	25 (100)
Intent-to-treat population[a]	14 (100)	11 (100)	25 (100)
Included in PK analysis population[b]	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)

Abbreviation: PK, pharmacokinetic.

[a] The intent-to-treat population included all subjects who received at least one infusion of GAMMAPLEX.

[b] One subject discontinued before PK sampling and was excluded from the PK analysis population. A second subject was later excluded from the PK analysis because limited PK samples were collected.

Sources: Section 14.1, Table 1, Appendix 16.2, Listing 1 and Pharmacokinetic Report, Appendix 16.1.12.

Reviewer Comment: *As Bio Products communicated to FDA, they had difficulties in recruiting pediatric subjects, mostly due to PK sampling and the long study duration, particularly in the youngest subject group, where only three out of the four planned subjects aged 2 to 5 years were enrolled, in spite of opening up additional sites in the United States and also a site in Israel.*

One subject (Subject (b) (6)) withdrew consent and discontinued from the study after the fourth infusion as they could not comply with the visit assessments specified in the protocol (ie. infusions every 21 or 28 days).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

For the primary efficacy analysis, the SABI rate for Gammaplex and the upper bound of its one-sided 99% CI were estimated by using the exact method for a one-sample Poisson rate. Treatment success was defined as a mean SABI event rate of < 0.5 per patient per year. Two subjects had SABI, lobar pneumonia (*see Section 6.1.12.4 for the narratives*). Two SABIs in 25 subjects resulted in a mean SABI event rate per year of 0.09 and a one-sided 99% upper confidence bound of 0.36. The observed SABI frequency was less than 0.5 per patient per year, thereby meeting the primary end point.

Reviewer Comment: *As per FDA guidance supported by historical data, a statistical demonstration of a SABI rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy. The study results show that the one-sided 99% upper CI is less than FDA's efficacy threshold value of 1.0, therefore meeting the pre-specified primary efficacy endpoint for Gammaplex.*

6.1.11.2 Analyses of Secondary Endpoints (N=25)

All trough 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.

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.

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).

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%).

Table 8: Secondary Endpoints

Efficacy Measure	**Incidence Rate N (%)**	**Descriptive Statistics SD**
Number of days of school missed because of infection	16 (64)	4.2 (8.28)
Number of days of hospitalization because of infection	22(88)	0.3 (0.87)
Number of visits to physician/emergency room for acute problems	18 (72)	4.0 (4.67)
Number of infectious episodes per subject per year	21 (84)	3.2 (2.713)
Number of days on therapeutic and prophylactic antibiotics	21 (84)	110.6 (137.10)

Comparison of secondary efficacy variables between GMX01 and GMX04
The GMX01 (pivotal) and GMX04 (pediatric PMR) studies evaluated the same variables but in adults and children in GMX01 (aged 3 years and above) and in children (aged 2 to 16 years) in GMX04. Fifty subjects were enrolled in the GMX01 study and 25 in the GMX04 study. Of the 50 subjects enrolled in the GMX01 study, six were 16 years of age or younger. There were no significant differences seen in these two studies.

Reviewer Comment: *The choice and the outcomes of the secondary efficacy endpoints are adequate in support of the primary endpoints and no issues were identified. For more details, please refer to the full statistical review memo.*

6.1.11.3 Subpopulation Analyses

The primary analysis was repeated for the age categories of subjects aged 2 to 5 years, 6 to 11 years and 12 to 16 years. 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) also experienced a SABI of lobar pneumonia. No SABIs occurred in the 2 to 5 year age group. Mean event rates per year (one-sided 99% upper

confidence bound) for the age groups 6 to 11 years and 12 to 16 years were 0.09 (0.57) and 0.11 (0.74), respectively.

Table 9: SABIs by Age Groups

Age Group	2 - 5 Years (n = 3)	6 - 11 Years (n = 12)	12 - 16 Years (n = 10)
Subjects with a serious, acute, bacterial infection, n (%)	0	1 (8.3)	1 (10.0)
Events of serious, acute, bacterial infection, n (%)	0	1	1
Mean event rate per year[a]	0	0.09	0.11
One-sided 99% upper confidence bound[b]	1.59	0.57	0.74

[a] Mean event rate calculated as total number of infections divided by total number of subject years.
[b] One-sided 99% upper confidence bound computed using the exact method for a one-sample Poisson rate
Sources: Section 14.2, Table 10.2 and Appendix 16.2, Listing 26.

Reviewer Comment: *The subpopulation analysis did not yield meaningful results for interpretation due to the small sample size.*

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.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety population consisted of all subjects who received at least 1 dose of Gammaplex (N=25).

