Clinical Review Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: August 27, 2009

To: To File (BLA STN 125329/0)

From: Hon-Sum Ko, Medical Officer, HFM-392

Through: Nisha Jain, Acting Branch Chief, HFM-392

CC: Debra Cordaro, RPM, HFM-370

Applicant: Bio Products Laboratory

Product: Immune Globulin Intravenous (Human), (IGIV)
Trade name: Gammaplex®

Subject: Final Review Memo

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I. Executive Summary

BPL submits BLA STN 125329 in support of its new Immune Globulin Intravenous (Human) (IGIV) 5% liquid product for the indication of primary humoral immunodeficiency (PID). There is a PK/safety study in healthy volunteers (GMX03) and a safety and efficacy study in patients with PID (GMX01) in this application.

GMX03 compared the pharmacokinetics (PK) of Gammaplex® with Vigam®, an IGIV product of BPL's which is not available in the United States. It enrolled 36 healthy volunteers dosed with either product at 400 mg/kg (12 subjects/group), with infusion rates up to 3 mL/min, and for Gammaplex, also up to 6 mL/min in a third group of 12 subjects. The PK findings of this study are detailed in Dr. I. Mahmood's review. No safety concerns were observed in the healthy volunteers studied.

In GMX01, the applicant studied Gammaplex as replacement therapy in patients with PID, following the recommendations in FDA's Guidance, *Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*. It was an open-label, uncontrolled study in 8 U.S. centers, with 50 subjects receiving Gammaplex 300 to 800 mg/kg at 3 or 4 week intervals for 12 months. A subset of 24 subjects was studied for pharmacokinetics of Gammaplex (see Dr. I. Mahmood's review).

The patients were between 9 to 78 years of age, with 46 of them having common variable immunodeficiency (92%) and the remainder X-linked agammaglobulinemia (%). There were 26 males (52%) and 24 females (48%). The majority of them were Caucasians (46, or 92%). The primary efficacy endpoint was the development of serious acute bacterial infections over a 12-month observation period (99% confidence interval upper bound of one serious acute bacterial infection per subject per year).

Results of GMX01 demonstrate the effectiveness of BPL IGIV as evidenced by the absence of acute serious bacterial infections developed during the one-year treatment period with either 21- or 28-day treatment cycle regimens. Safety is demonstrated by the rate of infusions associated with adverse events during and within 72 hours after infusion being similar to other IGIVs currently in-use (upper 95% limit <0.40). Two serious adverse reactions were reported in one subject during the study: thrombosis and chest pain. However, the safety profile is consistent with that in the labeling of currently licensed IGIV products.

Recommendation

Recommend approval with postmarketing requirement to conduct pediatric assessment in children and adolescent age groups for the treatment of primary humoral immunodeficiency.

II. Background

The primary humoral immunodeficiency diseases are characterized by hypogammaglobulinemia and/or defective antibody production and, as a consequence, increased susceptibility to infection. Replacement therapy with immunoglobulin G (IgG) purified from pools of plasma from multiple donors has been used since the early 1950s, first as intramuscular (IM), and more recently, as intravenous (IV) immunoglobulin (IGIV).

BPL IGIV (Gammaplex®) 5% is a new, purified, unmodified IGIV product manufactured by BioProducts Laboratory (BPL), United Kingdom, using plasma from healthy U.S. donors. It has 5 g human immunoglobulin and 5 g D-sorbitol (as stabilizer) 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. IgG purity reaches 100%, the pH is in the range of 4.8 to -(b)(4)-, and osmolality is ≥240 mOsmol/kg (typically 420 to 500 mOsmol/kg). It has an

IgA content of <10 μg/mL and a subclass distribution of: IgG_1 ~64%; IgG_2 ~30%; IgG_3 ~5%; IgG_4 ~1%, similar to the distribution in plasma. The product is to be protected from light and maintained at a temperature of 36°F to 77°F (2°C to 25°C). This product has never been marketed in the U.S. or other parts of the world.

BPL studied Gammaplex® under BB-IND -(b)(4)- for the indication of primary humoral immunodeficiency, and a pre-BLA meeting was held on 2/20/08. The applicant also holds BB-IND ----------(b)(4)----------. In the current BLA submission, only the primary humoral immunodeficiency indication is being sought.

The requested indication for BPL's IGIV is:

- The indication in the proposed package insert is "the treatment of patients with primary immunodeficiency associated with defects in humoral immunity, including, but not limited to, congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency and Wiscott-Aldrich syndrome."

The proposed proprietary name, "Gammaplex", is a registered trademark and has been found to be acceptable with concerns by APLB at the IND stage. The Division of Hematology agrees with acceptance of "Gammaplex" as proprietary name.

III. Clinical Section in Current BLA Submission

This BLA submission is in the ICH CTD format. The clinical section is in Module 5. Two human studies are submitted to support the application:

- Study GMX03. A comparison of the pharmacokinetics, safety and tolerance of two formulations of a liquid IVIg (Vigam® Liquid and Gammaplex®) using standard and accelerated infusion rates in healthy adult volunteers (three treatment arms)
- Protocol GMX01. A Phase III, Multicenter, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Gammaplex® in Primary Immunodeficiency Diseases

Comment GMX03 is a PK/safety study in healthy volunteers, and is reviewed by Dr. I. Mahmood for the PK data. As the study is not in the target population for which the product is to be indicated, the safety data will be briefly covered in this review. GMX01 is the principal study in this application to support an indication in primary humoral immunodeficiency and will be discussed in detail.

IV. Review of Clinical Studies Reported in BLA 125329/0

Study GMX03. A comparison of the pharmacokinetics, safety and tolerance of two formulations of a liquid IVIg (Vigam® Liquid and Gammaplex®) using standard and accelerated infusion rates in healthy adult volunteers (three treatment arms) [Initiated 8/25/04, completed 12/23/04]

Objectives

Primary: To compare the AUC_{0-84}, of a single intravenous infusion of Vigam® Liquid (infused at the licensed rate of up to 3 mL/min) with BPL IGIV (Gammaplex®) (infused at up to 3 mL/min and up to 6 mL/min).

Secondary: a) To compare the AUC_{0-21}, Cmax, tmax, MRT, t½, CL and Vz of a single intravenous infusion of Vigam® Liquid (infused at the licensed rate of up to 3 mL/min) with BPL IGIV (infused at up to 3 mL/min and up to 6 mL/min).

b) To evaluate the safety and tolerability of BPL IGIV (infused at up to 3 mL/min and up to 6 mL/min) compared to Vigam® Liquid (infused at up to 3 mL/min).

Design
Single centre, parallel, double-blind (Groups 1 and 2 only, Group 3 is open), single dose study consisting of a screening phase, a single dosing day and an 84-day follow-up period.

Subjects were randomized into one of 3 treatment groups of 12 subjects each (36 total).
- Group 1 received a single dose of Vigam® Liquid 400 mg/kg intravenously at an initial rate of 0.01 to 0.02 mL/kg/min, increasing to a maximum of 3 mL/min
- Group 2 received a single dose of BPL IGIV 400 mg/kg intravenously at an initial rate of 0.01 to 0.02 mL/kg/min increasing to a maximum of 3 mL/min
- Group 3 received a single dose of BPL IGIV 400 mg/kg intravenously at an initial rate of 0.01 to 0.02 mL/kg/min increasing to a maximum of 6 mL/min.

The batch number of the Vigam® Liquid was VLCN 6594 and the batch number for BPL IGIV was VLCX 6592.

Diagnosis and main criteria for inclusion
Healthy, normotensive, non-smoking male and female volunteers aged 18 to 60 who gave written informed consent and fulfilled all of the inclusion criteria and none of the exclusion criteria. Female volunteers of childbearing potential had a negative pregnancy test before entering the study and had to use either a double barrier method of contraception or use the oral contraceptive pill. Postmenopausal or surgically sterile female volunteers could be enrolled.

Duration of treatment. Subjects received a single i.v. dose of either Vigam® Liquid or BPL IGIV. In Groups 1 and 2, the infusion lasted between 184 minutes and 294 minutes. In Group 3, the infusion lasted between 96 minutes and 203 minutes.

Criteria for evaluation
- **Pharmacokinetics**

Area under concentration-time curve over Day 1 to Day 85 (AUC0-84), area under concentration-time curve over Day 1 to Day 22 (AUC0-21), area under concentration-time curve extrapolated to infinity (AUC0-∞), peak concentration (Cmax), time of peak concentration (tmax), mean residence time (MRT), elimination half-life (t½), clearance adjusted for body weight (CL) and volume of distribution adjusted for body weight (Vz). The above PK parameters were calculated for serum immunoglobulin G (IgG) for all subjects. Pharmacokinetic (PK) calculations were based on increments over pre-dose (baseline) concentration.

- **Safety**

Laboratory parameters (routine hematology, biochemistry, urinalysis and immunology) were collected, together with physical examination, 12 lead electrocardiogram (ECG), vital signs and adverse events (AEs). A venous blood sample was also tested for various viral markers (anti-HIV 1 and 2, anti-HCV and HBsAg) at screening, immediately before dosing and at the final visit.

Statistical methods
- **Pharmacokinetic parameters**

PK assessments were based on serum IgG increments over pre-dose baseline. Data were summarised by treatment group and include arithmetic and geometric means with corresponding 95% confidence intervals, median, minimum, maximum, standard deviation and standard error of the mean
.
For AUC0-21, AUC0-84, AUC0-∞ and Cmax, the values in the BPL IGIV treatment groups were compared to the Vigam® Liquid group as a reference using a one-way analysis of variance (ANOVA). All data were analyzed using the natural logarithm. Treatment ratios were calculated by taking the anti-logarithm of the difference between treatment least squared means. Using the pooled estimate of variance, 90% confidence intervals for each treatment ratio were obtained by taking the anti-logarithm of the 90% confidence interval endpoints for each mean difference. Bioequivalence was assumed if the 90% confidence interval for the parameter lay within the acceptable interval of 0.80-1.25.

- **Safety parameters**

All safety data were to be listed. AE data were listed and summarized. Summary statistics [mean, median, standard deviation (SD), minimum, maximum] were presented for changes from baseline in biochemistry and hematology laboratory parameters, vital signs and ECG.

Investigator
Dr David Wessels, PAREXEL, CPRU at Northwick Park Hospital, Watford Road, Harrow, HA1 3UJ, U.K.

Results

- **Pharmacokinetics**

All 36 subjects had measurable increments of IgG over baseline up to at least Day 22. Although demonstrating wide inter-subject variability, serum concentrations of IgG were similar in terms of mean data in all three treatment groups over time except at 15 minutes post-dose when mean incremental serum levels of IgG were marginally lower in the Vigam® Liquid treated group (8.0 g/L, 9.4 g/L and 9.8 g/L in Groups 1, 2 and 3, respectively). This was not considered clinically significant. From Day 3 onwards, mean incremental serum concentrations were almost identical in all three treatment groups. By Day 71, serum levels of IgG were less than 1 g/L over baseline in all three treatment groups.

The table below shows the results of ANOVA based on C_{max}, AUC_{0-21}, AUC_{0-84}, and $AUC_{0-\infty}$:

PK variable	Group 2 versus Group 1		Group 3 versus Group 1		Group 3 versus Group 2	
	PE	CI	PE	CI	PE	CI
C_{max}	114.2	103.1-126.6	119.0	107.4-131.9	104.2	94.0-115.5
AUC_{0-21}	110.6	94.2-129.9	102.8	87.5-120.7	92.9	79.1-109.2
AUC_{0-84}	106.1	80.4-139.9	96.3	73.0-127.1	90.8	68.9-119.8
$AUC_{0-\infty}$	98.7	72.2-134.8	92.7	67.9-126.7	94.0	69.2-127.6

Group 1: Vigam® Liquid (3 mL/min); Group 2: BPL IGIV (3 mL/min); Group 3: BPL IGIV (6 mL/min)
PE = point estimate for mean difference CI = confidence interval

With the exception of Cmax, where the lower confidence interval fell just above 100%, all PK variables used to compare Vigam® Liquid and BPL IGIV (with Vigam® Liquid as the reference) infused up to 3 mL/min (Group 2 versus Group 1), showed confidence intervals which straddled 100% with point estimates within approximately 10% of 100, suggesting comparable bioavailability between products. The intervals did however fall marginally outside the 80-125% window required to absolutely confirm bioequivalence. The wide confidence interval observed can be attributed to wide inter-subject variability in serum IgG. The difference in Cmax is not considered clinically relevant.

The results for the comparison of Vigam® Liquid and BPL IGIV infused up to 6 mL/min (Group 3 versus Group 1) also confirmed similar bioavailability. For this comparison, AUC_{0-21} data demonstrated bioequivalence with a confidence interval within the accepted range.

Increasing the maximum infusion rate for BPL IGIV (Group 3 versus Group 2) had no effect on drug bioavailability. The Cmax comparison confirmed bioequivalence while the AUC_{0-21} comparison approached bioequivalence (lower confidence interval 79.1%). Other derived confidence limits for this comparison did not absolutely confirm bioequivalence but did straddle the 100% value, suggesting that bioavailabilty was unaffected by the change in infusion rate.

CL was similar across all three treatment groups. Mean drug half-life (t½) and MRT were longer in Group 1 and Vz was marginally higher. These differences were not considered significant.

Comment The PK data are reviewed by Dr. I Mahmood. See his review for comments.

- **Safety**

A total of 28 subjects (77.8%) reported 100 AEs. Ninety of the AEs were mild and 10 were moderate in severity. There were no severe AEs. Forty-one AEs were reported in 9 subjects (75.0%) in Group 1, 30 AEs in 10 subjects (83.3%) in Group 2, and 29 AEs in 9 subjects (75.0%) in Group 3. There were no deaths or SAEs reported during the study and no AEs led to withdrawal.

The most commonly reported AEs were headache [29 AEs in 16 subjects (44.4%)] and nasopharyngitis [13 AEs in 11 subjects (30.6%)]. The most commonly reported drug-related AE, as assessed by the investigator, was headache [reported by 11 subjects (30.6%)]. There was a trend toward increased frequency of headaches in Group 3, but the clinically significance is unclear. There were no clinically significant differences in either the number or severity of other AEs between treatment groups.

There were no clinically significant changes in vital signs, ECG intervals, safety laboratory values or viral screen results during the study.

Safety Conclusions

- Both Vigam® Liquid and BPL IGIV had a good safety profile in healthy volunteers, and were well tolerated at a dose of 400 mg/kg and infusion rates of up to 3 mL/min (Vigam® Liquid) and 6 mL/min (BPL IGIV);
- There was no clinically significant increase in the number or severity of AEs following the higher rate of infusion of BPL IGIV up to 6 mL/min in healthy volunteers.
- As this study was conducted in healthy volunteers, the safety data may not necessarily be extrapolable to the target population of this product. The safety profile needs to be studied in the disease condition for which the product is indicated (See review of Study GMX01 for use of BPL IGIV in primary humoral immunodeficiency).

