CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125329/0
Product: Immune Globulin Intravenous (Human), 5% Liquid (Gammaplex)
Sponsor: Bio Product Laboratory
Indication: For the treatment of patients with primary immunodeficiency associated with defects in humoral immunity.
Date Received: November 17, 2008
Reviewer: Iftekhar Mahmood, Ph. D.
RPM: Debra Cordarro
Through: Basil Golding, M.D.

TABLE OF CONTENTS

INTRODUCTION

Gammaplex is a preparation of human normal immunoglobulin suitable for intravenous administration. The target indications are the treatment of primary immunodeficiency states (such as congenital agammaglobulinaemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and X-linked agammaglobulinaemia) and idiopathic thrombocytopenic purpura (ITP).

Gammaplex is manufactured from plasma collected in the USA by Bio Products Laboratory (BPL). Gammaplex contains sorbitol as a stabilizer, thereby reducing the risk of renal adverse events seen with sucrose-containing products in at-risk patients. The formulation has also been designed to be stored at room temperature, removing the constraints on patient usage, giving a product that is easier for hospitals and pharmacies to store (although long term stability data for

the full shelf-life at room temperature was not available and therefore Gammaplex was stored between 2-8°C).

The sponsor has submitted 2 pharmacokinetic studies in this Biologic License Application (BLA). One study is a comparability study (comparing Gammaplex with the licensed product Vigam liquid) and the other study is a Phase III study to evaluate the efficacy, safety, and pharmacokinetics of Gammaplex in primary immunodeficiency diseases. A review of these 2 pharmacokinetic studies is presented below.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action (deleted because this is not mechanism of action)

~~Gammaplex® contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against various infectious agents. Adequate doses of this product may restore abnormally low immunoglobulin G levels to the normal range.~~

Sponsor: please provide a brief description of mechanism of Action of Gammaplex® or IVIG (suggested reference: Simon HU . Allergy 2003; 58:543).

12.2 Pharmacodynamics: ~~Properties~~ (deleted because this is not pharmacodynamics)

~~Gammaplex® is in pharmacotherapeutic group: Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06B A02. Gammaplex® contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1,000 donors. Gammaplex® has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma.~~

Immunoglobulins are endogenous proteins produced by B lymphocyte cells. Gammaplex is an intravenous immunoglobulin and is prepared from pooled human plasma. The main component of Gammaplex is IgGA and a sub-class distribution of IgG1:IgG2:IgG3:IgG4 of approximately 62:31:6:1.

12.3 Pharmacokinetics: ~~Properties~~

~~Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between the plasma and extravascular fluid; after approximately 3 – 5 days equilibrium is reached between the intra- and extravascular compartments. The half-life of Gammaplex® has been found to be 21.7 days (mean after single dose) and 35.5 days (median at steady state). This half-life may vary from patient to patient, in particular in primary immunodeficiency. IgG and IgG complexes are broken down in cells of the reticuloendothelial system.~~

In the clinical study assessing safety and efficacy in primary immunodeficiency disease, the pharmacokinetics of Gammaplex was assessed for 28 days after administration to 24 subjects on 21- or 28-day infusion cycles. PK analysis was performed for 9 subjects receiving Gammaplex on the 21-day schedule and for 15 subjects receiving treatment on the 28-day schedule. The mean dose (range) for those on the 21-day schedule was 469.4 mg/kg (range: 330 - 693), and it was 466.2 mg/kg (range: 326 - 790) for those on the 28-day schedule. Blood samples for PK analysis were obtained after Infusion 7 for subjects on a 28-day schedule and after Infusion 9 for subjects on a 21-day schedule, i.e., during the sixth month after initiation of treatment. Table 4

summarizes the pharmacokinetic parameters of Gammaplex®, measured as serum concentrations of total IgG.

Any assessment of the clinical relevance of half-life measurements in this study should be viewed with caution. Although half-life estimates were provided for total IgG and the specific antibodies, drug elimination half-lives should be measured over a minimum period of at least 3 half-lives. ~~intervals (3 x $t_{1/2}$ days).~~ However, the short dosing intervals relative to the long half-lives in this clinical trial do not permit the accurate assessment of half-life. ~~Acceptable R^2 values were assessed on a case by case basis depending on the concentration data for the analyte(s) in question but generally required values ≥0.8.~~

Sponsor: Please convet g/dL unit for Cmax and AUC in microgram/mL.