For all subjects, the mean (SD) duration of exposure to Gammaplex was 342.3 (53.77) days, and median duration was 351.0 days with a range of 88 to 376 days. The duration of exposure was between 11 and 12 months for the majority of subjects (21 subjects, 84.0%). The mean dose (range) per infusion was 536 mg/kg (300-800 mg/kg) for all subjects. The mean dose (range) for subjects on the 21-day schedule was 545 mg/kg (429-689 mg/kg), and for subjects on the 28-day schedule was 521 mg/kg (316-800 mg/kg)(See Table 9). No doses were outside the planned range of 300 to 800 mg/kg.

Table 10: Exposure to GAMMAPLEX by Mean (SD) Total Dose

All Infusions Total Dose (mg/kg)	21-Day Schedule	28-Day Schedule	Total
All subjects (N = 25)	8764.2 (2401.98)	6776.4 (1961.48)	7889.6 (2396.35)
Age group 2 to 5 years (n = 3)	9925.0 (--)	7969.0 (974.39)	8621.0 (1322.89)
Age group 6 to 11 years (n = 12)	9453.4 (2039.72)	6613.7 (2368.00)	7796.9 (2590.30)
Age group 12 to 16 years (n = 10)	8188.4 (2725.19)	6153.0 (270.11)	7781.3 (2553.60)

Abbreviation: SD, standard deviation.
Source: Section 14.4, Table 19.1.

Safety data were collected from screening until 30 days after the last infusion of Gammaplex (approximately one year after the first infusion). A viral screen was conducted pre first infusion and at the final visit, 3 months after the last infusion of Gammaplex. Infusions of Gammaplex 5% were administered for approximately 1 year. After 6 months of treatment with Gammaplex 5%, the subjects had a PK profile performed between 2 sequential infusions (between infusions 9 and 10 for those on the 21-day schedule, or between infusions 7 and 8 for those on the 28-day schedule). The primary safety criterion was that the upper bound of the 95% CI indicates that not more than 40% of infusions were associated with an AE, irrespective of causality. All per-infusion AEs (during and up to 72 hours after infusion) were collected. Their relationship to Gammaplex was assessed by investigator.

AE was defined as any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment.

Infusion-Related Adverse Reactions (AR) were defined as all AEs temporally associated with infusion – occurring from the start of the infusion until 72 hours after the infusion.

AR were defined as all noxious and unintended responses to a medicinal product related to any dose administered. The phrase ‘response to a medicinal product’ means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

6.1.12.2 Overview of AEs

During the treatment period and up to 30 days after the last dose, all 25 subjects reported at least one AE. Altogether, there was a total of 365 AEs in the study. Fourteen subjects (56.0%) had an AR, defined as possibly, probably or definitely related to study drug. Two subjects (8.0%) had a Serious Adverse Event (SAE), not product-related. No subjects discontinued the study because of an AE.

Table11: Summary of Adverse Events

Subject Group	All Subjects (N = 25)	2 to 5 Years (n = 3)	6 to 11 Years (n = 12)	12 to 16 Years (n = 10)
Subjects with any AE, n (%)	25 (100)	3 (100)	12 (100)	10 (100)
Subjects with product-related AE,[a] n (%)	14 (56.0)	2 (66.7)	7 (58.3)	5 (50.0)
Subjects with any SAE,[b] n (%)	2 (8.0)	0	1 (8.3)	1 (10.0)
Subjects discontinued because of AEs	0	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.
[a] Includes all AEs that were possibly, probably or definitely related to product.
[b] Subject (b) (6) experienced an SAE that occurred before the first infusion and is, therefore, not included in this table.
Source: Section 14.3.1, Table 20.

The most common AEs (regardless of causality) were headache (39 events [13 subjects, 52.0%]), cough (19 events [8 subjects, 32.0%]), nasal congestion (17 events [8 subjects, 32.0%]), pyrexia (15 events [9 subjects, 36.0%]) and nasopharyngitis (11 events [8 subjects, 32.0%]).