Study GMX01. A Phase III, Multicenter, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Gammaplex® in Primary Immunodeficiency Diseases (Initiated 2/3/06, completed 11/6/07)

STUDY OBJECTIVES

Primary: to determine if BPL IGIV was efficacious with respect to the FDA's minimal requirement of no more than 1 serious, acute, bacterial infection per subject per year in subjects with PID.
Secondary:

- To assess the safety and tolerability of BPL IGIV
- To determine if BPL IGIV has a PK profile comparable with that of intact IgG in subjects with PID

STUDY DESIGN

Phase 3, multicenter, non-randomized, open-label study to be conducted at ~10 sites in the US, with ~50 subjects to be enrolled to give ≥40 evaluable subjects, and ≥20 subjects to give blood for pharmacokinetics (PK) of BPL IGIV: ≥7 of them on 21-day infusion cycles and ≥13 on 28-day cycles.

In designing the protocol for the current study, the following guidelines were followed:

- US Food and Drug Administration: *Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*
- Committee for Proprietary Medicinal Products: *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IGIV)*

Two batches of BPL IGIV, VSCN6845 (expiration date of 09 December 2006) and VSCN7045 (expiration date of 20 September 2007), were used in this study.

BPL IGIV Administration

Tests Before the First Infusion

- Levels of IgG and IgG Subclasses from the Previous IGIV Preparation. If data on trough IgG levels of the previous IGIV product used for 2 consecutive infusions immediately before entry were not available, samples for IgG levels were obtained at regularly scheduled IGIV infusions before the first infusion of BPL IGIV. IgG levels were obtained for all subjects at the screening visit and immediately before the first infusion of BPL IGIV [Visit 2 (I-1)]. This also applied to IgG subclasses. Trough IgG levels were documented to demonstrate that the subject was in a steady state, and the target trough level of IgG was >600 mg/dL. The dose, treatment interval, and trade name of the previous product were also recorded.
- IgA and IgM Levels. If levels of IgA and IgM in serum measured within the previous 12 months were not available, blood samples for IgA and IgM levels were obtained at the screening visit. Samples were taken before administration of BPL IGIV.

BPL IGIV Infusions

Infusions of BPL IGIV were performed every 21 or 28 (±4) days by means of an infusion pump, at a rate up to 0.08 mL/kg/min. If an AE of moderate or severe intensity occurred, the rate of the infusion at which this AE occurred was to be recorded, and the infusion rate was to be reduced to one-half the rate of that at which the event was observed; or if necessary, to a keep-open rate until symptoms subsided for resumption at a rate tolerated by the subject. This was an open-label study without blinding or randomization, and all subjects received BPL IGIV.

Concomitant Premedications

Subjects are not to be routinely given premedications before infusions. If a subject previously requiring premedication for IGIV was enrolled, he or she had to start this study without routine premedications. If an AE that might be prevented by the use of a premedication occurred 2 or 3 times consecutively, and depending on severity of the AE, premedications (such as antipyretics, antihistamines and or antiemetics, but not corticosteroids) could be given at the discretion of the Investigator before the remaining infusions.

Study Visits and Evaluations

See following tables for procedures at study visits.

Schedule of Assessments for Subjects on 21-Day Infusion Schedule

Evaluation (volume of blood)	Visit Number/Definition										
	1/S[a]	2/I-1	3/L[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	Laboratory	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 med hx	X										
Interval med hx		X		X	X	X	X	X	X	X	X
Phys exam	X	X		X	X	X	X	X	X	X	X
Chest X-ray	(X)[c]										
PK (9 mL)											X (Table 3)
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X
Lab A[e](6 mL)	X	X	X	X	X	X	X	X	X	X	X
Lab B[f](16 mL)	X	X	X	X					X		
Trough IgG (4 mL)	X	X		X	X	X	X	X	X	X	X
IgG Subclasses[g]	X	X		X	X	X	X	X	X	X	X
IgA, IgM (2 mL)	X										
Specific antibody levels (13 mL)[h]		X				X				X	
Direct Coombs' Test (2 mL)[i]	X	X	X	X							
Urinalysis	X	X	X		X		X		X		X
Concom meds	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[j]		X	X	X	X	X	X	X	X	X	X
C-reactive Protein (2 mL)	X	X				X				X	
Reserve Sample (5 mL)	X	X	X	X	X	X	X	X	X	X	X
Retention Sample (2 mL)		X									
Diary Cards		X		X	X	X	X	X	X	X	X
Total Blood Volume Required	**37mL**	**50 mL**	**29 mL**	**33 mL**	**15 mL**	**30 mL**	**15 mL**	**15 mL**	**31 mL**	**30 mL**	**15 mL + PK**

a) Screening visit may coincide with subject's scheduled infusion of a licensed IGIV product or may be scheduled separately. If scheduled with an infusion, required blood samples were drawn before the infusion was started. After the screening visit, the subject could not receive any blood or blood products (other than a licensed IGIV product or an investigational Phase III or IIIb product they are already receiving) until receiving BPL IGIV at Infusion 1. Two trough IgG levels and 2 trough levels of IgG subclasses, determined from blood samples drawn just before routine IGIV infusions, were obtained for each subject before the first study infusion was given.

b) The laboratory samples at this visit may be obtained by a nurse making a home visit. The samples must be taken 6 to 7 days ± 1 day after Infusion 1.

c) A chest x-ray was done unless a suitable chest x-ray taken within the last 12 months was available to be used as a baseline.

d) Vital signs were recorded 10 min before and at the start of each infusion, 10 minutes after the start of the infusion, 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.

e) Laboratory A consisted of ALT, AST, bilirubin, creatinine, BUN, LDH, and CBC with differential.

f) Laboratory B consisted of HCV and HIV NAT and serological tests for HBsAg, HCV, and HIV 1 & 2. At Visit 2 (immediately before the 1st infusion), the sample was also tested for Parvovirus B19 NAT. At Visit 3L, a 5-mL sample was drawn for Parvovirus B19 NAT testing only.

g) IgG subclasses were measured before infusion (blood volume required is captured in other draws at that time).

h) These samples could be omitted in subjects weighing < 37 kg.

i) All subjects had samples taken for a Direct Coombs' test and tests of hemolysis (haptoglobin and urine hemosiderin) at Visit 2 and at Visit 3. Subjects with a positive result had a Direct Coombs' test on blood drawn before every BPL IGIV infusion and at all follow up visits.

j) 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.

Schedule of Assessments for Subjects on a 21-Day Infusion Schedule (continued)

Evaluation (volume of blood)	Visit Number/Definition									
	12/I-10	13/I-11	14/I-12	15/I-13	16/I-14	17/I-15	18/I-16	19/I-17	F1[k]	F2[l]
	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 med hx										
Interval med hx	X	X	X	X	X	X	X	X	X	X
Phys exam	X	X	X	X	X	X	X	X	X	
Chest X-ray										
PK (9 mL)										
Vital Signs[m]	X	X	X	X	X	X	X	X		
Lab A (6 mL) [n]	X	X	X	X	X	X	X	X	X	
Lab B[o](16 mL)								X	X	X
Trough IgG (4 mL)	X	X	X	X	X	X	X	X	X	
IgG Subclasses[p]	X	X	X	X	X	X	X	X	X	
IgA, IgM (2 mL)									X	
Specific antibody levels (13 mL) [q]			X				X			
Direct Coombs' Test (2 mL) [r]									X	
Urinalysis		X		X		X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Adverse Events[s]	X	X	X	X	X	X	X	X	X	X
C-reactive Protein (2 mL)			X				X			
Reserve Sample (5 mL)	X	X	X	X	X	X	X	X	X	X
Retention Sample (2 mL)									X	
Diary Cards	X	X	X	X	X	X	X	X		
Total Blood Volume Required	**15 mL**	**15 mL**	**30 mL**	**15 mL**	**15 mL**	**15 mL**	**30 mL**	**31 mL**	**37 mL**	**23 mL**

k) This visit occurred 10 to 14 days after the last study infusion.

l) This visit occurred 3 months after the last study infusion. This was done when the subject came for regular infusion of a licensed IGIV product.

m) Vital signs were recorded 10 min before and at the start of each infusion, 10 minutes after the start of the infusion, 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 is stopped, at the time that the infusion was stopped, and 15 and 30 minutes after stopping the infusion.

n) Laboratory A consisted of ALT, AST, bilirubin, creatinine, BUN, LDH, and CBC with differential.

o) Laboratory B consisted of HCV and HIV NAT and serological tests for HBsAg, HCV, and HIV 1 & 2. At Visit 2 (immediately before the 1st infusion), the sample was also tested for Parvovirus B19 NAT. At Visit 3L, a 5-mL sample was drawn for Parvovirus B19 NAT testing only.

p) IgG subclasses were measured before infusion (blood volume required is captured in other draws at that time.).

q) These samples may be omitted in subjects weighing < 37 kg.

r) If the result of the Direct Coombs' test was positive, subjects had a Direct Coombs' test on blood drawn before every subsequent infusion and at all follow-up visits.

s) 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.

Schedule of Assessments for Subjects on a 28-Day Infusion Schedule

Evaluation (volume of blood)	Visit Number/Definition								
	1/S[a]	2/I-1	3/L[b]	4/I-2	5/I-3	6/I-4	7/I-5	8/I-6	9/I-7
	Screen	Infusion 1	Laboratory	Infusion 2	Infusion 3	Infusion 4	Infusion 5	Infusion 6	Infusion 7
Eligibility	X	X							
Consent	X								
HCG urine test	X								
Complete med hx	X								
Interval med hx		X		X	X	X	X	X	X
Phys exam	X	X		X	X	X	X	X	X

Chest X-ray	**(X)**[c]								
PK (9 mL)									**X** (Table 3)
Vital Signs[d]	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Laboratory A (6 mL)[e]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Laboratory B (16 mL)[f]	**X**	**X**	**X**	**X**				**X**	
Trough IgG (4 mL)	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**
IgG Subclasses[g]	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**
IgA, IgM (2 mL)	**X**								
Specific antibody levels (13 mL)[h]		**X**				**X**			
Direct Coombs' Test (2 mL)[i]	**X**	**X**	**X**	**X**					
Urinalysis	**X**	**X**	**X**		**X**		**X**		**X**
Concom meda	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events[j]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
C-reactive Protein (2 mL)	**X**	**X**				**X**			
Reserve Sample (5 mL)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Retention Sample (2 mL)		**X**							
Diary Cards		**X**		**X**	**X**	**X**	**X**	**X**	**X**
Total Blood Volume Required	**37 mL**	**50 mL**	**29 mL**	**33 mL**	**15 mL**	**30mL**	**15 mL**	**31 mL**	**15 mL + PK**

a) Screening visit may coincide with subject's scheduled infusion of a licensed IGIV product or may be scheduled separately. If scheduled with an infusion, required blood samples were drawn before the infusion was started. After the screening visit, the subject could not receive any blood or blood products (other than a licensed IGIV product or an investigational Phase III or IIIb product they are already receiving) until receiving BPL IGIV at Infusion 1. Two trough IgG levels and 2 trough levels of IgG subclasses, determined from blood samples drawn just before routine IGIV infusions, were obtained for each subject before the first study infusion was given.

b) The laboratory samples at this visit may be obtained by a nurse making a home visit. The samples must be taken 6 to 7 days ± 1 day after Infusion 1.

c) A chest x-ray was done unless a suitable chest x-ray taken within the last 12 months was available to be used as a baseline.

d) Vital signs were recorded 10 min before and at the start of each infusion, 10 minutes after the start of the infusion, 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.

e) Laboratory A consisted of ALT, AST, bilirubin, creatinine, BUN, LDH, and CBC with differential.

f) Laboratory B consisted of HCV and HIV NAT and serological tests for HBsAg, HCV, and HIV 1 & 2. At Visit 2 (immediately before the 1st infusion), the sample was also tested for Parvovirus B19 NAT. At Visit 3L, a 5-mL sample was drawn for Parvovirus B19 NAT testing only.

g) IgG subclasses were measured before infusion (blood volume required is captured in other draws at that time).

h) These samples could be omitted in subjects weighing < 37 kg.

i) All subjects had samples taken for a Direct Coombs' test and tests of hemolysis (haptoglobin and urine hemosiderin) at Visit 2 and at Visit 3. Subjects with a positive result had a Direct Coombs' test on blood drawn before every BPL IGIV infusion and at all follow up visits.

j) 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.

Schedule of Assessments for Subjects on a 28-Day Infusion Schedule (continued)

Evaluation (volume of blood)	**Visit Number/Definition**							
	10/I-8	**11/I-9**	**12/I-10**	**13/I-11**	**14/I-12**	**15/I-13**	**F1**	**F2**
	Infusion 8	Infusion 9	Infusion 10	Infusion 11	Infusion 12	Infusion 13	Follow-up[k]	Follow-up[l]
Eligibility								
Consent								
HCG urine test								
Complete med hx								
Interval med hx	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Phys exam	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Chest X-ray								
PK (9 mL)								
Vital Signs[m]	**X**	**X**	**X**	**X**	**X**	**X**		
Laboratory A (6 mL)[n]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Laboratory B (16 mL)[o]						**X**	**X**	**X**

Trough IgG (4 mL)	X	X	X	X	X	X	X	
IgG Subclasses[p]	X	X	X	X	X	X	X	
IgA, IgM (2 mL)							X	
Specific antibody levels (13 mL) [q]	X				X			
Direct Coombs' Test (2 mL) [r]							X	
Urinalysis		X		X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Adverse Events[s]	X	X	X	X	X	X	X	X
C-reactive Protein (2 mL)	X				X			
Reserve Sample (5 mL)	X	X	X	X	X	X	X	X
Retention Sample (2 mL)							X	
Diary Cards	X	X	X	X	X	X		
Total Blood Volume Required	**30 mL**	**15 mL**	**15 mL**	**15 mL**	**30 mL**	**31 mL**	**37 mL**	**23 mL**

k) This visit occurred 10 to 14 days after the last study infusion.
l) This visit occurred 3 months after the last study infusion. This was done when the subject came for regular infusion of a licensed IGIV product.
m) Vital signs were recorded 10 min before and at the start of each infusion, 10 minutes after the start of the infusion, 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 is stopped, at the time that the infusion was stopped, and 15 and 30 minutes after stopping the infusion.
n) Laboratory A consisted of ALT, AST, bilirubin, creatinine, BUN, LDH, and CBC with differential.
o) Laboratory B consisted of HCV and HIV NAT and serological tests for HBsAg, HCV, and HIV 1 & 2. At Visit 2 (immediately before the 1st infusion), the sample was also tested for Parvovirus B19 NAT. At Visit 3L, a 5-mL sample was drawn for Parvovirus B19 NAT testing only.
p) IgG subclasses were measured before infusion (blood volume required is captured in other draws at that time.).
q) These samples may be omitted in subjects weighing < 37 kg.
r) If the result of the Direct Coombs' test was positive, subjects had a Direct Coombs' test on blood drawn before every subsequent infusion and at all follow-up visits.
s) 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.