Table 4 Pharmacokinetic Parameters of Gammaplex ® in Subjects with PID

Parameter (unit)	**21-day Dosing Interval (n=9)**		**28-day Dosing Interval (n=15)**	
	Mean ±SD	Median (Range)	Mean (SD)	Median (Range)
C_{max} (g/dL)	2.16 ± 0.38 (0.38~~26~~)	2.02 (1.63-2.73)	2.14 (0.4313)	2.02 (1.59-3.10)
T_{max} (hr)	5.39 (7.210)	3.33 (2.15-24.5)	6.11 (11.62)	3.27 (2.42-48.1)
$AUC_{0\text{-}tau}$ (days*g/dL)	28.9 (4.068)	28.8 (21.4-36.5)	34.6 (5.206)[a]	34.0 (26.3-45.5)[a]
Half-Life (days)	41.6 (26.49)	33.9 (21.6-108)	40.8 (13.82)[a]	40.7 (22.3-69.7)[a]
Clearance (mL/days/kg)	0.587 (0.2424)	0.603 (0.194-1.02	0.583 (0.2651)[a]	0.481 (0.245-1.28)[a]

a: n=14 for these calculations; tau = dosing interval

Pharmacokinetic parameters were also assessed for total IgG and specific antibodies to *Cytomegalovirus, Streptococcus pneumoniae*, and *Haemophilus influenzae* B. ~~The following~~ Ttable 5 summarizes the pharmacokinetic parameters for antibodies to specific antigens. ~~The two infusion schedules (21-day and 28-day) had similar values.~~

Sponsor: For a prescribing physician, the interpretation of PK data in Table 5 may be difficult. Please provide some information such as protective levels of Gammaplex in terms of Cmax and AUC (or in terms of trough levels). Tmax is of no practical value and can be deleted. Table looks very busy. The column "statistics" can be deleted and the information can be placed as a footnote (such as numbers in parenthesis are range). Please ensure that the units of all the parameters in Table 5 are in microgram/mL.

Table 5 PK Parameters (mean ± sd) for Antibodies to Specific Antigens

Parameter (unit)	**Statistic**	**21-day Dosing Interval (n=9)**			**28-day Dosing Interval (n=15)**		
		C_{max} (g/dL)	T_{max} (hr)	$AUC_{0\text{-}tau}$ (days*g/dL)	C_{max} (g/dL)	T_{max} (hr)	$AUC_{0\text{-}tau}$ (days*g/dL)
Cytomegalovirus	Mean (SD)	61.6 (21.88)	5.48 (7.735)	954 (293.0)	62.9 (23.92)	15.2 (26.07)	1270 (601.7)
	Median (Range)	54.0 (46.0-117.0)	2.75 (2.15-26.1)	858.0 (795.0-1720.0)	57.0 (43.0-142.0)	3.27 (2.08-96.3)	1090 (773-3190)
Haemophilus influenzae B	Mean (SD)	7.04 (1.145)	13.6 (20.44)	70.1 (20.72)	5.89 (1.658)	8.67 (14.10)	63.3 (17.88)
	Median (Range)	6.87 (5.68-8.85)	3.65 (2.17-50.3)	65.2 (45.2-115.0)	5.9 (3.37-9.0)	3.37 (2.27-50.4)	58.1 (46.1-96.0)
Streptococcus pneumoniae Type 4	Mean (SD)	2.69 (0.7833)	5.7 (7.397)	34.0 (8.467)	3.07 (2.138)	36.7 (93.97)	41.3 (21.23)
	Median (Range)	2.3 (1.6-4.0	3.5 (2.15-49.1)	32.5 (23.9-48.4)	2.3 (0.9-9.9)	3.33 (2.37-340.0)	34.2 (14.2-84.4)
Streptococcus pneumoniae Type 14	Mean (SD)	23.0 (12.05)	8.44 (15.25)	31.9 (189.2)	17.3 (5.767)	3.32 (0.667)	257.0 (87.54)
	Median (Range)	20.8 (12.5-53.2	3.5 (2.15-49.1)	286.0 (172.0-806.0)	15.3 (8.5 - 29.3)	3.33 (2.37-5.0)	229.0 (140.0-510.0)
Streptococcus pneumoniae Type 19	Mean (SD)	10.6 (2.959)	8.69 (15.53)	129 (38.15)	19.6 (20.14)	63.4 (148.9)	167.0 (99.79)
	Median (Range)	12.2 (6.6-14.1)	3.65 (2.15-50.1)	133.0 (79.5- 192.0)	14.0 (6.7-85.0)	3.75 (2.08-504.0)	129.0 (92.4-445.0)
Streptococcus pneumoniae Type 6B	Mean (SD)	11.0 (3.072)	5.71 (7.511)	129.0 (28.82)	11.1 (4.725)	6.37 (11.98)	161.0 (109.7)
	Median (Range)	11.4 (7.2-16.9)	3.5 (2.15-25.7)	124 (87.2-174.0)	8.6 (4.4-21.7)	3.33 (2.08-49.6)	136.0 (72.0-527.0)
Streptococcus pneumoniae Type 9V	Mean (SD)	10.1 (2.153)	5.7 (7.397)	123.0 (32.96)	8.95 (2.907)	12.4 (25.79)	125.0 (35.56)
	Median (Range)	9.6 (7.3-13.8)	3.5 (2.15-25.4)	111.0 (801.1-175.0)	7.08 (5.5-14.6)	3.42 (2.37-96.0)	128.0 (64.3-197.0)

RECOMMENDATION

The pharmacokinetic study design and analysis of Gammaplex is acceptable. The sponsor should incorporate the clinical pharmacology labeling of Gammaplex as suggested by the FDA.