Table 12: AEs Occurring with a Frequency of 5% or More Subjects

System Organ Class Preferred Term	All Subjects (N = 25)	Number of
Number of subjects with at least one adverse event, n (%)	25 (100)	365
Blood and lymphatic system disorders		
Lymphadenopathy	2 (8.0)	3
Cardiac disorders		
Tachycardia	3 (12.0)	6
Gastrointestinal disorders		
Nausea	6 (24.0)	8
Vomiting	5 (20.0)	8
Diarrhoea	3 (12.0)	4
Abdominal pain upper	2 (8.0)	2
General disorders and administration site conditions		
Pyrexia	9 (36.0)	15
Fatigue	5 (20.0)	11
Malaise	5 (20.0)	7
Chest discomfort	3 (12.0)	6
Infusion site erythema	2 (8.0)	2
Pain	2 (8.0)	2
Infections and infestations		
Nasopharyngitis	8 (32.0)	11
Acute sinusitis	7 (28.0)	9
Upper respiratory tract infection	6 (24.0)	8
Viral upper respiratory tract infection	5 (20.0)	7
Pharyngitis streptococcal	4 (16.0)	4
Sinusitis	3 (12.0)	7
Gastroenteritis viral	3 (12.0)	4
Pharyngitis	3 (12.0)	4
Bronchitis	2 (8.0)	3
Lobar pneumonia	2 (8.0)	3
Bronchitis acute	2 (8.0)	2
Influenza	2 (8.0)	2
Otitis media	2 (8.0)	2
Otitis media acute	2 (8.0)	2
Pneumonia	2 (8.0)	2
Rhinitis	2 (8.0)	2

Injury, poisoning and procedural complications		
Joint sprain	2 (8.0)	2
Skin laceration	2 (8.0)	2
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (16.0)	4
Myalgia	2 (8.0)	13
Nervous system disorders		
Headache	13 (52.0)	39
Respiratory, thoracic and mediastinal disorders		
Cough	8 (32.0)	19
Nasal congestion	8 (32.0)	17
Rhinorrhoea	4 (16.0)	4
Dyspnoea	3 (12.0)	3
Pharyngolaryngeal pain	3 (12.0)	3
Epistaxis	2 (8.0)	3
Nasal oedema	2 (8.0)	3
Wheezing	2 (8.0)	3
Skin and subcutaneous tissue disorders		
Eczema	2 (8.0)	3
Vascular disorders		
Hypotension	4 (16.0)	12
Diastolic hypertension	3 (12.0)	5

Sources: Section 14.3.1, Table 24 and Table 25.

ARs:

Fourteen subjects (56.0%) had at least one AR. There were 74 AR, none of which were serious. By age group, two subjects (66.7%) had 19 product-related AEs in the 2 to 5 year age group, seven subjects (58.3%) had 29 product-related AEs in the 6 to 11 year age group and five subjects (50.0%) had 26 product-related AEs in the 12 to 16 year age group.

The most common ARs were headache (19 events [8 subjects, 32.0%]), myalgia (12 events [1 subject, 4.0%]) and hypotension (8 events [4 subjects, 16.0%]). Twelve product-related AEs were vascular (hypotension and diastolic hypertension) (five subjects, 20.0%). Four product-related AEs of tachycardia were reported by three subjects (12.0%); one of these subjects (Subject) also reported product-related AEs of diastolic hypertension, diastolic hypotension and hypotension, but these events did not occur at the same time as the two events of tachycardia.

Table 13: Number and Percent of Subjects with Product-related Adverse Events Occurring with a Frequency of 5% of Subjects or More

System Organ Class Preferred Term	All Subjects (N = 25)	Number of Events
Number of subjects with at least one adverse event, n (%)	14 (56.0)	74
Cardiac disorders		
Tachycardia	3 (12.0)	4
Gastrointestinal		
Vomiting	2 (8.0)	2
General disorders and administration site conditions		
Pyrexia	3 (12.0)	3
Chest discomfort	2 (8.0)	5
Fatigue	2 (8.0)	3
Infusion site erythema	2 (8.0)	2
Nervous system disorders		
Headache	8 (32.0)	19
Vascular disorders		
Hypotension	4 (16.0)	8
Diastolic hypertension	2 (8.0)	4

Source: Section 14.3.1, Table 27.

Infusion-Related ARs

Out of 368 infusions, 97 were associated with an AR. A summary of adverse reactions reported by three or more subjects and the associated number of infusions is below:

Table 14: Infusion-related ARs

Preferred Term	Subjects (N = 25) n (%)	Infusions (N = 368) n (%)
Any adverse reaction, n (%)	25 (100)	97 (26.4)
Headache	11 (44.0)	21 (5.7)
Acute sinusitis, sinusitis	6 (24.0)	8 (2.2)
Hypotension	4 (16.0)	10 (2.7)
Tachycardia	3 (12.0)	5 (1.4)
Body temperature increased, pyrexia	3 (12.0)	4 (1.1)
Diastolic hypertension, systolic hypertension	3 (12.0)	4 (1.1)
Fatigue	3 (12.0)	4 (1.1)
Infusion site erythema, infusion site pain, infusion site reaction, infusion site swelling	3 (12.0)	4 (1.1)
Dry skin, eczema	3 (12.0)	3 (0.8)
Nasal congestion	3 (12.0)	3 (0.8)
Upper respiratory tract infection, viral upper respiratory tract infection	3 (12.0)	3 (0.8)
Abdominal pain, abdominal pain upper	3 (12.0)	2 (0.5)