Schedule of Assessments for Subjects in the Pharmacokinetic Investigation

Evaluation (volume of blood)	**Time before start of infusion**	**Time after end of infusion[a]**								
	-5 min	**0 min**	**60 min**	**24 hours**	**48 hours**	**4 days**	**7 days**	**14 days**	**21 days**	**28 days**
IgG (4 mL)	X	X	X	X	X	X	X	X	X	X
Specific antibody levels (10 mL)[b]	X	X	X	X	X	X	X	X	X	X
Reserve sample (5 mL)	X	X	X	X	X	X	X	X	X	X
Total Blood Volume Required (mL)	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**	**19**

a) Samples were taken after Infusion 7 for subjects on a 28-day schedule, and after Infusion 9 for subjects on a 21-day schedule.
b) Specific antibodies for *Streptococcus pneumoniae*, *Haemophilus influenzae* B, and C*ytomegalovirus.*

Study Population

Inclusion Criteria

1. The subject was 3 years of age or older, of either sex, belonging to any ethnic group, and above a minimum weight of 27.5 kg. This weight was based on the amount of blood required for testing. If a subject was participating in the PK segment, the minimum weight required was ≥ 37 kg.
2. The subject had a primary immunodeficiency disease, which had a significant component of hypogammaglobulinemia and/or antibody deficiency (e.g., common variable immunodeficiency, X-linked and autosomal forms of agammaglobulinemia, hyper-IgM syndrome, Wiskott-Aldrich syndrome). Isolated deficiency of a single IgG subclass, or of specific antibodies without hypogammaglobulinemia per se, did not qualify for inclusion.
3. The subject had been receiving licensed or investigational (Phase III or IIIb) IGIV replacement therapy at a dose that had not changed by ± 50% of the mean dose for at least 3 months before study entry and was between 300 and 800 mg/kg/infusion. The infusion interval must have been between 21 and 28 days inclusive. The subject was required to have maintained a trough level at

least 300 mg/dL above baseline serum IgG levels (defined as before initiation of any gamma globulin treatment for that subject). The trough level had to be ≥ 600 mg/dL.

4. Trough levels of IgG and trough IgG subclasses, dose of IGIV, treatment intervals, and the trade name of the IGIV treatments used for the last 2 consecutive routine (licensed or investigational product) was documented for each subject before the first infusion in this study was administered.
5. If a subject was a female of child-bearing potential, she was to have a negative result on a human chorionic gonadotropin (HCG)-based pregnancy test.
6. If a subject was a female who was or became sexually active, she was required to practice contraception by using a method of proven reliability for the duration of the study.
7. The subject was willing to comply with all aspects of the protocol, including blood sampling, for the duration of the study.
8. The subject had signed an informed consent form (if at least 18 years old) or the subject's parent or legal guardian had signed the informed consent form. If appropriate, the subject had signed a child assent form.

Exclusion Criteria

1. The subject had a history of any severe anaphylactic reaction to blood or any blood-derived product.
2. The subject was known to be intolerant to any component of BPL IGIV, such as sorbitol (i.e., intolerance to fructose).
3. The subject had selective IgA deficiency, history of reaction to products containing IgA, or has a history of antibodies to IgA.
4. Subjects who had completed the study and subjects who had withdrawn could not participate in the study for a second time.
5. 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 III or IIIb study, within the prior 3 months.
6. The subject had been exposed to blood or any blood product or derivative within the last 6 months, other than a commercially available IGIV or other forms of commercially available and licensed ISG or an ISG product that was in Phase 3 or 3b studies.
7. The subject was pregnant or was nursing.
8. The subject was positive for any of the following at screening:
   - Serological test for HIV 1&2, HCV, or HBsAg
   - NAT for HCV
   - NAT for HIV
9. The subject, at screening, had levels greater than 2.5 times the upper limit of normal, as defined at the central laboratory, of ALT or AST.
10. The subject had a severe renal impairment (defined as serum creatinine greater than 2 times the upper limit of normal or BUN greater than 2.5 times the upper limit of normal 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 (DVT), 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, could have interfered with the conduct of the study.
14. The subject had an acquired medical condition, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (absolute neutrophil count < 1000 x 10^9/L).
15. The subject was receiving the following medication:
    - Immunosuppressive drugs
    - The subject was receiving long-term, daily steroids at a dose ≥ 0.15 mg /kg/day of prednisone, or equivalent doses of prednisolone or other corticosteroids. The requirement for burst or intermittent courses did not exclude the subject.
    - Immunomodulatory drugs
16. The subject had non-controlled arterial hypertension (systolic blood pressure (SBP) > 160 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg).
17. The subject had anemia (hemoglobin < 10 g/dL) at screening.

Removal of Subjects from Study

- The subject withdrew from the study on his/her own volition.
- The subject was uncooperative and non-compliant (defined as 2 consecutive or 3 overall missed study visits) with respect to provisions of the protocol.
- The subject missed 2 scheduled infusions.
- The subject developed hepatitis B, hepatitis C, or HIV as determined by NAT tests for hepatitis C or HIV, or the appropriate serological tests for HBsAg, HCV and HIV 1 & 2.
- The subject had a serious AE (SAE) while participating in the study and, at the discretion of the site investigator, was withdrawn.
- The subject became pregnant while participating in the study (the pregnancy was to be recorded as an SAE unrelated to BPL IGIV and followed through to the birth of the child).
- The subject required treatment with any of the medications listed under the exclusion criteria.

Investigators could withdraw subjects at any time if they felt it was not in the subject's best interest to continue. Subjects who withdrew from the study were not replaced.

Treatments

BPL IGIV 5 % (5 g in 100 mL) was administered at a dose of 300 to 800 mg/kg/infusion, IV through an infusion line with infusion pump. The infusion line was to include a 15-20 micron filter. Investigators could administer BPL IGIV from the bottle or by pooling the product into an infusion bag; if they pooled the product, it was administered within 2 hours after pooling. All product for a given infusion had to be from one lot. The total duration of treatment for each subject was 12 months. Infusions were initiated at a rate of 0.01 mL/kg/min for the first 15 minutes, to be advanced as shown below.

Starting, Incremental, and Maximum Infusion Rates of BPL IGIV

Elapsed Time (min)	Infusion	Rate	
		(mL/kg/min)	(mg/kg/hr)
0–15	Starting	0.01	30
16–30	Increment to	0.02	60
31–45		0.04	120
46-60		0.06	180
61–until end of infusion	Maximum	0.08	240

The frequency of the infusions was the same that was used to establish steady state with the previous IGIV therapy. The dosage schedule, every 21 or 28 days, was dependent upon the schedule that the subject was on before study entry. Subjects received BPL IGIV at 300 to 800 mg/kg per infusion.

Prior and Concomitant Therapy. Subjects could not routinely be given premedications before infusions. If a subject requiring premedication before infusion was to be enrolled, the study is started without premedications before infusions. If an AE(s) that may be prevented by the use of a premedication occurred 2 or 3 times consecutively, and depending on severity of the AEs, premedications (such as antipyretics, antihistamines, or antiemetics, but not corticosteroids) could then be used at the discretion of the investigator before the remaining infusions.

Evaluated Variables

Primary efficacy variable was the number of serious, acute, bacterial infections/subject/year; these infections were bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis. The definitions are taken from the FDA guidance document, *Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*.

Secondary efficacy variables were:

- Number and proportion of subjects with trough IgG levels that were ≤600 mg/dL from Week 15 onwards (estimated 5 half-lives)
- Number of days of work/school missed because of infection per subject year
- Number of 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, a positive result on a radiograph, and/or culture
- Number of infectious episodes per subject per year

- Number of days on therapeutic antibiotics

Safety variables were:

- Adverse Events
  - Number and percent of infusions associated with AEs that began during the infusion or within 48 hours and 72 hours after completion of the infusion were calculated.
  - Nature, severity, and frequency of AEs (tolerability)
  - SAEs
  - Suspected unexpected serious adverse reactions (SUSARs), if any
- Vital signs
- Physical examination
- Clinical laboratory tests, Direct Coombs' Test and Testing for Transmission of viruses
  The following clinical laboratory tests were done by a central laboratory:
  - Laboratory A. Alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), bilirubin, creatinine, blood urea nitrogen (BUN), and a complete blood count (CBC) with differential
  - Laboratory B. The presence of Parvovirus B19, HCV, and HIV was determined with PCR (NAT). The presence of HBsAg and antibodies to HIV 1 & 2, and HCV was tested serologically.
  - During Screening, a Direct Coombs' test was performed on all subjects. Samples were collected at Visits 2 and 3 from all subjects for a Direct Coombs' test and tests for hemolysis (haptoglobin and urine hemosiderin). Subjects with a positive result had a Direct Coombs' test performed on blood drawn before every subsequent IGIV infusion and at all follow-up visits.
  - A sample for C-reactive protein.
  - Blood was also obtained for 2 additional purposes: (a) Reserve Sample: A 5-mL sample (≥1 mL serum) was obtained before the infusion at each visit, to be stored at -70°C at the central laboratory in the event that repeat tests were required. These samples were discarded at the completion of the study. (b) Retention Sample: To comply with the European CPMP requirements, 4 mL of blood was collected from each subject immediately before the first infusion and at the F1 visit to be sent at the end of the study to ----(b)(4)--- in the UK for storage. Serum (1 mL) will be stored in 2-mL tubes at -70°C for 15 years. These samples will be used for serology and NAT testing if required in the future.
- Urinalysis with microscopic examination at the central laboratory.

Pharmacokinetics

Total IgG. A minimum of 20 subjects (≥7 subjects on a 21-day infusion schedule and ≥13 subjects on a 28-day infusion schedule, including children weighing ≥37 kg) were to participate in the PK segment of the study. The blood samples for PK analysis of total IgG were obtained after Infusion 7 for subjects on a 28-day schedule and after Infusion 9 for subjects on a 21-day schedule. Sampling times were:

- just before infusion
- immediately at the end of infusion
- 1 hour after the end of infusion
- 24 hours, 2 days, 4 days, 7 days, 14 days, 21 days, and 28 days after the start of the infusion

For subjects on a 21-day schedule, the infusion after the one used for the PK sampling was delayed until the 28-day sample was obtained. The next infusion was given within the next 14 days to get the subject back on his/her original schedule. The subject then continued on a 21-day schedule.

Specific Antibodies. Samples were collected at the same time as the samples for analysis of total IgG for PK profile of specific antibodies for *Cytomegalovirus* (CMV), *Streptococcus pneumoniae* (Subtypes 4, 6B, 9V, 14, 19), and *Haemophilus influenzae* B.

Trough Levels of Total IgG, IgG Subclasses and Specific Antibodies.
Two trough IgG levels and 2 trough levels of IgG subclasses were obtained for the 2 consecutive infusions of the previous IGIV preparation used immediately before entry and while the subject was on a stable treatment regimen. Samples were collected at each infusion visit and at Follow-Up 1 to determine survival of IgG subclasses during BPL IGIV treatment, before its administration. The samples were obtained for measurement of trough levels and the function of antibodies against the specific antigens: CMV, *Tetanus, Streptococcus pneumoniae* (Subtypes 4, 6B, 9V, 14, 19) and *Haemophilus influenzae* B. These samples were taken immediately before Infusions 1, 4, 8, and 12 for subjects on a 28-day schedule, and before Infusions 1, 4, 8, 12, and 16 for subjects on a 21-day schedule.

Statistical and Analytical Plans
Summary statistics consisted of frequencies and percents of responses in each category for categorical variables; and of means, medians, standard deviations, and minimum and maximum values for continuous variables. Where appropriate, 95% confidence intervals were calculated.

Determination of Sample Size.

- It was assumed that the number of events for the primary efficacy end-point (serious, acute, bacterial infections) followed a Poisson distribution, and the true underlying event rate was 0.5 per subject per year. A sample size of 40 evaluable subjects woould ensure 80% power to reject a null hypothesis of 1 or more events per subject per year. This calculation is based on a 1-sided test at α-level of 0.01. and 50 subjects were to be enrolled to meet the requirement for 40 evaluable subjects.
- For the PK study, a minimum of 20 subjects (13 on a 28-day schedule and 7 on a 21-day schedule) were to be used. This number was based on FDA guidance, *Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*.

All subjects who received at least 1 infusion of BPL IGIV were included in the intent-to-treat (ITT) population. The ITT population was used for all safety and efficacy analyses.

Comment The design of Study GMX01 is consistent with FDA's Guidance on the study of IGIV products in the replacement therapy of primary humoral immunodeficiency.

INVESTIGATORS
The following table shows the sites and number of subjects enrolled to each site.

Investigators and Sites of Study GMX01

Site	Investigator	Location	#of subjects
001	Mark Ballow	Women & Children's Hospital, 219 Bryant street, Buffalo, NY 14222	**5**
002	Mary Beth Fasano	U of Iowa Hospitals & Clinics, 200 Hawkins Drive, Iowa City, IA 52242	0
004	Robyn J Levy	5555 Peachtree Dunwoody Road, Suite 340, Atlanta, GA 30342	6
005	James N Moy	1725 W Harrison Street, Suite 117, Chicago IL 60612	12
006	AM Scharenberg	307 Westlake Ave North, Suite 300, Seattle, WA 98109	7
008	Mark R Stein	840 US Highway #1, Suites 230-250, North Palm Beach, FL 33408	7
009	Robert L Roberts	10833 Le Conte Ave, Los Angeles, CA 90095	6
010	Daniel Suez	1115 Kinwest Parkway, Suite 100, Irving, TX 75063	7
		Total	50

RESULTS
A. Disposition of Subjects
Subject disposition is shown in the following table.

Disposition of Subjects

Enrolled (n = 50)			
Received BPL IGIV (n = 50)			
21-Day Infusion Cycle (n=22)		**28 Day Infusion Cycle (n=28)**	
Completed Treatment and Both Follow-up Visits	(n=21)	Completed Treatment and Both Follow-up Visits	(n = 24)
Discontinued BPL IGIV During Treatment Phase	(n = 1)	Discontinued BPL IGIV During Treatment Phase	(n = 4)
Adverse Event	(n = 1)	Adverse Event	(n = 2)
Lost to follow-up	(n = 0)	Lost to follow-up	(n = 1)
Withdrew consent	(n = 9)	Withdrew consent	(n = 1)
Also Participated in Pharmacokinetic Substudy	(n = 9)	Also Participated in Pharmacokinetic Substudy	(n = 15)

B. Protocol Deviations
Sites 001 and 010 did not use a 15-20 micron in-line filter during all infusions. Once the error was noticed, the correct filter size was used in subsequent infusions. This was noted for some infusions in the following

subjects: ----------(b)(6)----------.

One subject (-(b)(6)-) received one infusion of BPL IGIV at a faster infusion rate than the maximum rate stipulated in the protocol (0.08 mL/kg/min). During the final infusion for this subject (infusion number 13), the rate was increased at 15 minute intervals as follows: 0.022 mL/kg/min, 0.044 mL/kg/min, 0.087 mL/kg/min, 0.131 mL/kg/min, and finally to 0.174 mL/kg/min. The subject continued on the rate of 0.174 mL/kg/min until the end of the infusion. There were no AEs temporally associated with this infusion. This deviation was documented in a memo to file.

Specifications for the collection of naive (prior IGIV) trough antibody levels changed during the course of the study (Section 9.8.1). Waivers were given for the following subjects in relation to naive trough values: ----------(b)(6)----------. In some cases, no naive trough levels were available, and this deviation was documented in a memo to file (Subjects ----------(b)(6)----------).