Iftekhar Mahmood, Ph. D.
Senior Clinical Pharmacology Reviewer
Division of Hematology
Office of Blood Review & Research

Basil Golding, MD
Division Director, Division of Hematology
Office of Blood Review & Research

Study #1

Study Title: 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).

The primary objective of the study was to compare the $AUC_{(0\text{-}84)}$ of a single intravenous infusion of Vigam Liquid (infused at the licensed rate of up to 3 mL/min) with Gammaplex (infused at up to 3 mL/min and up to 6 mL/min).

This was a single centre, parallel, double-blind (Groups 1 and 2 only, Group 3 is open), single dose study. The study consisted of a screening phase, a single dosing day and an 84-day follow-up period. Subjects were randomized into one of three treatment groups.

Group 1: 12 subjects received a single dose of Vigam Liquid 400 mg/kg intravenously, infused at an initial rate of 0.01 ml/kg/min increasing to a maximum of 3 mL/min.

Group 2: 12 subjects received a single dose of Gammaplex 400 mg/kg intravenously infused at an initial rate of 0.01 mL/kg/min increasing to a maximum of 3 mL/min.

Group 3: 12 subjects received a single dose of Gammaplex 400 mg/kg intravenously infused at an initial rate of 0.01 mL/kg/min increasing to a maximum of 6 mL/min.

The subjects were healthy, normotensive, non-smoking male (n = 17) and female (n = 19) volunteers aged 18 to 60 years. 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. Vigam Liquid and Gammaplex human normal immunoglobulin for intravenous administration were provided by BPL as a colorless liquid in 100 mL vials (5 g IVIG in 100 mL). The following Table shows the constituents of the vials.

A comparison of the constituents of Vigam® Liquid and Gammaplex®

Vigam® Liquid	Gammaplex®
(b)(4) IgG	50 g/L IgG
(b)(4) Sucrose	50 g/L Sorbitol
(b)(4)	40 mM Sodium chloride
(b)(4) Glycine	80 mM Glycine
(b)(4) Sodium acetate	20 mM Sodium acetate
pH (b)(4)	pH 4.95

Neither product contains antibacterial preservative

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. For pharmacokinetic study, blood samples were taken at pre-dose, and at the following times after the end of infusion: 15 minutes, 4, 24, 30, and 48 hours and on days 4, 8, 11, 15, 18, 22, 29, 36, 43, 50, 57, 71, and 85. For pharmacokinetic analysis, serum IgG concentrations were corrected by subtracting pre-dose values from post-dose values for each subject.

The Pharmacokinetic parameters were calculated for serum immunoglobulin G (IgG) for all subjects and were estimated by non-compartmental analysis. For comparability study, 90% confidence interval was constructed on log transformed C_{max} and AUC. Bioequivalence was assumed if the 90% confidence interval for C_{max} and AUC lay within the acceptable interval of 0.80-1.25. The pharmacokinetic parameters of Vigam Liquid and Gammaplex are summarized in Table 1. The rate of infusion (3 vs 6 mL/min) does not appear to have any impact on the pharmacokinetics of Gammaplex. The clearance and half-life were comparable between the two infusion rates.

Table 1
Pharmacokinetic parameters of IgG in 3 groups of healthy subjects (mean ± sd)

Parameters	Group 1	Group 2	Group 3
C_{max} (g/L)	8.3 ± 1.5	9.4 ± 1.2	9.8 ± 1.2
$AUC_{(0\text{-}84)}$ h*g/L	3811 ± 1234	3876 ± 1106	3516 ± 1088
$AUC_{(0\text{-}\infty)}$ h*g/L	4654 ± 1666	4346 ± 1327	4114 ± 1424
CL (mL/h/kg)	0.12 ± 0.12	0.10 ± 0.05	0.11 ± 0.04
Half-life (hrs)	632 ± 216	518 ± 146	524 ± 205

Group 1 = Vigam liquid (3 mL/min); Group 2 = Gammaplex (3 mL/min); Group 3 = Gammaplex (6 mL/min)