Source: Section 14.3.2, Table 37

The most common events reported during infusions were headache, hypotension, tachycardia and diastolic hypertension. Headache was experienced by more subjects (five subjects, 20.0%) than any other AE during infusion, and most of these subjects (three subjects, 12.0%) reported the AE of headache during an infusion rate of 0.08 mL/kg/min.

Table 15: Number and Percent of Subjects with Adverse Events during Infusion Occurring with a Frequency of 5% of Total Subjects or More as a Function of Infusion Rate

All Subjects (N = 25)	Unknown AE Onset Time[a]	Infusion Rate 0.01 mL/kg/min	Infusion Rate 0.02 mL/kg/min	Infusion Rate 0.04 mL/kg/min	Infusion Rate 0.06 mL/kg/min	Infusion Rate 0.08 mL/kg/min	Total
Number of subjects with no AEs during infusion, n (%)	7 (28.0)	23 (92.0)	20 (80.0)	21 (84.0)	21 (84.0)	16 (64.0)	2 (8.0)
Number of subjects with at least 1 AE during infusion, n (%)	18 (72.0)	2 (8.0)	5 (20.0)	4 (16.0)	4 (16.0)	9 (36.0)	23 (92.0
Cardiac disorders							
Tachycardia	0	1 (4.0)	1 (4.0)	0	0	2 (8.0)	3 (12.0)
General disorders and administration site conditions							
Chest discomfort	0	0	0	1 (4.0)	2 (8.0)	1 (4.0)	2 (8.0)
Infusion site erythema	0	1 (4.0)	0	0	0	1 (4.0)	2 (8.0)
Pyrexia	0	0	0	0	1 (4.0)	1 (4.0)	2 (8.0)
Infections and infestations							
Acute sinusitis	2 (8.0)	0	0	0	0	0	2 (8.0)
Sinusitis	2 (8.0)	0	0	0	0	0	2 (8.0)
Nervous system disorders							
Headache	1 (4.0)	0	0	1 (4.0)	1 (4.0)	3 (12.0)	5 (20.0)
Respiratory, thoracic and mediastinal disorders							
Cough	1 (4.0)	0	1 (4.0)	0	0	0	2 (8.0)
Dyspnoea	1 (4.0)	0	0	0	0	1 (4.0)	2 (8.0)
Nasal oedema	2 (8.0)	0	0	0	0	0	2 (8.0)
Skin and subcutaneous tissue							
Eczema	2 (8.0)	0	0	0	0	0	2 (8.0)
Vascular disorders							
Hypotension	0	0	4 (16.0)	1 (4.0)	0	3 (12.0)	4 (16.0)
Diastolic hypertension	0	0	0	1 (4.0)	0	2 (8.0)	3 (12.0)

Abbreviation: AE, adverse event.
Note: Subjects with an AE during an interruption to an infusion are included in the total column.
[a] These are AEs on the day of an infusion but without an onset time. Conservatively these are assumed to start during the infusion.
Source: Section 14.3.1, Table 28.

6.1.12.3 Deaths

There were no deaths in the study.

6.1.12.4 Nonfatal SAEs

Two subjects (8%) 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 (b) (6) experienced an SAE of lobar pneumonia (left lower lobe pneumonia) of severe intensity. Neither of the SAEs was considered related to study drug.

Subject
A 7-year-old male subject had a history of patchy infiltrations in the left lower lung lobe and suspected pneumonitis in the right lung base on chest X-ray during May 2011. He had also experienced a series of upper respiratory tract infections requiring antibiotics in the month before beginning treatment with Gammaplex. The subject received his first infusion of Gammaplex on 17 February 2012 at a dose level of 347 mg/kg (28-day infusion schedule). Between 25 and 29 February 2012, he was started on an antibiotic, guaifenesin and prednisone, which he completed 5 to 9 days later. On , one week after the second infusion of Gammaplex, the subject was hospitalized with a fever (101.8°F), tachycardia, dyspnea, hypoxia and vomiting. His diagnosis was patchy, left lower lobe pneumonia diagnosed by chest X-ray on the day of admission. However, no bacterial etiology was identified by blood cultures, and the Principal Investigator considered the pneumonia to be of viral origin or possibly due to an exacerbation of the subject's asthma. He was discharged from the hospital on . The event was resolved on 02 April 2012. The investigator considered the lobar pneumonia not related to study drug. For the purposes of the data reporting and analysis, this SAE was assumed to be bacterial in nature and, therefore, met the FDA definition of a SABI.