Subject ---(b)(6)--- had a trough IgG level of 597 mg/dL and did not meet inclusion criteria #3. A waiver was granted for this subject to be enrolled in the study.

Three waivers were granted regarding the 21-day or 28-day infusion schedule. Subject --(b)(6)--- changed from a 21-day schedule to a 28-day infusion schedule after infusion 5. Two subjects received waivers since they did not have a 21-day or 28-day infusion schedule before entering the study (Subject --(b)(6)---, 14-day schedule; Subject --(b)(6)---, 3.5 week schedule). Waivers were granted for both subjects.

The majority of the other deviations involved rescheduling of visits outside of visit windows and isolated problems with shipment of lab samples.

C. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics are shown in the following table.

Demographic and Baseline Characteristics (Intent-to-Treat Population)

Category Statistic/Response	21-day Infusion Schedule N=22	28-Day Infusion Schedule N=28	Total N=50
Age			
Mean	39.6	47.4	44.0
SD	18.41	19.26	19.10
Median	39.0	45.5	44.5
Range	10 - 70	9 - 78	9 - 78
Sex			
Male	11 (50.0%)	15 (53.6%)	26 (52.0%)
Female	11 (50.0%)	13 (46.4%)	24 (48.0%)
Ethnicity			
Caucasian	21 (95.5%)	25 (89.3%)	46 (92.0%)
African-American	0 (0.0%)	2 (7.1%)	2 (4.0%)
Hispanic	1 (4.5%)	1 (3.6%)	2 (4.0%)
Diagnosis			
Common Variable Immunodeficiency	21 (95.5%)	25 (89.3%)	46 (92.0%)
X-Linked Agammaglobulinemia	1 (4.5%)	3 (10.7%)	4 (8.0%)
Baseline Chest X-ray			
Normal	20 (90.9%)	24 (85.7%)	44 (88.0%)
Abnormal	2 (9.1%)	4 (14.3%)	6 (12.0%)

The following conditions were part of at least 20% of the subjects' medical histories: chronic sinusitis (22 subjects, 44.0%), pneumonia (21 subjects, 42.0%), asthma (19 subjects, 38.0%), drug hypersensitivity (16 subjects, 32.0%), rhinitis allergic (15 subjects, 30.0%), gastro-esophageal reflux disease (14 subjects, 28.0%), headache (13 subjects, 26.0%), sinusitis (11 subjects, 22.0%), tonsillectomy (11 subjects, 22.0%), and hypertension (10 subjects, 20.0%).

Prior IGIV Therapy. The most common products used for the prior therapy were Gamunex® (21 subjects, 42.0%), Gammagard® (17 subjects, 34.0%), Carimune® (16 subjects, 32.0%), Octagam® (8 subjects, 16.0%), and investigational product (5 subjects, 10.0%). Forty-two subjects (84.0%) did not have a documented adverse event related to the prior IGIV therapy. For the remaining 8 subjects, adverse events included chills, nausea, headache, vomiting, malaise, and other (joint ache/pain, shaking, lack of energy, body aches, fluid retention, and leg cramps) in the previous 6 months.

Comment The subjects in this study were somehow preselected and might not necessarily be representative of the target population, as the great majority (42/50, or 84%) did not have a documented adverse event related to prior IGIV therapy. This could also have been due to poor previous documentation, acclimatization on the previous IGIV product therapy, or self-selection by subjects more tolerant of IGIV adverse events. However, the low rate of previous events might actually highlight an adverse safety profile of BPL IGIV, should its administration be associated with greater frequency of adverse events, particularly if the event rates remain high after reaching steady state.

The table below shows the number and percent of subjects within the ITT population with infections during prior IGIV therapy in the past 6 months. Two subjects were taking medication for ongoing infections associated with prior IGIV therapy: subject --(b)(6)--- was taking levofloxacin for respiratory infection; --(b)(6)--- taking nasal and oral antibiotics for sinus infection.

Number and Percent of Subjects with Infections during Prior IGIV Therapy

Category	Response	Subjects n (%)
Any infection in past 6 months?	Yes	27 (54.0%)
	No	23 (46.0%)
Number of infections in past 6 months?	0	23 (46.0%)
	1	23 (46.0%)
	2	2 (4.0%)
	3	2 (4.0%)
	4 or more	0 (0.0%)
Any serious, acute, bacterial infections in past 6 months	Yes	6 (12.0%)
	No	44 (88.0%)
Number of serious, acute, bacterial infections in past 6 months	0	44 (88.0%)
	1	5 (10.0%)
	2	0 (0.0%)
	3	1 (2.0%)
	4 or more	0 (0.0%)
Any ongoing infections?	Yes	2 (4.0%)
	No	48 (96.0%)

Prior Medications. Although 27 subjects had an infection in the previous 6 months, 5 of them did not require antimicrobial medication: 22 subjects (44.0%) had at least 1 course of antimicrobial medication during this time. The following antimicrobials were previously taken by $\geq$5% of the subjects: amoxicillin clavulanate (6 subjects, 12.0%), azithromycin (6 subjects, 12.0%), and levofloxacin (4 subjects, 8.0%). The majority of subjects (48 subjects, 96.0%) had taken at least one non-antibiotic prior medication. The following medications were taken by >20% of the population: cotylenol (18 subjects, 36.0%), salbutamol (17 subjects, 34.0%), montelukast (12 subjects, 24.0%), and fluticasone/salmeterol (12 subjects, 24.0%).

C. Efficacy Data

Analysis of Primary Efficacy Variable

No serious, acute, bacterial infections (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, or visceral abscess) occurred in any subject with an onset date between the first infusion of BPL IGIV and the first follow-up visit, inclusive. Thus, the mean event rate of serious, acute, bacterial infections per year was zero.

One subject, --(b)(6)---, was completing treatment for bacterial pneumonia at the time of the first BPL IGIV infusion. Antibiotic treatment started 4 days before the first BPL IGIV infusion, and ended 10 days later. Since the start date of the infection was before the first BPL IGIV infusion date, this infection was excluded from the efficacy calculation.

Number of Serious, Acute, Bacterial Infections (Intent-to-Treat Population)

Category and Statistic	**Result** (N=50)
Serious, acute, bacterial infection rate: Mean event rate per subject per year	0
1-sided 99% Upper confidence bound	0.101

Analysis of Secondary Efficacy Variables

1. Trough IgG Levels Two subjects had total IgG levels below 600 mg/dL at some point after 15 weeks on BPL IGIV, with one subject in each infusion schedule. The total IgG level for Subject --(b)(6)--- was 589 mg/dL at Visit 12 of the 21-day infusion schedule. The total IgG level for Subject --(b)(6)--- was 525 mg/dL at Visit 6 of the 28-day infusion schedule. All other total IgG levels for these two subjects were >600 mg/dL. All other subjects consistently had a total IgG level above 600 mg/dL after Week 15.

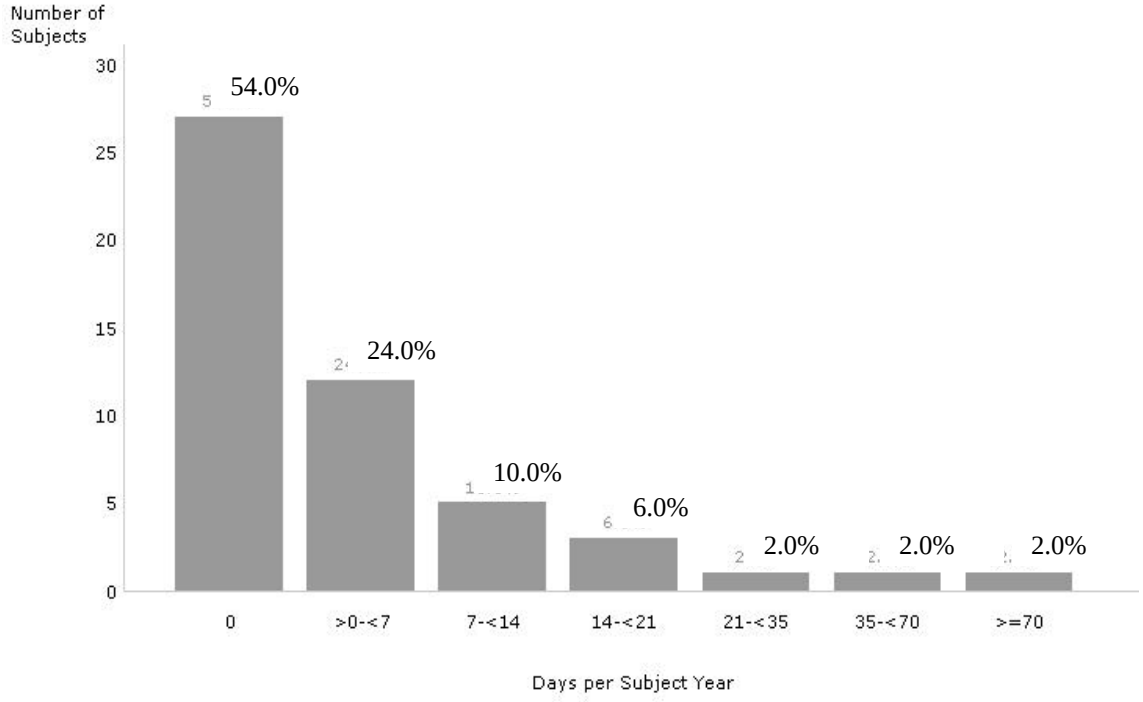
2. Number of Days of Work/School Missed The majority of the subjects who missed days of work/school (17 of 23, 74%) missed less than 14 days per year.

Number of Days off Work/School per Subject per Year Because of Infection or Other Medical Problem (Intent-to-Treat Population)

Category **Statistic**	**Result** **(N=50)**
Any days off work/school because of infection or other medical problem, n (%)	
Yes	23 (46.0%)
No	27 (54.0%)
Number of days off work/school because of infection or other medical problem[a]	
Mean	8.73
SD	34.41
Median	0
Range	0 - 241

a The number of days off work/school were counted for each week of diary data, divided by the number of days of diary data, and multiplied by 365, to give the value per subject per year.

Number of Days Off Work/School Per Year Because of an Infection or Other Medical Problem [Intent-to-Treat Population (N=50)]



3. Number of Visits for Acute Problems

Physician or Hospital Emergency Room Visits per Subject per Year

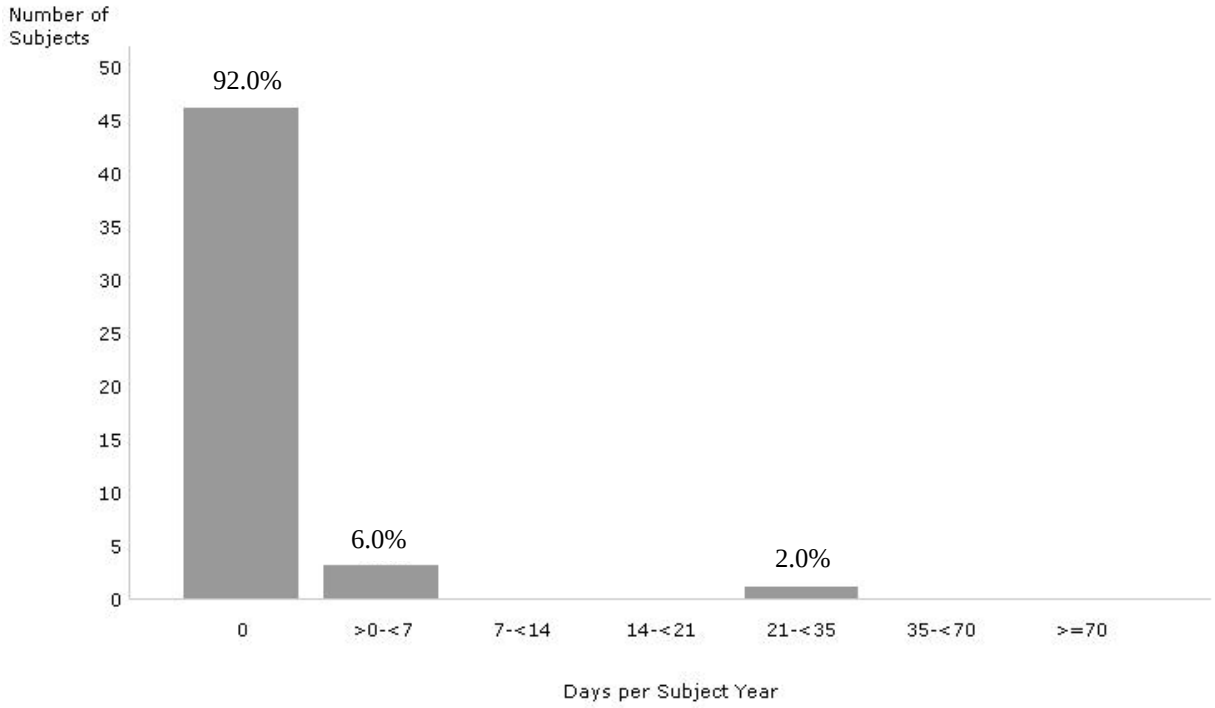
Category	Statistic	Physician Visit	Hospital ER Visit	Physician and/or Hospital ER Visit
Any visit to (physician; hospital ER; physician and/or hospital ER) because of a medical problem, n(%)	Yes No	39 (78.0%) 11 (22.0%)	12 (24.0%) 38 (76.0%)	41 (82.0%) 9 (18.0%)
Number of visits per year to (physician; hospital ER; physician and/or hospital ER) because of an infection or other medical problem	Mean Std Dev Median Min Max	5.55 8.242 2.14 0 42.1	0.40 0.847 0 0 4.12	5.95 8.478 3.13 0 43.1
Number of visits per year to (physician; hospital ER; physician and/or hospital ER) because of an infection or other medical problem, n (%)	0	11 (22.0%)	38 (76.0%)	9 (18.0%)
	>0-<1 >1-<2 >2-<3 >3-<7	28 (56.0%)	1 (2.0%) 6 (12.0%) 4 (8.0%) 1 (2.0%)	30 (60.0%)
	7-<14 14-<21 21-<35 35-<70 >=70	5 (10.0%) 2 (4.0%) 3 (6.0%) 1 (2.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	5 (10.0%) 2 (4.0%) 3 (6.0%) 1 (2.0%) 0 (0.0%)

Subject --(b)(6)--- had the maximum number of visits per year: multiple visits surrounding a planned lumbar surgery, recurrent events of wheezing, and an unrelated SAE (squamous cell carcinoma).

4. Number and Days of Hospitalization The vast majority of subjects (46 subjects, 92.0%) did not require hospitalization during study. The overall mean (SD) number of days of hospitalization was 0.75 (4.32) days per subject per year. Of the 4 subjects who were hospitalized, 3 of them were in the hospital for <7 days per year:

- Subjects --(b)(6)--- and --(b)(6)--- for planned lumbar surgery and uterine hemorrhage, respectively. The uterine hemorrhage was an exacerbation of uterine bleeding and was treated as out-patient visit.
- Subject --(b)(6)--- for viral gastroenteritis.
- Subject --(b)(6)--- for the equivalent of 30.2 days per year: first hospitalization for planned disk replacement surgery, next 2 admissions for thrombosis and chest pain.