Table 2
Results of ANOVA

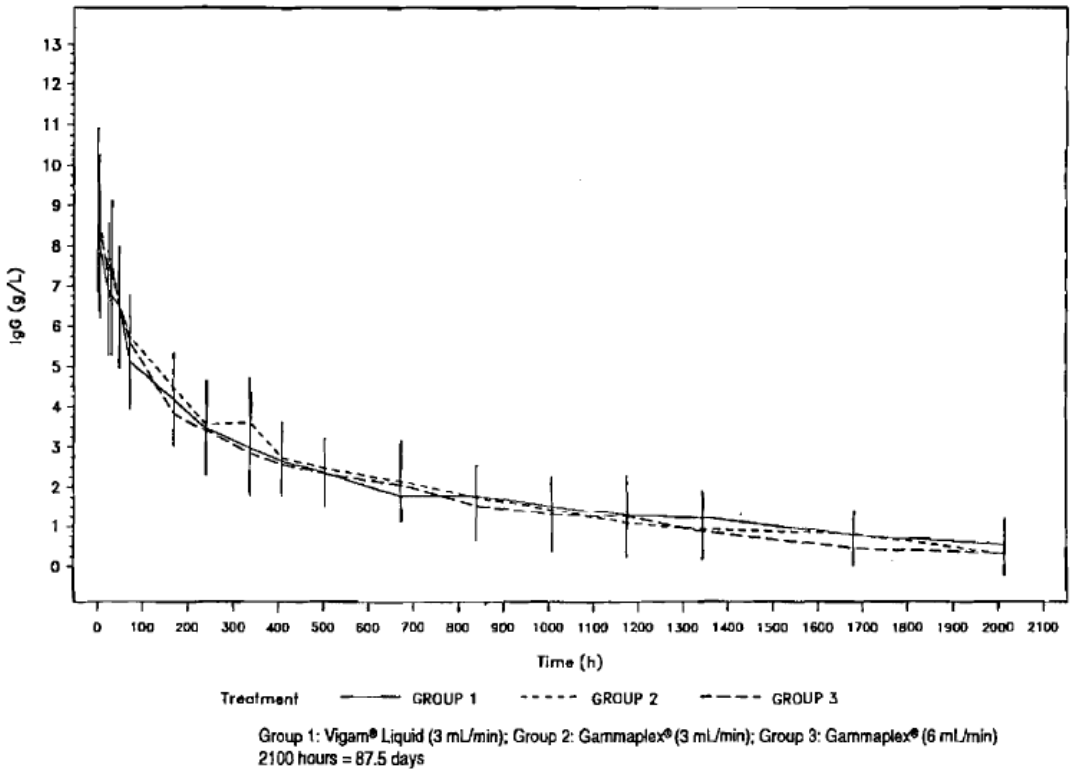
PK variable	Group 2 versus Group 1		Group 3 versus Group 1		Group 3 versus Group 2	
	PE	CI	PE	CI	PE	CI
C_{max}	114.2	103.1-126.6	119.0	107.4-131.9	104.2	94.0-115.5
$AUC_{0\text{-}21}$	110.6	94.2-129.9	102.8	87.5-120.7	92.9	79.1-109.2
$AUC_{0\text{-}84}$	106.1	80.4-139.9	96.3	73.0-127.1	90.8	68.9-119.8
$AUC_{0\text{-}\infty}$	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: Gammaplex® (3 mL/min); Group 3: Gammaplex® (6 mL/min)
PE = point estimate for mean difference CI = confidence interval

The results of ANOVA are summarized in Table 2. The analysis indicates that the point estimates differed less than 20% for a given parameter between two groups (1 & 2). However, the confidence intervals for C_{max} and AUC were outside the limits of 80 to 120%, indicating that Vigam and Gammaplex are not bioequivalent. The wide confidence interval observed can be attributed to wide inter-subject variability.

Figure 1

IgG serum concentrations by time and treatment groups



Group 1: Vigam® Liquid (3 mL/min); Group 2: Gammaplex® (3 mL/min); Group 3: Gammaplex® (6 mL/min)
2100 hours = 87.5 days

Conclusions: Gammaplex can be described as a low clearance drug with a long half-life (see comment). The rate of infusion (3 vs 6 mL/min) does not appear to have any impact on the pharmacokinetics of Gammaplex. The clearance and half-life were comparable between the two infusion rates. The 90% confidence interval indicates that the C_{max} and $AUC_{(0-\infty)}$ of Vigam Liquid and Gammaplex are outside the acceptable interval of 0.80-1.25, therefore, these 2 products are not comparable (or bioequivalent).

Comment

The half-life of Gammaplex should be interpreted with caution. Gammaplex concentrations-time data in individual subjects reveal that in the majority of subjects half-life can not be estimated due to the lack of a systematic elimination phase. In other words, the nature of the data is such that one can not estimate half-life with any degree of accuracy in most of the subjects. Two representative plots of Gammaplex concentrations-time data in two subjects are shown in Figures 2 & 3.