Subject
A 17-year-old male subject, had a medical history that included chronic bronchitis and asthma since 3 years of age and pneumonia. The subject received his first infusion of GAMMAPLEX on 05 February 2013 at a dose level of 400 mg/kg (28-day infusion schedule). His last dose of GAMMAPLEX received before onset of the AE was administered on 25 June 2013 at the same dose level. On 06 July 2013, the subject developed fever and chills. On 11 July 2013, the subject developed a productive cough with yellow phlegm, dyspnea, chest pain and tachycardia. A chest X-ray revealed a 4 cm retrocardiac left lung base infiltrate. Laboratory results included a WBC count of 26.4 × 109/L (reference range 4.8-10.8 × 109/L), band neutrophils 23% (reference range 50-80%) and lymphocytes 6% (reference range 20-50%). On 14 July 2013, the subject was hospitalized for the treatment of severe left lower lobe pneumonia. A chest X-ray showed patchy air space opacities in the left lower lobe consistent with pneumonia. The SAE of left lower lobe pneumonia resolved on 16 July 2013. The investigator considered the lobar pneumonia not related to study drug. In the opinion of the investigator, the event was related to a concurrent upper respiratory infection and met the FDA definition of a SABI.

6.1.12.5 AEs of Special Interest (AESI)

No thrombo-embolic events, which have boxed warning in this class of products, where reported in the study. No cases of hemolytic events were reported as well.

6.1.12.6 Clinical Test Results

Results of hematology, chemistry and urinalysis testing did not suggest evidence of hemolysis or thrombotic events, immunogenicity, or any other safety signals.
No subject tested positive for hepatitis B surface antigen, hepatitis C virus, or HIV.

6.1.13 Study Summary and Conclusions

Out of the 368 total number of infusions in GMX04, 97 (26.4%) were temporally associated with at least one AE irrespective of causality (occurring within 72 hours of the end of infusion). The upper one sided 95% confidence limit for the proportion of Gammaplex infusions with at least one temporally associated AE (regardless of causality) was 30.4% which was less than the established historical control of 0.40 (40%). Therefore, the primary safety criterion was met.

7. INTEGRATED OVERVIEW OF EFFICACY

Only one study was submitted in support of this efficacy supplement.

8. INTEGRATED OVERVIEW OF SAFETY

Only one study was submitted in support of this efficacy supplement.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.3 Pediatric Use and PREA Considerations

The pediatric assessment in this submission and the associated labeling changes were presented to the PREA Subcommittee [Pediatric Review Committee (PeRC)] on May 27, 2015. The PeRC agreed that the PMR for PREA deferral has been fulfilled by the current efficacy supplement, and found the pediatric population adequately addressed in the proposed language of the package insert.

10. CONCLUSIONS

- Bio Products have fulfilled the PMR for PREA deferral with submission of the clinical study report for GMX04, which included pediatric assessment in 25 pediatric subjects.
- Bio Products have already received a PREA waiver previously for submission of pediatric assessment in neonates and pediatric patients two years of age and younger.
- BioProducts have updated the package insert for Gammaplex to incorporate the pediatric findings and revised it with FDA recommendations.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

There are currently no concerns regarding the risk/benefit ratio. Thromboembolic events have been described after the administration of IGIVs. Measures to mitigate the risk of thromboembolic events following use of Gammaplex are highlighted in the label as boxed warning.

The clinical study showed that Gammaplex is reasonably safe and effective in the pediatric population, without clinically significant differences from the adult population. As for all age groups, dosing for pediatric subjects is also based on body weight and the labeling clearly instructs dosing to be titrated to patient's clinical response. No pediatric-specific dose requirements are necessary to achieve the desired serum IgG levels.

11.4 Recommendations on Regulatory Actions

Approval of this efficacy supplement is recommended from a clinical stand point.

11.5 Labeling Review and Recommendations

The final labeling was agreed upon and was submitted in the Amendment number 11.

11.6 Recommendations on Postmarketing Actions

This submission fulfills the PMR. No further postmarketing clinical studies are needed at this time.