Number of Days of Hospitalization Per Year Because of an Infection or Other Medical Problem



5. Number of Infectious Episodes per Subject per Year Forty subjects (80.0%) had ≥1 infection during study: 23 subjects (46.0%) had fewer than 3 episodes per subject per year. The median number of infectious episodes per subject per year was 3.07 (range of 0-14.9). The majority of infections (in 38 of 40 subjects) were also classified as AEs under the MedDRA SOC of Infections and Infestations.
Subject --(b)(6)--- had sinus infection started at the F1 follow-up visit, which fell outside the window for classification as AE. Subject --(b)(6)--- had 3 preferred terms relating to an infection (pyrexia, chills, and sinus congestion) that were classified under other SOCs in the AE analyses.

There were 4 infections considered severe in intensity:

- Subject --(b)(6)--- had bacterial pneumonia with onset date before the first BPL IGIV infusion.
- Subject --(b)(6)--- had a severe case of viral gastroenteritis reported as an SAE.
- Subject --(b)(6)--- and Subject --(b)(6)--- each had one case of severe bronchitis treated with antibiotics, and the infections resolved.

The most common types of infections were:

- upper respiratory tract infection (22 subjects, 44.0%)
- sinus infection (19 subjects, 38.0%)
- lower respiratory tract infection (10 subjects, 20.0%)
- gastrointestinal infection (9 subjects, 18.0%)
- urinary tract infection (6 subjects, 12.0%) and
- others (19 subjects, 38.0%).

6. Episodes of Temperature per Subject per Year Eighteen subjects (36.0%) had ≥1 episode of fever (>38°C). The mean number of days of fever was 1.09 ± 1.970 days per subject per year. The maximum number of days of fever was 8.90 days per subject per year. Thirty-seven subjects (74.0%) had ≥1 episode of temperature <36°C. The mean number of days with a temperature below 36°C was 24.3 ± 44.68 days per subject per year. The median number of days with a temperature below 36°C was 6.37 days with a range of 0 - 210 days.

7. Antibiotics Use

Systemic Antibiotics Overall, 42 subjects (84.0%) had at least 1 course of systemic antibiotic medication for any reason (i.e., therapeutic or prophylactic use).

- For therapeutic use, the majority of subjects (38 subjects, 76.0%) had at least 1 course of systemic antibiotic medication. The prevalence of subjects on therapeutic systemic antibiotic medications during each month on study ranged from 11.1-25.5%. All 108 courses of treatment involved

antibacterials for systemic use. The most common oral medications given therapeutically were fluoroquinolones (18 subjects, 36.0%), macrolides (14 subjects, 28.0%), combinations of penicillins (13 subjects, 26.0%), penicillins with extended spectrum (5 subjects, 10.0%), and tetracyclines (5 subjects, 10.0%). Two subjects (----------(b)(6)----------) were not treated with systemic antibiotics for an upper respiratory tract infection and nasopharyngitis, respectively.

Number and Percent of Subjects Taking Therapeutic Systemic Antibiotic Medications and Number of Courses Taken During Study (Intent-to Treat Population)

	Subjects n (%)	Number of Courses
No therapeutic systemic antibiotic medications during study	12 (24.0%)	0
Any therapeutic systemic antibiotic medications during study	38 (76.0%)	108
Antibacterials for systemic use	**38 (76.0%)**	**108**
Beta-lactam antibacterials, penicillins	17 (34.0%)	29
Combinations of antibacterials	1 (2.0%)	1
Macrolides, lincolides, and streptogramins	15 (30.0%)	27
Other antibacterials	3 (6.0%)	3
Other beta-lactam antibacterials	4 (8.0%)	5
Quinolone antibacterials	18 (36.0%)	26
Sulfonamides and trimethoprim	4 (8.0%)	6
Tetracyclines	5 (10.0%)	11

- For prophylaxis, 16 subjects (32.0%) took ≥1 course of systemic antibiotic medication during study. The proportion of subjects on prophylactic systemic antibiotic medications during each month on study ranged from 16.0 - 25.0%.

Other Antimicrobial Medication Ten subjects (20.0%) were given topical antibiotic medication. One subject (2.0%) was given an antiviral medication during the study and 9 subjects (18.0%) antifungal medication.

Subgroup Analysis for Efficacy
No formal comparison of subgroup analysis was planned. Randomization was not part of the study design.

Comment BPL should be asked to provide analyses of demographic subsets including age, sex and race for efficacy. With respect to age analysis, there should be data on pediatric age subpopulations to comply with PREA or submission of requests for waiver/deferral. Indeed, BPL has applied for waiver for the neonate and infancy age groups (no subjects studied), and deferral for the child and adolescent age groups (2 subjects between 3 and 11 and 4 subjects between 12 and 16 studied). BPL has submitted a clinical protocol synopsis for the deferral study on children and adolescents, to study 6 subjects in each of the two age groups (see Appendix I). This application has been discussed at the Pediatric Review Committee (PeRC) on 8/26/09. The committee concurs on the partial waiver for the neonatal and infant age groups, and suggested including PK evaluation in the deferral study for children and adolescents.

Pharmacokinetics
The pharmacokinetics section is reviewed by Dr. I. Mahmood and will not be discussed in this review.

Trough Levels of IgG
1. Trough Levels of Total IgG

- Trough levels of total IgG were fairly stable over the course of study. Median values of total IgG ranged from 909 - 1160 mg/dL. The following 3 visits had minimum values <600 mg/dL: 532 mg/dL (Visit 2, Subject --(b)(6)---), 525 mg/dL (Visit 6, Subject --(b)(6)---), and 589 mg/dL (Visit 12,
- Subject --(b)(6)---).
- There were 48 subjects consistently having a total IgG level >600 mg/dL after 15 weeks (~5 half-lives) on BPL IGIV. Exceptions are: Subject --(b)(6)--- (525 mg/dL, Visit 6) and Subject --(b)(6)--- (589 mg/dL, Visit 12).
- Median values for total IgG for subjects in the 21-day infusion schedule were between 936 and 1240 mg/dL. The actual range of total IgG trough values was 589 mg/dL (Subject --(b)(6)---, Visit 12) to 2010 mg/dL (Follow-up-1). Median values for total IgG for subjects in the 28-day infusion schedule

were between 833 and 1140 mg/dL. The actual range of total IgG trough values was 525 mg/dL (Subject --(b)(6)---, Visit 6); the maximum value was 1990 mg/dL (Visit 6 and Follow-up 1).

2. Trough Levels of IgG Subclasses A total of 29 subjects provided data on trough levels of IgG subclasses on prior IGIV (i.e., before Screening Visit).

- IgG1 Median trough levels of IgG1 in the 29 subjects on prior IGIV were 659 mg/dL. Median trough levels of IgG1 antibodies for all 50 subjects were 674 mg/dL at Visit 1 (screen) and 575 mg/dL at Visit 2 (infusion I-1) (both visits prior to starting BPL IGIV).
    - During the course of treatment with BPL IGIV, median trough levels of IgG1 antibodies remained close to 600 mg/dL, with a range from 566 mg/dL (at Visit 10) to 662 mg/dL (at Visit 17). Data from Visit F1 was not considered since this visit occurred 10 to 14 days after the last BPL IGIV infusion. Changes in levels of IgG1 antibody compared with prior IGIV treatment were calculated for the 29 subjects with data relating to prior IGIV treatment: median changes from prior IGIV in this sub-group of subjects ranged from -39.0 mg/dL (Visit 12) to +33.5 mg/dL (Visit 4).
- IgG2 Median trough levels of IgG2 in the 29 subjects on prior IGIV were 332 mg/dL. Median trough levels of IgG2 antibodies for all 50 subjects were 338 mg/dL at Visit 1 (screen) and 281 mg/dL at Visit 2 (infusion I-1) (both visits prior to starting BPL IGIV).
    - During the course of treatment with BPL IGIV, median trough levels of IgG2 antibodies generally remained in the region of 280 to 300 mg/dL, with a range from 278 mg/dL (at Visit 13) to 303 mg/dL (at Visit 17) (excluding data from Visit F1). Changes in levels of IgG2 antibody compared with prior IGIV treatment were calculated for the 29 subjects with data relating to prior IGIV treatment: median changes from prior IGIV in this sub-group of subjects ranged from -37.3 mg/dL (Visit 12) to -5.25 mg/dL (Visit 7).
- IgG3 Median trough levels of IgG2 in the 29 subjects on prior IGIV were 25.1 mg/dL. Median trough levels of IgG3 antibodies for all 50 subjects were 25.4 mg/dL at Visit 1 (screen) and 21.6 mg/dL at Visit 2 (infusion I-1) (both visits prior to starting BPL IGIV).
    - During the course of treatment with BPL IGIV, median trough levels of IgG3 antibodies generally remained in the region of 21 to 25 mg/dL, with a range from 22.1 mg/dL (at Visit 12) to 24.9 mg/dL (at Visit 13) (excluding data from Visit F1). Changes in levels of IgG3 antibody compared with prior IGIV treatment were calculated for the 29 subjects with data relating to prior IGIV treatment: median changes from prior IGIV in this sub-group of subjects ranged from -1.38 mg/dL (Visit 6) to + 1.60 mg/dL (Visit 4).
- IgG4 Median trough levels of IgG4 in the 29 subjects on prior IGIV were 23.9 mg/dL. Median trough levels of IgG4 antibodies for all 50 subjects were 25.1 mg/dL at Visit 1 (screen) and 19.2 mg/dL at Visit 2 (infusion I-1) (both visits prior to starting BPL IGIV).
    - During the course of treatment with BPL IGIV, median trough levels of IgG4 antibodies showed a gradual decline, reaching a value of 6.6 mg/dL at Visit 10. Median trough IgG4 levels remained stable thereafter. Changes in levels of IgG4 antibody compared with prior IGIV treatment were calculated for the 29 subjects with data relating to prior IGIV treatment: median changes from prior IGIV in this sub-group of subjects ranged from -11.7 mg/dL (Visit 12) to -6.30 mg/dL (Visit 4).

Comment For both IgG2 and IgG4, the median changes from trough levels during prior IGIV therapy in those who had available data showed decrease, particularly with IgG4. The decline in median trough IgG4 antibody levels during the course of treatment with BPL IGIV was observable with both the 21-day and the 28-day schedules, more pronounced in the latter group. The lowest recorded median trough IgG4 antibody level for subjects on the 21-day schedule was 6.9 mg/dL (Visit 9), and the corresponding value was 4.6 mg/dL for the subjects on the 28-day schedule (Visits 8, 12, 14 and 15). The study report has not presented an analysis of the pharmacokinetics of IgG subclasses. Since the BPL IGIV product is purported to provide normal distribution of IgG subclasses, this decline in IgG4 over time in patients treated with BPL IGIV remains unexplained.

3. Trough Levels of IgG Antibodies to Certain Antigens
Trough levels of IgG antibodies against CMV, *H. influenzae* B, tetanus, and *S. pneumoniae* serotypes were determined at several visits during the course of the study and found to be fairly stable. When analyzed by infusion schedule, the trend and range of values were similar between the two infusion schedules.

Drug-Drug and Drug-Disease Interactions
Such interactions were not assessed in this study.

Efficacy Conclusions
BPL IGIV has met the primary and secondary efficacy endpoints and objectives set for it in this study, as (1) infusion of BPL IGIV into subjects with PID prevented the development of serious, acute, bacterial infections over the duration of this study, (2) acute infections that did occur could usually be managed with medical intervention at the physician's office and therapeutic use of systemic antibiotics, and (3) PK results of BPL IGIV were consistent with those of an intact IgG product.

SAFETY EVALUATION
Extent of Exposure
Duration of exposure was calculated as the difference between the date of the last visit (excluding 2nd follow-up) and the date of the first BPL IGIV infusion, plus 1 day. The mean (SD) duration of exposure to BPL IGIV was 334.3 (67.35) days. The median duration of exposure was 351.0 days with a range of 29 - 374 days. Similar values were seen when the ITT population was split by the 21- or 28-day infusion schedule [338.8 (64.83) and 330.8 (70.24) days, respectively]. The duration of exposure was >11 months and ≤12 months for the majority of subjects (44 subjects, 88.0%).

Extent of Exposure-Total Dose (mg/kg) in Intent-to-Treat Population

Statistic	21-Day Schedule	28-Day Schedule	Combined
n	22	28	50
Mean	7589	5623	6488
Std Dev	2321	1875	2284
Median	7613	5428	6411
Min	965	898	898
Max	11670	10278	11670

For a single infusion, the minimum exposure was 279 mg/kg (I-1 for Subject ---(b)(6)---) and maximum 799 mg/kg (I-2 for Subject --(b)(6)---). The median dose for all subjects was similar across infusion visits 1 – 13, with a range of 434.0 mg/kg to 444.5 mg/kg. Infusion visits 14-17 only occurred for subjects on the 21-day schedule, and the maximum median dose for these infusions was 469.0 mg/kg (Infusion 16). The mean dose (range) per infusion for those on the 21-day schedule was 469.4 mg/kg (330 - 693). The mean dose (range) per infusion for those on the 28-day schedule was 466.2 mg/kg (326 - 790). The maximum total exposure was 11,670 mg/kg. As described in Section 10-2, the infusion rate for one subject at Site 10 exceeded the parameters specified in the protocol.

Adverse Events
Brief Summary of Adverse Events
All 50 subjects had an AE. Twenty-four subjects (48.0%) had an AE that was considered product-related. Five subjects had at least one SAE; one subject had 2 product-related SAEs and 1 non-product related SAE. Three subjects discontinued because of an AE and are discussed further in Section 12.3.1.3.

Summary of Adverse Events

	Subjects n (%)
Subjects with any AE	50 (100.0%)
Subjects with no AE	0 (0.0%)
Subject with product-related AE[a]	24 (48.0%)
Subjects with no product-related AE	26 (52.0%)
Subjects with any SAE	5 (10.0%)
Subjects with any product-related SAE[b]	1 (2.0%)
Subjects with no product-related SAE	49 (98.0%)
Subjects discontinued because of AE	3 (6.0%)

Only AEs with onset between first infusion date and 30 days after the last infusion are included. [a]Includes all AEs that were possibly, probably, or definitely related to product. [b]Includes all SAEs that were possibly, probably, or definitely related to product.

Analysis of Adverse Events

1. All Adverse Events
All 50 subjects had at least 1 AE; the 50 subjects had a total of 581 AEs. Adverse events occurring with a frequency of ≥5% in subjects are shown in the following table. The most common AEs, regardless of causality, were headache (18 subjects, 36.0%), sinusitis (17 subjects, 34.0%), pyrexia (15 subjects, 30.0%), upper respiratory tract infection (13 subjects, 26.0%), diarrhea (10 subjects, 20.0%), and nausea (9 subjects, 18.0%). Thirty-eight subjects (76.0%) had a total of 122 AEs within the Infections and

Infestations SOC. Almost half of these events occurred as one of the following three preferred terms: sinusitis, upper respiratory tract infection and nasopharyngitis.