Figure 2

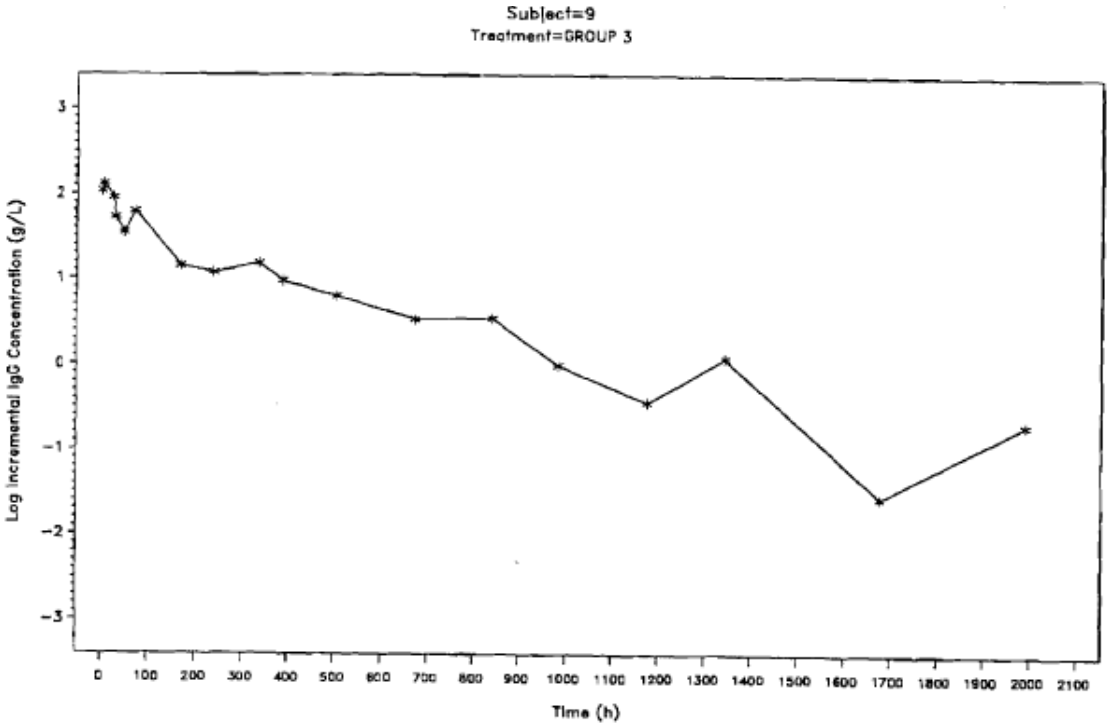
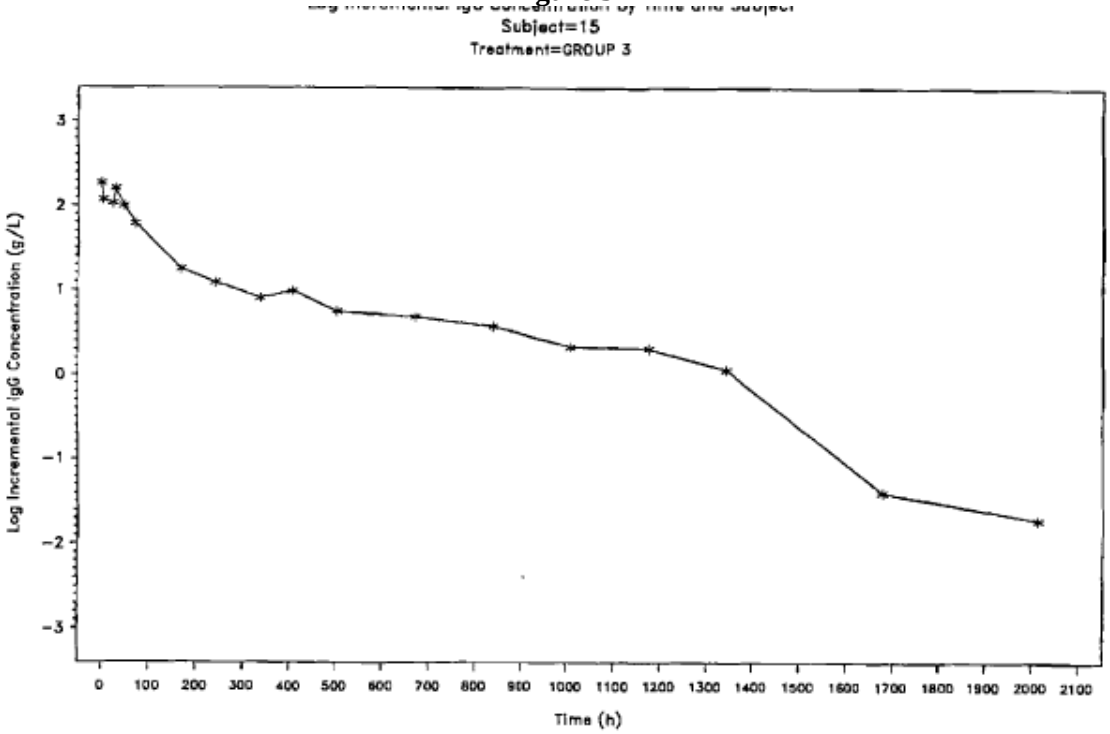


Figure 3



Study #2

Study Title: A Phase III multicenter, open-label study to evaluate the efficacy, safety, and pharmacokinetics of Gammaplex® in primary immunodeficiency diseases (protocol # GMX01).