Number and Percent of Subjects with Adverse Events Classified by Severity (Preferred Terms with a Frequency of ≥5% of ITT Population)

System, Organ, Class Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Any Adverse Event	47 (94.0%)	35 (70.0%)	16 (32.0%)	50 (100.0%)
Eye Disorders				
Conjunctivitis	2 (4.0%)	2 (4.0%)	0 (0.0%)	4 (8.0%)
Gastrointestinal Disorders				
Diarrhea	8 (16.0%)	2 (4.0%)	0 (0.0%)	10 (20.0%)
Nausea	5 (10.0%)	4 (8.0%)	0 (0.0%)	9 (18.0%)
Upper abdominal pain	4 (8.0%)	1 (2.0%)	0 (0.0%)	5 (10.0%)
Vomiting	1 (2.0%)	2 (4.0%)	0 (0.0%)	3 (6.0%)
General disorders and administration site conditions				
Pyrexia	9 (18.0%)	6 (12.0%)	0 (0.0%)	15 (30.0%)
Fatigue	5 (10.0%)	2 (4.0%)	0 (0.0%)	7 (14.0%)
Pain	2 (4.0%)	3 (6.0%)	0 (0.0%)	5 (10.0%)
Chills	1 (2.0%)	3 (6.0%)	0 (0.0%)	4 (8.0%)
Chest Pain	1 (2.0%)	1 (2.0%)	1 (2.0%)	3 (6.0%)
Infections and Infestations[a]				
Sinusitis	10 (20.0%)	7 (14.0%)	0 (0.0%)	17 (34.0%)
Upper respiratory tract infection	8 (16.0%)	5 (10.0%)	0 (0.0%)	13 (26.0%)
Nasopharyngitis	5 (10.0%)	2 (4.0%)	0 (0.0%)	7 (14.0%)
Bronchitis	4 (8.0%)	2 (4.0%)	0 (0.0%)	6 (12.0%)
Gastroenteritis viral	2 (4.0%)	3 (6.0%)	1 (2.0%)	6 (12.0%)
Bronchitis acute	1 (2.0%)	2 (4.0%)	1 (2.0%)	4 (8.0%)
Urinary tract infection	2 (4.0%)	2 (4.0%)	0 (0.0%)	4 (8.0%)
Cystitis	2 (4.0%)	1 (2.0%)	0 (0.0%)	3 (6.0%)
Influenza	0 (0.0%)	3 (6.0%)	0 (0.0%)	3 (6.0%)
Injury, poisoning and procedural complications				
Contusion	1 (2.0%)	2 (4.0%)	0 (0.0%)	3 (6.0%)
Musculoskeletal and connective tissue disorders				
Back pain	2 (4.0%)	3 (6.0%)	0 (0.0%)	5 (10.0%)
Myalgia	3 (6.0%)	2 (4.0%)	0 (0.0%)	5 (10.0%)
Arthralgia	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (6.0%)
Muscle spasms	1 (2.0%)	2 (4.0%)	0 (0.0%)	3 (6.0%)
Nervous system disorders				
Headache	7 (14.0%)	8 (16.0%)	3 (6.0%)	18 (36.0%)
Sinus headache	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (6.0%)
Psychiatric disorders				
Insomnia	1 (2.0%)	1 (2.0%)	1 (2.0%)	3 (6.0%)
Respiratory, thoracic and mediastinal disorders				
Pharyngolaryngeal pain	5 (10.0%)	2 (4.0%)	0 (0.0%)	7 (14.0%)
Nasal congestion	5 (10.0%)	1 (2.0%)	0 (0.0%)	6 (12.0%)
Asthma	0 (0.0%)	3 (6.0%)	1 (2.0%)	4 (8.0%)
Sinus congestion	2 (4.0%)	2 (4.0%)	0 (0.0%)	4 (8.0%)
Cough	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (6.0%)
Wheezing	2 (4.0%)	1 (2.0%)	0 (0.0%)	3 (6.0%)
Skin subcutaneous tissue disorders				
Rash	4 (8.0%)	1 (2.0%)	0 (0.0%)	5 (10.0%)
Vascular disorders				
Hypertension	0 (0.0%)	1 (2.0%)	2 (4.0%)	3 (6.0%)

Note: Only AEs with onset between first infusion date and 30 days after the last infusion are included. AEs are coded using MedDRA version 8.1.

[a]Two additional subjects had symptoms included on Listing 22, Infections. Subject --(b)(6)--- had a sinus infection and fungal infection starting at the first follow-up visit, which was 1 day after the 30 day cut-off for AEs. The second subject, --(b)(6)---, had three terms that were classified under other SOC categories in the AE analysis. The three terms were pyrexia, chills, and sinus congestion.

2. Product-Related Adverse Events

Approximately half of the subjects (24 Subjects, 48.0%) had at least one product-related AE. There were 186 product-related AEs. A greater percentage of subjects with the 21-day infusion cycle had at least

1 product-related AE (14 of 22 subjects, 63.6%) as opposed to subjects with the 28-day infusion cycle (10 of 28 subjects, 35.7%). This may be expected since the subjects on the 21-day infusion cycle had more exposure to BPL IGIV, both in terms of the number of infusions of BPL IGIV and total dose. Product-related AEs occurring with a frequency of ≥5% in subjects are shown in the following table.

Number and Percent of Subjects with Product-related Adverse Events Occurring with a Frequency of 5% or More (Intent-to-Treat Population, N=50)

System, Organ, Class Preferred Term	AEs Subjects n (%)	Number of Events
Gastrointestinal Disorders		
Nausea	6 (12.0%)	7
Vomiting	3 (6.0%)	3
General disorders and administration site conditions		
Fatigue	6 (12.0%)	16
Pyrexia	6 (12.0%)	11
Pain	3 (6.0%)	4
Musculoskeletal and connective tissue disorders		
Myalgia	3 (6.0%)	4
Nervous system disorders		
Headache	18 (36.0%)	76
Vascular disorders		
Hypertension	3 (6.0%)	10

Of the 24 subjects with an AE that was possibly, probably, or definitely related to BPL IGIV, 3 had AEs considered definitely related to BPL IGIV. These events were: headache (Subjects ----------(b)(6)----------), pyrexia (Subject --(b)(6)---), tachycardia (Subject --(b)(6)---), chest discomfort (Subject --(b)(6)---), and hypertension (Subject --(b)(6)---).

3. Adverse Events Temporally Associated with the Infusions

BPL analyzed AEs in this category to include all AEs that began either during the infusion or within 48 and 72 hours after the completion of the infusion. AEs starting either on the day of the infusion or on the following 2 and 3 days and for which no onset time was recorded in the CRF were assumed to fall within these 48-hour and 72-hour windows, respectively. BPL also analyzed by excluding from the above: a) those AEs judged to be possibly or probably related to previous medical conditions; b) those AEs judged medically as being very unlikely to be infusion related; and c) those AEs starting 3 days after infusion and known to have occurred >72 hours respectively after the completion of the infusion.

Comment FDA's Guidance uses a time frame corresponding to the duration of infusion and within 72 hours after the end of infusion regardless of causality determination. Only this time frame will be used in reviewing the AEs associated with infusions.

AEs were also analyzed at 1, 24, 48, and 72 hours after the start of the infusion.

Number of Infusions and Temporally Related Adverse Events at Various Time Cutoffs after the End of Infusion (Intent-to Treat Population, N=50)

	Time (hr) from the Start of the Infusion Through the Indicated Time after Infusion[a]					
Infusion and AE Datasets	**1**	**24**	**48**	**72**	**>72** [b]	**No Time Recorded**
Infusions associated with all AEs	N-A[c]	N-A	137 [d]	149 [d]	N-A	N-A
Number of AEs	54	102	121 [d]	144 [d]	344	93
Infusions associated with product-related AEs	N-A	N-A	59	64	N-A	N-A
Number of product-related AEs	47	74	82	90	71	25

[a] The data in columns labeled 1, 24, 48, and 72 hr are cumulative.
[b] AEs occurring >72 hours after infusion are not temporally associated with infusion; they are included as information in this table.
[c] N-A=not available in summary format.
[d] The number of infusions associated with AEs may be greater than the number of AEs because the 93 AEs with no start time recorded on the day of infusion were not added to the AE totals at the specific time-points.

Of the 703 infusions, 149 (21.2%) were temporally associated with AEs up to 72 hours. Overall, 237 AEs (the sum of the 72-hour and No-Time-Recorded columns: 144+93) were temporally related to an infusion. Given the total of 703 infusions, the incidence of AEs per infusion was 0.34.

The most frequently reported AEs (in >5% of subjects) that were temporally associated with infusion are shown in the following Table.

Adverse Events Occurring in >5% of Subjects with PI during a BPL IGIV Infusion or within 72 Hours after the End of an infusion, *Irrespective of Causality*

Adverse Event	Subjects (%) [n=50]	Infusions (%) [n=703]
Headache	18 (36%)	55 (7.8%)
Sinusitis	8 (16%)	9 (1.3%)
Pyrexia	7 (14%)	10 (1.4%)
Nausea	7 (14%)	7 (1.0%)
Chills	3 (6%)	5 (0.7%)
Fatigue	6 (12%)	9 (1.3%)
Hypertension	4 (8%)	6 (0.9%)
Insomnia	3 (6%)	3 (0.4%)
Nasal Congestion	3 (6%)	3 (0.4%)
Pain	5 (10%)	5 (0.7%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)

A total of 64 (9.1%) infusions were temporally associated with "product-related AEs" up to 72 hours after the infusion, with the upper 95% confidence limit for infusions with at least 1 temporally associated, "product-related AE" being 11.1% by 72 hours. There were 115 infusion-associated, "product-related AEs" (i.e., 90+25), giving an overall incidence of 0.16 "product-related AEs" per infusion.

- The most common "product-related AEs" temporally associated with infusion (cumulatively reported) across all the temporally associated time-points were:
    - headache (36 AEs in 16 [32%] of subjects by 72 hours)
    - pyrexia (5 AEs in 4 [8%] subjects)
    - nausea (4 AEs in 4 [8%] subjects)

4. Adverse Events in Relation to the Pore size of the Filter

During the study, product was administered either without a filter in the infusion line, or by using filters with a pore size of 15 to 20µm or 180µm. The effect of the use of filters on all AEs (regardless of relationship) during infusion and up to 72 hours after infusion is shown below.

Rate of Infusion-Related Adverse Events in Relation to Filter Use (ITT Population, N=50)

Scenario	No. of Infusions	Infusion-Associated AEs	AEs per Infusion	Infusions with AE	95% Confidence Interval
AEs that began during an infusion or within 72 hours after the completion of an infusion					
No filter	33	16	0.485	10 (30.3%)	14.6% - 46.0%
No filter (excluding infections)	33	14	0.424	8 (24.2%)	9.6% - 38.9%
15 to 20-µm filter	647	218	0.337	136 (21.0%)	17.9% - 24.2%
180-µm filter	23	3	0.130	3 (13.0%)	-0.7% - 26.8%
Overall	703	237	0.337	149 (21.2%)	18.2% - 24.2%

Comment Although there is some suggestion of lower rate of AEs with the 180-µm filter, these data are not conclusive because of the small sample size (23 infusions and all at 1 study site). It seems counter-intuitive that filters with larger pore size would give lower AE rate. Most of the data, and largest contribution to the overall results, were obtained with use of the 15 to 20-µm filter, and the results with 15 to 20-µm filter and the overall results are almost the same. Since the 95% confidence intervals for all the groups overlap, the impact of using filters of different pore sizes cannot be established. An analysis of "product-related AEs" gives similar results.

5. AEs in Relation to Infusion Rate

Number and % of Subjects with AEs *During* Infusion as a Function of Infusion Rate (ITT Population)

	Infusion Rate (mL/kg/min)					Total
Overall	**0.01 n (%)**	**0.02 n (%)**	**0.04 n (%)**	**0.06 n (%)**	**0.08 n (%)**	**n (%)**
Subjects with no AE during infusion	48 (96.0%)	48 (96.0%)	47 (94.0%)	46 (92.0%)	41 (82.0%)	38 (76.0%)
Subjects with ≥1 AE during infusion	2 (4.0%)	2 (4.0%)	3 (6.0%)	4 (8.0%)	9 (18.0%)	12 (24.0%)
Preferred Term						
Headache	1 (2.0%)	1 (2.0%)	2 (4.0%)	2 (4.0%)	6 (12.0%)	8 (16.0%)
Hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	2 (4.0%)	3 (6.0%)
Inf site reaction	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (2.0%)	2 (4.0%)
Bradycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)[a]
Bronchospasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)[a]
Chest discomfort	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
Chills	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
Hypoaesthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
Hypotension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)[a]
Nausea	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Paraesthesia	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
Tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
Tinnitus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)

Note: Three AEs did not occur at the rates indicated. Please see footnote a.

a) Bradycardia and hypotension occurred in Subject --(b)(6)--- between 0.06 mL/kg/min and 0.08 mL/kg/min. Bronchospasm occurred in Subject --(b)(6)--- between 0.01 mL/kg/min and 0.02 mL/kg/min

Overall, there was an increased frequency of AEs during infusions once the infusion rate was increased from 0.01 mL/kg/min. At 0.08 mL/kg/min, 9 subjects (18.0%) had at least one AE during an infusion. An increased frequency of headache occurred with increased infusion rate. Hypertension was not observed until the infusion rate was 0.06 mL/kg/min.

6. Adverse Events by Severity

See table on page 23. Most subjects had an AE that was mild (47 subjects, 94.0%) or moderate (35 subjects, 70.0%). Of 16 subjects (32.0%) with severe AEs, headache (3 subjects, 6.0%) and hypertension (2 subjects, 4.0%) were reported in more than one subject. The other AEs occurred in one subject each (2%): asthma, actinic keratosis, acute bronchitis, basal cell carcinoma, chest pain, insomnia, hemangioma, hypotension, intervertebral disc degeneration, pregnancy, pruritic rash, squamous cell carcinoma, sunburn, syncope vasovagal, thrombosis, viral gastroenteritis, and decreased white blood cell count.

7. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths were reported, but 5 subjects (10.0%) had a total of 7 SAEs between the first BPL IGIV infusion and the first follow-up visit, inclusive, and are summarized below. The majority of SAEs (5 of 7) were considered not to be related to BPL IGIV. Two separate events were considered possibly related to BPL IGIV and occurred in the same subject (Subject --(b)(6)---). Only 1 SAE had an infective etiology (viral gastroenteritis, Subject --(b)(6)---). One additional SAE began before the first infusion of BPL IGIV. Subject --(b)(6)--- started treatment for bacterial pneumonia 4 days before this subject's first infusion with BPL IGIV.

Comments Two of the SAEs were considered possibly related to BPL IGIV and occurred in the same subject (--(b)(6)---): thrombosis and chest pain. There is a known relationship between IGIV use and thrombotic events. The subject's anti-phospholipid syndrome was diagnosed after the first thrombosis event. Antiphospholipid syndrome is also known to increase a subject's risk for thrombosis. As well, the patient had a venous access port, which could place her at an increased risk of thrombosis.

Serious Adverse Events

Subject Number	Preferred Term[a]	Con-meds Taken	Action Taken[b]	Relationship to Product	Outcome
--(b)(6)---	Sq cell carcinoma	No	No action	Not related	Resolved
--(b)(6)---	Gastroenteritis viral	Yes[c]	Hosp	Not related	Resolved
--(b)(6)---	Pneumonia bacterial[d]	Yes[e]	Hosp	Not related	Resolved
--(b)(6)---	Basal cell carcinoma	No	No action	Not related	Resolved
--(b)(6)---	Pregnancy	No	Discon	Not related	Resolved
--(b)(6)---	Thrombosis	Yes[f]	Hosp	Possibly	Resolved
--(b)(6)---	Chest pain	No	Hosp	Possibly	Resolved
--(b)(6)---	Syncope vasovagal	No	Hosp	Not related	Resolved

a Coded using MedDRA Version 8.1
b Action taken: Hosp=Hospitalized, Discon=Discontinued
c Medication was intravenous levofloxacin and metronidazole.
d Onset date for bacterial pneumonia was before the first BPL IGIV infusion
e Medication was intravenous ceftriaxone followed by oral amoxicillin/clavulanate potassium
f Medication was intravenous heparin drip.

Other Significant Adverse Events. Three subjects had a total of 3 adverse events that resulted in discontinuation from the study: mild paresthesia, moderate bronchospasm, and pregnancy.

Comments It is noted that there was a high prevalence of asthma in the subject population of this study (19 subjects, 38.0%). While paresthesia is not a well-recognized complication of IGIV therapy, mild, transient paraesthesia occurred in one subject that led to product discontinuation.

8. Clinical Laboratory Findings

A. Biochemistry

Median values for ALT, AST, total bilirubin, BUN, and creatinine were within their normal ranges over the course of the study. This trend was observed with both the 21- and 28-day infusion cycles. Two subjects on the 28-day infusion cycle had elevated creatinine levels: both subjects had abnormally high creatinine levels at screening and Visit 2.

- Levels for Subject --(b)(6)--- were the same (141 μmol/L) at screening and Visits 2, 3, and 13.
- Levels for Subject --(b)(6)--- were 150 μmol/L at screening and Visits 2 and 6 and were 141 μmol/L at Visits 3, 4, 7, 8, 10, 14, and follow-up 1.

For LDH, median values were within normal range for subjects with the 21-day infusion schedule. The mean values for LDH also stayed within the normal range. The median values for LDH remained within the normal range at all visits for subjects with the 28-day infusion schedule. In contrast, mean values for LDH went above the upper limit of the normal range at 5 visits for subjects with the 28-day infusion schedule (Visits 8, 11, 12, 13, and 15). The LDH levels were very high in the following 5 subjects:

- Subject --(b)(6)---, Visit 13, 1179 U/L
- Subject --(b)(6)---, Visit 11, 719 U/L
- Subject --(b)(6)---, Visit 11, 1346 U/L
- Subject --(b)(6)---, Visit 12, 953 U/L and
- Subject --(b)(6)---, Visit 8, 884 U/L

There were no consistent abnormal values (including hemoglobin, hematocrit, AST/SGOT, bilirubin, haptoglobin, and urine hemosiderin) associated with these elevated LDH values.

Comment There was no laboratory or clinical evidence of hemolysis.

C-reactive Protein (CRP)

Median CRP levels were stable for both infusion schedules and ranged from 3.90 - 3.95 mg/L (normal range <5 mg/L). Overall, 31 subjects had a total of 88 events of above-normal CRP results: 20 of them had abnormally high CRP values at Screening and/or Visit 2 (Infusion 1), and 2 subjects had shift from normal at screening and Visit 2 to a value >3 times upper limit of normal during the study (Subject --(b)(6)---, Visit 18; Subject --(b)(6)---, Visit 14). Neither of these subjects had elevated WBC counts or record of an infection at the same time as the abnormal CRP levels.

B. Hematology Laboratory Results

For both infusion schedules, median and mean values of each hematological variable remained within the respective normal ranges except for eosinophils. The mean for the proportion of eosinophils in the differential was higher than the normal range (0.00 - 0.03) for 17 of the visits for the 21-day schedule and

10 of the visits for the 28-day schedule. However, both the mean and median for the absolute count of eosinophils were within normal range (0.00 - 0.03 x 10^9/L). Several hematology results were also reported as AEs and are summarized below.

Hematology Laboratory Values Reported as an "Adverse Event"

AE Preferred Term[a]	Subject Number	Test Name	Value
Direct Coombs' test positive	--(b)(6)---	Direct Coombs test	Positive
Hemoglobin decreased	--(b)(6)---	Hemoglobin	9.4 g/dL[b]
Eosinophilia	--(b)(6)---	CBC	0.6 x 10^9/L[c]
WBC count decreased	--(b)(6)---	CBC	1.8 x 10^9/L[c]
Blood Iron Decreased	--(b)(6)---	Not available[d]	Not available
Blood Iron Decreased	--(b)(6)---	Not available[d]	Not available
Blood Iron Decreased	--(b)(6)---	Not available[d]	Not available
Iron deficiency	--(b)(6)---	Not available[d]	Not available
Blood cholesterol increased	--(b)(6)---	Not available[d]	Not available
Blood potassium decreased	--(b)(6)---	Not available[d]	Not available

a If the same AE was reported more than once for a subject, the worst result is shown.
b Value was 2 days prior to AE date.
c Last laboratory value in database. AE occurred approximately 3 weeks later.
d These were results of additional laboratory tests ordered by the physician that were not specified in the protocol.

Direct Coombs' Test

- For subjects with the 21-day-infusion schedule, 1 subject (--(b)(6)---) was positive for the Direct Coombs' test at screening. This subject continued to have a positive Direct Coombs' result for every subsequent visit except Visit 10. There were 4 subjects, including Subject --(b)(6)---, who tested positive at Visit 3, and 2 subjects, including Subject --(b)(6)---, at Follow-up 1.
- For subjects with the 28-day infusions schedule, 2 subjects were positive for the Direct Coombs' test at screening (Subjects ----------(b)(6)----------). All subjects were negative after screening with the exception of Subject --(b)(6)---, who had a positive Direct Coombs' test result at both Visit 3 and 4.

The protocol required subjects who had a positive Direct Coombs' test provide a sample for analysis of hemosiderin and haptoglobin levels. The presence of hemosiderin in the urine was negative except for a positive result at Visit 4 for Subject --(b)(6)---. The haptoglobin level for this subject at Visit 4 was normal (1.66 g/L). Levels of haptoglobin for Subjects ----------(b)(6)----------were *above* normal limits at several visits. They were followed until the haptoglobin levels returned to the normal range. None of the subjects with a positive Direct Coombs' test result had haptoglobin levels below the normal range.

Comment None of the positive Coombs' test results were associated with an abnormal hemoglobin level at the same visit. Additional tests with hemosiderin and haptoglobin also did not establish evidence of hemolysis upon use of BPL IGIV. Neither could the data on bilirubin or LDH support hemolysis associated BPL IGIV infusions in this study.

Follow-up Laboratory Results for Subjects with Positive Direct Coombs' Test Result

Subject Number	Direct Coombs' Positive Visit	Test Visit	Haptoglobin g/L	Urine Hemosiderin
--(b)(6)---	Follow-up 1	Follow-up 1	1.38	Neg
--(b)(6)---	Screening	Screening	1.21	Neg
	3	3	1.22	Neg
	4	4	1.13	Neg
	5	5	1.29	Neg
	7	7	1.50	Neg
	8	8	1.29	Neg
	9	9	1.35	Neg
--(b)(6)---	3	3	0.49	Neg
--(b)(6)---	3	3	2.21[a]	Neg
	3	4	1.99	Neg
	3	5	2.12[a]	Neg
	3	6	1.74	Neg
	3	7	1.44	Neg
--(b)(6)---	3	3	1.49	Neg
	4	4	1.19	Neg
--(b)(6)---	Screening	1	1.92	Neg
	Screening	3	1.87	Neg
	Screening	4	1.66	Pos
	Screening	5	2.01[a]	Neg
	Screening	6	3.21[a]	Neg
	Screening	7	2.06[a]	Neg
	Screening	8	1.59	Neg

a Value above normal range. Normal range was 0.34 - 2.00 g/L.

C. Urine.

Median values for pH and specific gravity were within normal range throughout the study for both infusion schedules. The presence of bilirubin, casts, or crystals in the urine was negative for all subjects. The presence of ketones, nitrite, uribilirubin, or glucose was negative for most subjects except for some sporadic positive results. Findings of blood in urine are as follows:

- For subjects with the 21-day infusion schedule, there were 8 results of trace blood, 7 results of 1+ blood, 3 results of 2+ blood, and 4 results of 3+ blood. Of the 10 subjects with positive blood results, 7 were female. All of the 2+ and 3+ results occurred in females between the ages of 12 and 50 years, suggesting that menstrual blood may have been present in the sample.
- With the 28-day infusion schedule, there were 5 results of trace blood, 2 results of 1+ blood, and 1 result of 2+ blood in this population. The 2+ blood result was in a 45 year old female subject (--(b)(6)---), suggesting that menstrual blood may have been present in the sample.

The frequency of subjects with WBC in urine was similar between the infusion schedules and ranged from 3.6 - 16.0% at any particular visit. A trend of similar frequencies was seen with leukocyte esterase levels, presence of squamous epithelial cells, and mucus.

D. Viral Transmission Tests

With the exception of one indeterminate result for HIV NAT (Subject --(b)(6)---, Visit 4), all tests were negative for transmission of HBV, HCV, HIV, and Parvovirus B19. Repeat analysis of the Visit 4 sample from Subject --(b)(6)--- gave a negative result for viral transmission.

Safety Conclusions

- A total of 703 infusions of BPL IGIV were administered to 50 subjects with PID. All 50 subjects had an AE. Most of the AEs were mild (47 subjects, 97.0%) or moderate (35 subjects, 70.0%) in severity. The most common AEs were consistent with those expected with other IGIV therapies, and the most common adverse reactions ("product-related AEs") were: headache (18 subjects, 36.0%), fatigue (6 subjects, 12.0%), nausea (6 subjects, 12.0%), pyrexia (6 subjects, 12.0%), hypertension (3 subjects, 6.0%), myalgia (3 subjects, 6.0%), pain (3 subjects, 6.0%), and vomiting (3 subjects, 6.0%).
- The overall rate of AEs, regardless of relationship, was 0.34 per infusion. The rate of "product-related AEs" was 0.16 per infusion.
- Of the 703 infusions, 149 (21.2%) were temporally associated up to 72 hours. The upper 95% confidence limit for BPL IGIV infusions with at least 1 temporally associated AE (regardless of

relationship) was 23.9% by 72 hours after the infusion. The infusion of BPL IGIV met the major safety objectives of the study, as the upper bound of the 1-sided 95% confidence interval for the proportion of infusions with a temporally associated AE is <0.40.

- There was an increased frequency of AEs during infusion with increased infusion rate.
- Five subjects had at least one SAE between the first BPL IGIV infusion and the first follow-up visit. One subject (--(b)(6)---) had two product-related SAEs. The first event was thrombosis; the second event was chest pain. Thrombosis is a known complication of IGIV therapy, and the patient had a venous access port as well as anti-phospholipid syndrome, both being risk factors for thrombosis.
- In the 703 infusions, there was no indication of pathogenic viral transmission or hemolysis.

OVERALL CONCLUSION

BPL IGIV has met the efficacy and safety endpoints in the treatment of primary humoral immunodeficiency as specified in Protocol GMX01.

V. Information Request from Mid-Cycle Review

At the time of Mid-Cycle Review, there appeared to be adequate safety and efficacy data from Study GMX-01 to support licensure for BPL's IGIV in the treatment of primary humoral immunodeficiency. However, there were several issues that required resolution and an Information Request was sent to BPL, to which the firm responded by a submission dated May 26, 2009 (received May 27, 2009 as Amendment 13).

BPL's Response to IR Request

Issue #1. The subjects in Study GMX01 were somehow preselected and might not necessarily be representative of the target population, as the great majority (42/50, or 84%) did not have a documented adverse event related to prior IGIV therapy. This might also have been due to poor previous documentation, acclimatization on the previous IGIV product therapy, or self-selection by subjects more tolerant of IGIV adverse events. Please provide an analysis of the adverse event profile of Gammaplex® in patients after reaching steady state in comparison with the profile before initiating Gammaplex® therapy.

BPL Response

As mentioned, 42 (84%) of subjects did not report any AEs within the previous 6 months whilst on prior therapy. However, if we also look at the number of infections experienced by the subjects in this study, in the six months prior to entering the GMX01 study, 27 of the 50 subjects (54%) had a total of 33 documented infections (equivalent to 66/50 = 1.32 infections per patient per year). The fact that these subjects experienced infections prior to entering the study, shows there was not any "pre-selection" based on using only "well" subjects. The most likely explanation for the discrepancy in the incidence of AEs is that during the course of the study patients recorded prospectively all evidence of AEs in a diary card, whereas data for the six months prior to the study was obtained retrospectively from the patients' hospital notes, and as such, would miss any relatively minor AEs treated by primary care clinicians.

With regard to comparing the adverse event profile for subjects who have reached steady state to the profiles before initiating Gammaplex, we find that subjects did acclimatize to Gammaplex over the course of the study. This can be seen by the number of AEs associated with each infusion. Figure 1 (not shown here) represents the percentage of subjects who had a product-related AE that was temporally associated with an infusion (i.e. within 72 hours of the end of the infusion) throughout the study.

It is clear as the study progresses the number of product-related AEs experienced with each successive infusion declines, thus suggesting acclimatization to the product. This is consistent with previous observations where there has also been some evidence of fewer AEs after the second infusion of another IGIV, Flebogamma® (Berger et al 2004). Product-related AEs within 72 hours of the infusion were reported with 8.2% of infusions of Flebogamma® (Berger et al 2004), 9% of the infusions of Privigen (Stein et al, 2009) and 10% of infusions of Flebogamma DIF (EMEA, 2007). These reports are similar to the GMX01 study in which 9.1% of infusions were associated with a product-related AE. Stein et al (2009) also noted that overall 21% of AEs (both related and unrelated) were associated within 72 hrs of an infusion, mirroring the 21.1%

presented in GMX01 study. Therefore it would appear that subjects do acclimatize to intravenous immunoglobulin over a period of time, thus explaining why there were very few AEs noted with previous IVIG therapy in the 6 months prior to the Gammaplex study.

Comment Response acceptable

2. Please provide analyses of demographic subsets including age, sex and race for efficacy and safety, including analyses for pediatric age subpopulations.

BPL Response
We could not find any guidance on the provision of subgroup analysis for gender, race and age (other than for pediatric groups) in the FDA Guidance document: "Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency". Therefore, data for efficacy and safety, split by demographic subsets, were not analyzed due to the small numbers involved, i.e., for most of the subsets, the analysis would not be statistically valid.

The following tables represent the numbers of subjects in the GMX01 study split into subsets for age, gender and ethnicity; and detail the small numbers of subjects involved for each subset.

Split by age
No specific guidance has been provided as to the suggested age range split, however, the following age ranges have been presented: 2-18yrs (n=7), 19-40yrs (n=13), 41-60yrs (n=18) and over 60yrs (n=12).

The following table shows the number of subjects who participated in the GMX01 study (n=50) per age range and also further split by sex.