This was a multicenter, open-label, non-randomized study. Fifty subjects were to be enrolled in order to obtain 40 evaluable subjects. Twenty-four subjects participated in the pharmacokinetic (PK) sub-study. There were 9 subjects on the 21-day infusion schedule, and 15 subjects were on the 28-day infusion schedule. Gammaplex was infused (300 to 800 mg/kg/infusion every 21 or 28 days) by an infusion pump and the maximum rate for an infusion was 0.08 mL/kg/min. The mean dose for 21-day or 28-day schedule was 469.4 mg/kg (330-693) or 466.2 mg/kg (326-790), respectively.

The primary objective of this study was to determine if Gammaplex is efficacious with respect to Food and Drug Administration's minimal requirements (no more than 1 serious, acute, bacterial infection per subject per year) in subjects with primary immunodeficiency disease (PID). The secondary objectives were to assess the safety and tolerability of Gammaplex and to determine if Gammaplex has a PK profile comparable with that of intact immunoglobulin G (IgG) in subjects with PID. The total planned duration of treatment was 12 months.

Diagnosis and Main Criteria for Inclusion:

1. There were 26 males and 24 females in the study and their age ranged from 9 to 78 years.
2. The subject had been receiving licensed or investigational (Phase III or IIIb) IVIG 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 was between 21 and 28 days inclusive. The subject had 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.
3. If a subject was a female of child-bearing potential, she must have had a negative result on an HCG-based pregnancy test.
4. If a subject was a female who was or became sexually active, she had to practice contraception by using a method of proven reliability for the duration of the study.

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. At infusion 7 or infusion 9, blood samples were obtained just before the infusion, immediately at the end of the infusion, 1 hour after the end of the infusion, 24 hours, and on days 2, 4, 7, 14, 21, and 28 after the start of the infusion. Total IgG levels were determined using the N antisera to human immunoglobulins (IgG, IgA, IgM) kit manufactured by ---(b)(4)---. The PK profile of specific antibodies for Cytomegalovirus (CMV), Streptococcus pneumoniae (subtypes

4, 6B, 9V, 14, 19), and Hemophilus influenza B were also estimated. Levels of antibodies specific to H. influenza B were determined by enzyme immunoassays. Levels of antibodies specific to CMV and S. pneumoniae were determined by ----------(b)(4)---------- assay and ---------(b)(4)----------, respectively. Non-compartmental analysis was used to estimate the PK parameters of total IgG and specific antibodies. The results of the study are summarized below.

Pharmacokinetics of Total IgG:

Total IgG median C_{max} and median T_{max} values were 2.02 g/dL and 3.30 hr, respectively. Total exposure, as measured by $AUC_{(0\text{-tau})}$ was slightly greater for the 28-day infusion schedule than 21-day infusion schedule (Table 1). The mean half-life was 41.1 ± 19.2 days for all 24 subjects (41.6 ± 26.5 days for the 21-day infusion schedule, and 40.8 ± 13.8 days for the 28-day infusion schedule). Figures 1 and 2 represent total IgG plasma concentration-time data for 21-day or 28-day infusion schedule.

Table 1
Pharmacokinetic parameters of total IgG in patients with PID (mean ± sd)

Parameters	21-day schedule	28-day schedule
C_{max} (g/L)	2.16 ± 0.38	2.14 ± 0.43
T_{max} (hrs)	5.4 ± 7.2	6.1 ± 11.6
$AUC_{(0\text{-tau})}$ (days*g/dL)	28.9 ± 4.1	34.6 ± 5.2
CL (mL/days/kg)	0.59 ± 0.24	0.58 ± 0.26
Half-life (days)	41.6 ± 26.5	40.8 ± 13.8

Pharmacokinetics of antibodies specific against S. pneumoniae serotypes, hemophilus influenza B, and cytomegalovirus:

The results of Pharmacokinetics of antibodies specific against S. pneumoniae serotypes, hemophilus influenza B, and cytomegalovirus are presented in Tables 2 -5.

Trough Levels of IgG

Trough Levels of Total IgG: Trough levels of total IgG were measured over the course of the study treatment. Trough levels of total IgG were fairly stable over the course of the study. The median values for total IgG for subjects in the 21-day infusion schedule ranged from 936 -1240 mg/dL. The minimum total IgG value was 589 mg/dL and the maximum value was 2010 mg/dL. The median values for total IgG for subjects in the 28-day infusion schedule ranged from 833 - 1140 mg/dL. The minimum total IgG value was 525 mg/dL and the maximum value was 1990 mg/dL.