Range (Yrs)	Pediatric age ranges			Adult age ranges		
	0-2	2-12	12-18	19-40	41-60	Over 60
Male	0	2	3	7	9	5
Female	0	0	2	6	9	7
All subjects	0	2	5	13	18	12

….. Therefore, due to this low number of pediatric subjects in this study, it was felt that a further split into the FDA pre-defined age groups of neonates, infants, children and adolescents, would not provide high enough number of subjects (per subset) to perform any kind of significant analyses…….

Comment The applicant provides tables on efficacy and safety data with very small numbers in the cells for any meaningful interpretation. They believe that older subjects (age >60) tend to have fewer AEs and product-related AEs. However, there were only 12 subjects aged >60 and so any further conclusions would be unwarranted. The applicant states that for the neonates and infants, they have requested PREA waiver, and provided a deferral plan for children and adolescents.

Split by ethnicity
To the knowledge of the applicant, there is no evidence that the efficacy or safety of intravenous therapy is influenced by the ethnicity of a subject. The GMX01 study included subjects from thee different ethnic origin: Caucasian, Hispanic and Afro-Americans. The following table shows the split of subjects (n=50) by ethnicity, and this has been further split by sex.

Ethnicity	Caucasian	Hispanic	Afro-Americans
Male	22	2	2
Female	24	0	0
All subjects	**46**	**2**	**2**

It is clear that the overwhelming majority of subjects (92%) were of Caucasian origin. The other two ethic origins made up the other 8% of the subjects, i.e. as an equal split of 4% each. …. …. analysis of differences between the three ethnic groups represented in this study would not provide any significant conclusions.

Comment The applicant provides tables on efficacy and safety data with very small numbers in the cells for non-Caucasians to make any meaningful interpretation.

Split by gender

On the three subsets of data analyzed, the subset for gender has provided the most interesting results. The number of subjects participating in GMX01 was split fairly evenly between the sexes, i.e. 26 males (52%) to 24 females (48%).

This study was not designed to analyze the effects of gender on the efficacy or safety of Gammaplex…… [The applicant provides tables on efficacy and safety data comparing data between sexes, and there was significant difference between females and males, as females tended to have more AEs and product-related AEs than males.]

	AEs				**Product-related AEs**			
	Males n=26		**Females n=24**		**Males n=26**		**Females n=24**	
	#subjects	#AEs	#subjects	#AEs	#subjects	#AEs	#subjects	#AEs
Any AE	**26**	**230**	**24**	**351**	**-**	**-**	**-**	**-**
Any Product-relad AE	**-**	**-**	**-**	**-**	**8**	**41**	**16**	**165**
Cardiac	2	2	3	5	0	0	1	1
Ear and labyrinth	2	5	3	5	0	0	3	4
Gastrointestinal	8	17	11	23	2	6	5	11
General & Administration site condition	9	24	16	60	2	5	11	37
Metabolism/Nutrition	1	1	3	3	1	1	2	2
Muscular/Connective tissue	5	8	11	26	1	3	4	13
Nervous system	7	26	14	88	5	17	13	67
Psychiatric	0	0	3	6	0	0	1	1
Respiratory, thoracic, mediastinal	14	42	11	25	2	2	1	3
Vascular	2	7	4	6	1	6	4	6

Comment The Statistical Reviewer, Dr. Xue Lin, has analyzed the safety data and has obtained slightly different figures (highlighted in the table below).

	AEs				**Product-related AEs**			
	Males n=26		**Females n=24**		**Males n=26**		**Females n=24**	
	#subjects	#AEs	#subjects	#AEs	#subjects	#AEs	#subjects	#AEs
Any AE	**26**	**257**	**24**	**375**	**-**	**-**	**-**	**-**
Any Product-relad AE	**-**	**-**	**-**	**-**	**8**	**43**	**16**	**147**
Cardiac	2	2	3	3	0	0	1	1
Ear and labyrinth	2	5	3	5	0	0	3	4
Gastrointestinal	8	18	11	23	2	7	5	11
General & Administration site condition	10	25	17	63	2	5	11	37
Metabolism/Nutrition	1	1	3	3	1	1	2	2
Muscular/Connective tissue	5	8	11	26	1	3	4	13
Nervous system	8	34	14	93	5	18	13	69
Psychiatric	0	0	3	6	0	0	1	1
Respiratory, thoracic, mediastinal	14	46	11	26	2	2	1	3
Vascular	3	8	4	6	1	6	4	6

When analyzed for the infusions with AEs, the following information has been provided:

	Males n=26			**Females n=24**		
	#Infusions and rate	**# subjects**	**#AE/subject***	**#Infusions and rate**	**# subjects**	**#AE/subject***
Infusions with	55/382 (14.4%)	21/26	86/21	82/321 (25.5%)	22/24	151/22

AEs	upper 95% CL 17.7%	(80.8%)	(4.1)	upper 95% CL 29.9%	(91.7%)	(6.9)
Infusions with product-related AEs	12/382 (3.1%) upper 95% CL 5%	N/A	N/A	47/321 (14.6%) upper 95% CL 18.3%	N/A	N/A

Comment The Statistical Reviewer, Dr. Xue Lin, does not believe it to be appropriate to construct confidence limits on the percentage of infusions with AEs, since infusions given to the same person are correlated: when constructing confidence intervals, all infusions are treated as being independent. There are also slight differences in the figures.

	Males			Females		
	#Infusions and rate	**# subjects**	**#AE**	**#Infusions and rate**	**# subjects**	**#AE**
Infusions with AEs (within 48 hrs)	55/382 (14.4%)	20/26 (76.9%)	75 (2.9/subject)	82/321 (25.5%)	22/24 (91.7%)	139 (5.8/subject)
Infusions with product-related AEs (within 48 hrs)	12/382 (3.1%)	6/26 (23.1%)	20 (0.8/subject)	47/321 (14.6%)	16/24 (66.7%)	87 (3.6/subject)
Infusions with AEs (within 72 hrs)	59/382 (15.4%)	21/26 (80.8%)	86 (3.3/subject)	90/321 (28.0%)	22/24 (91.7%)	151 (6.3/subject)
Infusions with product-related AEs (within 72 hrs)	14/382 (3.7%)	6/26 (23.1%)	25 (1.0/subject)	50/321 (15.6%))	16/24 (66.7%)	90 (3.8/subject)

General Comment on Gender Differences The differences between males and females are statistically significant from these figures. I went through the adverse event databases of clinical trials of some marketed IGIVs in primary immunodeficiency patients and it appears that in all instances, females tend to have higher adverse event rates than males. Dr. Ann Gaines reviewed the postmarketing adverse event reporting of a number of IGIV products and has noted similar findings. Subset analyses of this nature (post-hoc) re not definitive and only for hypothesis generation. It remains to be explored (a) whether the higher rate of AEs in females is a general phenomenon, (b) whether this is unique to IGIV products, or (b) whether it is related to the indication of primary immunodeficiency. However, this information does not impact decision on this BLA and no specific regulatory action is needed.

3. For both IgG2 and IgG4, the median changes from trough levels during prior IGIV therapy in those who had available data showed decrease, particularly with IgG4. Please (a) present an analysis of the pharmacokinetics of IgG subclasses, and (b) account for the decline of both subclasses, particularly IgG4, over Gammaplex® therapy, as this product is purported to provide normal distribution of IgG subclasses for replacement.

BPL Response

IgG2. The apparent decline in IgG2 over time as noted in the CSR is an artifact as a result of only having prior data on IgG2 levels for 29 subjects (at infusion -1). BPL shows that there is variability of trough IgG2 levels prior to initiation of Gammaplex therapy among infusions -1, 0 and 1 (trough IgG2 levels on prior therapy, at screening, and before infusion 1, respectively). While infusion -1 data were available in 29 subjects, data prior to infusions 0 and 1 were available in all 50 subjects. Using the trough level prior to therapy at infusion 1 as baseline, there was no decrease over the course of study.

IgG4. ……. The decline in IgG4 over time was observed in both the 21-day and the 28-day schedules, but was more pronounced in the latter group. Gammaplex is virtually 100% IgG, and the ratio of the four IgG subclasses of immunoglobulins present is approximately: 62% IgG1, 31% IgG2, 6% IgG3, and 1% IgG4. This is similar to distribution of IgG sub-classes found in normal plasma, although normal plasma has higher level of IgG4 of around 3-6%.

As with the IgG2 discussion, the levels of IgG4 for infusions -1, 0 and 1 showed variability. In both cases, the baseline trough level before Infusion 1 was lower than those prior to infusion -1 and screening (infusion 0). However, it is still clear that there is a further decline in IgG4 from infusion

2 onwards, and appears to plateau out between infusions 4 and 5). The applicant states: “It is not certain why this decrease has occurred in this study. The decline over time to a lower plateau could be secondary to the relatively low IgG4 content in the Gammaplex product.

Comment Response acceptable. As the physiologic function of IgG4 is not clear, and the plasma level ultimately plateaus out, albeit at a lower level, no additional measures would seem warranted.

VI. Conclusion

BPL IGIV 5% Liquid has met the efficacy and safety criteria in the treatment of primary humoral immunodeficiency as detailed in the Guidance “Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency”.

VII. Recommendations

1. Recommend licensure for BPL’s IGIV 5% Liquid.

2. To fulfill PREA requirements, recommend (a) granting waiver for submission of pediatric assessment of neonates and infants, and (b) post-approval study on children and adolescents in the treatment of primary humoral immunodeficiency, including pharmacokinetic evaluation, as recommended by the Pediatric Review Committee.

3. Recommend draft labeling to be revised as per attachment to this review memo.

Appendix I. Protocol Synopsis: A Phase III, Multicentre, Open-Label Study to Evaluate the Efficacy and Safety of GAMMAPLEX® in Primary Immunodeficiency Diseases in Children and Adolescents

Type of study/ Study Design:
A Phase III, Multicentre, Open-Label Study to Evaluate the Efficacy and Safety of GAMMAPLEX® in Primary Immunodeficiency Diseases in Children and Adolescents

Drug information:
- Route of administration: Intravenous Infusion
- Formulation: Immune Globulin (Human), 5%
- Dosage: 300–800 mg/kg/infusion
- Regimen: every 21 or 28 days

Age group and population in which study will be performed:
1. Children aged 2 to 11 (inclusive)
2. Adolescents aged 12 to 16 (inclusive)

Number of patients to be studied or power of study to be achieved:
Plan to provide data on a total of 12 evaluable subjects in two treatment groups, i.e. six children aged 2 to 11 years and six adolescents aged 12 years to 16 years.

Entry criteria:
Inclusion criteria: **1.** The subject is between 2 to 16 years of age, of either sex, belonging to any ethnic group, and above a minimum weight of 10 kg. This weight is based on the amount of blood required for testing. **2.** The subject has a primary immunodeficiency disease, which has as a significant component of hypogammaglobulinemia and/or antibody deficiency (e.g., common variable immunodeficiency, X-linked and autosomal forms of agammaglobulinemia, hyper-IgM syndrome, Wiskott-Aldrich Syndrome). Isolated deficiency of a single IgG subclass, or of specific antibodies without hypogammaglobulinemia per se, does not qualify for inclusion. **3.** The subject has been receiving licensed or investigational (Phase III or IIIb) IGIV replacement therapy at a dose that has not changed by + 50% of the mean dose for at least 3 months before study entry and has maintained a trough level at least 300 mg/dL above baseline serum IgG levels (defined as before initiation of any gamma globulin treatment for that subject). **4.** The subject has documented trough levels of IgG, dose of IGIV, and treatment intervals for the last 2 consecutive routine IGIV treatments (licensed or investigational product) must be documented for each subject before the first infusion in this study can be administered. **5.** If a subject is a female of child-bearing potential, she must have a negative result on an HCG-based pregnancy test. **6.** If a subject is a female who is or becomes sexually active, she must practice contraception by using a method of proven reliability for the duration of the study. **7.** The subject is willing to comply with all aspects of the protocol, including blood sampling, for the duration of the study. **8.** The subject, if old enough (generally 6 years to 16) has signed a Child Assent form and the subject's parent or legal guardian has signed the informed consent form, both approved by the Institutional Review Board (IRB).

Exclusion Criteria: **1.** The subject has a history of any severe anaphylactic reaction to blood or any blood-derived product. **2.** The subject is known to be intolerant to any component of GAMMAPLEX®, such as sorbitol (i.e., intolerance to fructose). **3.** The subject has selective IgA deficiency, history of reaction to products containing IgA, or has a history of antibodies to IgA. **4.** Subjects who have completed the study and subjects who have withdrawn cannot participate in the study for a second time. **5.** The subject is currently receiving, or has received, any investigational agent, other than an immune serum globulin (ISG) preparation that is being evaluated in a Phase III or IIIb study, within the prior 3 months. **6.** The subject has been exposed to blood or any blood product or derivative within the last 6 months, other than a commercially available IGIV or other forms of commercially available and licensed ISG or an ISG product that is in Phase III or IIIb studies. **7.** The subject is pregnant or is nursing. **8.** The subject is positive for any of the following at screening: (Serological test for HIV 1&2, HCV, or HBsAg; NAT for HCV; NAT for HIV). **9.** The subject, at screening, has levels greater than 2.5 times the upper limit of normal as defined at the central laboratory of any of the following: (Alanine transaminase (ALT); Aspartate transaminase (AST) Lactate dehydrogenase (LDH)). **10.** The subject has a severe renal impairment (defined as serum creatinine greater than 2 times the upper limit of normal or BUN greater than 2.5 times the upper limit of normal for the range of the laboratory doing the analysis); the subject is on dialysis; the subject has a history of acute renal failure. **11.** The subject is known to abuse alcohol,

opiates, psychotropic agents, or other chemicals or drugs, or has done so within the past 12 months. **12.** The subject has a history of DVT, or thrombotic complications of IGIV therapy. **13.** The subject suffers 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 interfere with the conduct of the study. **14.** The subject has an acquired medical condition, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (ANC < 1000 x 10^9/L) or AIDS known to cause secondary immune deficiency, or is s/p hematopoetic stem cell transplantation. **15.** The subject is receiving the following medication: Systemic corticosteroids(Steroids (long-term, i.e. not intermittent or burst, daily, >1 mg of prednisone equivalent/kg/day); Topical steroids (i.e. nasal, inhaled for asthma, and/or skin preparations for eczema) are not exclusionary – requirement for burst or intermittent courses would not exclude subject; Immunosuppressive drugs; Immunomodulatory drugs). **16.** The subject has anemia (hemoglobin < 10 g/dL) at screening.

Clinical endpoints:

Study variables and criteria for evaluation:

1.1 Primary Efficacy Variable

The primary variable is the number of serious, acute, bacterial infections per subject year, and will be based on the total of all of the following events as defined by the FDA: bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, bacterial meningitis:

1.2 Secondary Efficacy Variables

Secondary efficacy will be determined by using the following variables:

- 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.

1.3 Safety Variables

The variables used to assess safety will be the following: number and percent of adverse events (AEs); vital signs; clinical laboratory tests and Direct Coombs' Test; transmission of viruses; physical examination.

Timing of assessments: To be determined

Statistical information (statistical analyses of the data to be performed): To be determined

Timeframe for submitting reports of the studies: 2012