Figure 1: Total IgG Levels Measured for Pharmacokinetic Assessment (Mean ± 1 Std Error) 21-Day Infusion Schedule (N=9)

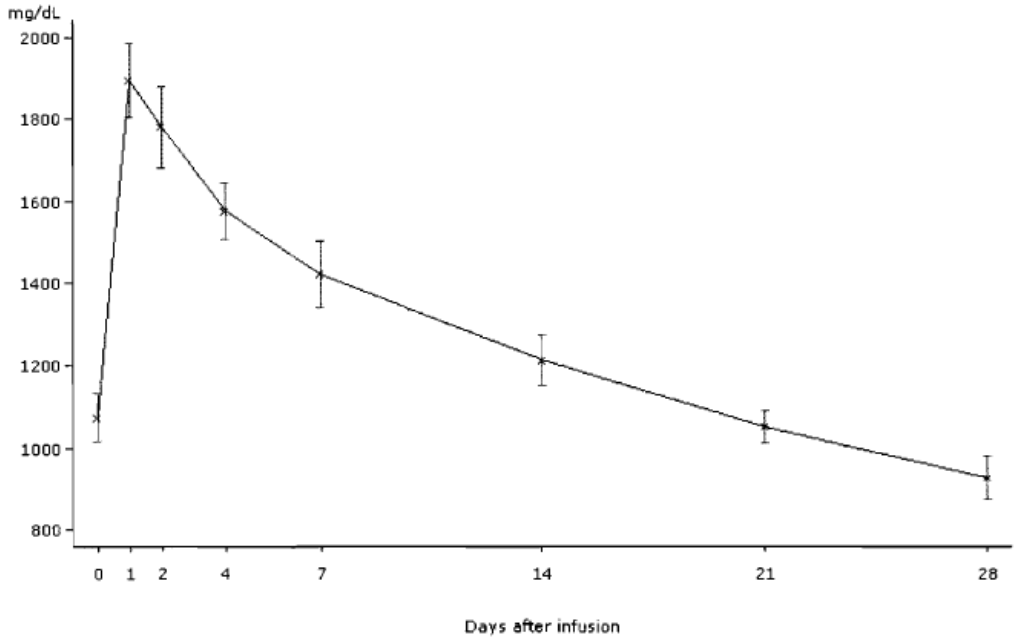


Figure 2: Total IgG Levels Measured for Pharmacokinetic Assessment (Mean ± 1 Std Error) 28-Day Infusion Schedule (N=15)

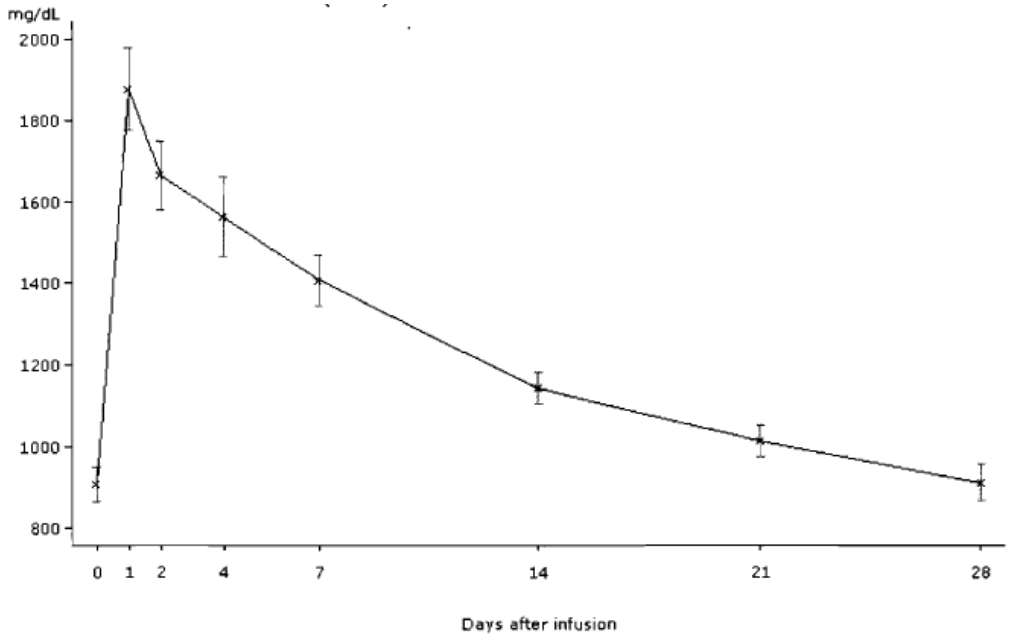


Table 2
S. pneumoniae serotypes pharmacokinetic parameters (mean ± sd) (21-day schedule)

Parameters	S. pneumoniae serotypes				
	4	14	19	6B	9V
C_{max} (µg/mL)	2.7 ± 0.8	23.0 ± 12.0	10.6 ± 2.9	11.0 ± 3.1	10.1 ± 2.1
$AUC_{(0-21)}$ (days* µg/mL)	34 ± 9	319 ± 189	129 ± 38	129 ± 29	123 ± 33
Half-life (days)	26.5 ± 7.1	28.8 ± 12.1	26.8 ± 8.2	25.2 ± 6.8	26.1 ± 10.4

Table 3
S. pneumoniae serotypes pharmacokinetic parameters (mean ± sd) (28-day schedule)

Parameters	S. pneumoniae serotypes				
	4	14	19	6B	9V
C_{max} (µg/mL)	3.1 ± 2.1	17.3 ± 5.8	19.6 ± 20.1	11.1 ± 4.7	8.9 ± 2.9
$AUC_{(0-28)}$ (days* µg/mL)	41 ± 21	257 ± 88	167 ± 100	161 ± 110	125 ± 36
Half-life (days)	23.8 ± 8.3	26.3 ± 12.4	27.2 ± 9.6	24.0 ± 5.3	23.2 ± 8.5

Table 4
Hemophilus influenza B, and cytomegalovirus pharmacokinetic parameters (mean ± sd) (21-day schedule)

Parameters	**H. influenza B**	**cytomegalovirus**
C_{max}	7.04 ± 1.1	61.6 ± 21.9
$AUC_{(0-21)}$	70.1 ± 20.7	954 ± 293
Half-life (days)	**3.0 ± 0.4**	27.5 ± 3.6

Units for C_{max} for cytomegalovirus = AU/mL, for H. influenza B = mg/L

Units for AUC for cytomegalovirus = days*AU/mL, for H. influenza B = (days*mg/L)

Table 5
Hemophilus influenza B, and cytomegalovirus pharmacokinetic parameters (mean ± sd) (28-day schedule)

Parameters	**H. influenza B**	**cytomegalovirus**
C_{max}	5.9 ± 1.7	62.9 ± 23.9
$AUC_{(0-28)}$	63.3 ± 17.9	1270 ± 602
Half-life (days)	19.2 ± 7.6	33.4 ± 14.8

Units for C_{max} for cytomegalovirus = AU/mL, for H. influenza B = mg/mL

Units for AUC for cytomegalovirus = days*AU/mL, for H. influenza B = (days*mg/L)

Trough Levels of IgG Subclasses:

IgG1 Antibodies: A total of 29 subjects provided data on trough levels of IgG1 antibodies on prior IVIG (before screening visit), and median trough levels of IgG1 antibodies on prior IVIG 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 (both visits prior to starting Gammaplex). During the course of treatment with Gammaplex, 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). Changes in levels of IgG1 antibody compared with prior IVIG treatment were calculated for the 29 subjects with data relating to prior IVIG treatment. During the course of treatment with Gammaplex, median changes from prior IVIG in this sub-group of subjects ranged from -39.0 mg/dL (visit 12) to +33.5 mg/dL (visit 4).

IgG2 Antibodies: A total of 29 subjects provided data on trough levels of IgG2 antibodies on prior IVIG (before screening visit), and median trough levels of IgG2 antibodies on prior IVIG 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 (both visits prior to starting Gammaplex). During the course of treatment with Gammaplex, 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). Changes in levels of IgG2 antibody compared with prior IVIG treatment were calculated for the 29 subjects with data relating to prior IVIG treatment. During the course of treatment with Gammaplex, median changes from prior IVIG in this sub-group of subjects ranged from -37.3 mg/dL (visit 12) to -5.25 mg/dL (visit 7).

IgG3 Antibodies: A total of 29 subjects provided data on trough levels of IgG3 antibodies on prior IVIG (before screening visit), and median trough levels of IgG2 antibodies on prior IVIG 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 (both visits prior to starting Gammaplex). During the course of treatment with Gammaplex, median trough levels of IgG3 antibodies generally remained in the region of 2l to 25 mg/dL, with a range from 22.1 mg/dL (at visit 12) to 24.9 mg/dL (at visit 13). Changes in levels of IgG3 antibody compared with prior IVIG treatment were calculated for the 29 subjects with data relating to prior IVIG treatment. During the course of treatment with Gammaplex, median changes from prior IVIG in this sub-group of subjects ranged from -1.38 mg/dL (visit 6) to + 1.60 mg/dL (visit 4).

IgG4 Antibodies: A total of 29 subjects provided data on trough levels of IgG4 antibodies on prior IVIG (before screening visit), and median trough levels of lgG4 antibodies on prior IVIG 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 (both visits prior to starting Gammaplex). During the course of treatment with Gammaplex, 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 IVIG treatment were calculated for the 29 subjects with data relating to prior IVIG treatment. During the course of treatment with Gammaplex, median changes from prior IVIG in this sub-group of subjects ranged from -11.7 mg/dL (visit 12) to -6.30 mg/dL (visit 4).

Comment

Any assessment of the clinical relevance of half-life measurements in this study should be viewed with caution. Although half-life estimates were provided for total IgG and the specific antibodies, drug elimination half-lives should be measured over a minimum period of at least 3 half-life intervals. However, the short dosing intervals relative to the long half-lives in this clinical trial do not permit the accurate assessment of half-life.