CLINICAL PHARMACOLOGY FINAL REVIEW MEMO
Division of Hematology
Office of Blood Review & Research

STN   125389

Product: Biotest Immune Globulin Intravenous (Human) 10% (Biotest-IVIG
                   10%); Trade Name, Bivigam

Sponsor: Biotest Pharmaceuticals Corporation
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Study Report: OPEN-LABEL, PHASE III SAFETY, EFFICACY, AND
                   PHARMACOKINETIC STUDY OF NABI-IGIV 10% [IMMUNE
                   GLOBULIN INTRAVENOUS (HUMAN)] IN SUBJECTS WITH
                   PRIMARY IMMUNE DEFICIENCY DISORDERS (PIDD)

Study Number: Nabi-7101

Indication: Primary Immunodeficiency Disorders (PID)

Date Received: November 3, 2010

Reviewer: Harold Boxenbaum, Ph. D.
RPM: Pratibha Rana, M.S.
Through: Iftekhar Mahmood, Ph.D.

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(human), 10% (IGIV, 10%) administered intravenously or subcutaneously in subjects with
primary immunodeficiency diseases (PID).   6

INTRODUCTION

Biotest Pharmaceuticals was formed as part of the acquisition of Nabi Biopharmaceuticals' Biologics business unit by Biotest AG on December 4, 2007. As a result, the ownership of the Nabi-1720 clinical study was transferred to Biotest Pharmaceuticals (the Nabi study will be discussed in study section).

Immune Globulin Intravenous (IGIV) isolated from human plasma is an important treatment modality for a majority of patients with Primary Immune Deficiency Disorders (PIDD). IGIV has been available in clinical practice since about 1980. The introduction of an additional liquid IGIV product with a favorable protein concentration (10%) and absence of a sugar stabilizer would supplement existing IGIV supplies in the US, thereby reducing the risk of IGIV shortages that negatively impact the management of PID. Furthermore, 10% liquid preparations allow for reduced volume load with the corresponding benefit to patients and clinicians of reducing infusion time and associated costs.

CLINICAL PHARMACOLOGY LABELING CHANGES
(These are indicated by cross-marks [example] and yellow highlighting)

1.1 Mechanism of Action
BIVIGAM is a replacement therapy in the patients with primary antibody deficiencies (e.g., agammaglobulinaemia, hypogammaglobulinaemia, CVID, SCID).

The broad spectrum of neutralizing IgG antibodies against bacterial and viral pathogens and their toxins helps to avoid recurrent serious opportunistic infections. IgG antibodies are opsonins that increase phagocytosis and elimination of pathogens from the circulation. The mechanism of action has not been fully elucidated in PIDD.

In the clinical study assessing the efficacy and safety of BIVIGAM in 63 subjects with PIDD (*see Clinical Studies [14.1]*), serum concentrations of total IgG and IgG subclasses were measured in 21 subjects (ages 18 to 75) following the 4th infusion for the 5 subjects on the 3-week dosing interval and following the 5th infusion for the 16 subjects on the 4-week dosing interval. The dose of BIVIGAM used in these subjects ranged from 300 mg/kg to 800 mg/kg. After the infusion, blood samples were taken until Day 21 and Day 28 for the 3-week and 4-week dosing intervals, respectively. Table 3 summarizes the Total IgG Pharmacokinetic Parameters of BIVIGAM, based on serum concentrations of total IgG.

Table 3. Total IgG Pharmacokinetic Parameter Estimates (PK Population)

Parameters	3-week cycle (n = 5)		4-week cycle (n = 16)		Total (n = 21)	
	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%
C_{max} (mg/dL)	2184 (293)	13.4	2121 (425)	20.0	2136 (391)	18.3
T_{max} (h) [a]	4.05 (2.7 – 26.1)	NA	3.5 (2.6 – 78.6)	NA	3.5 (2.6 – 78.6)	NA
AUC_{tau} (h*mg/dL)	668,173 (118,197)	17.7	852,213 (155,333)	18.2	806,203 (165,545)	20.5
$t_{1/2}$ (d)	19.6 (4)	21.1	33.5 (10.7)	32.0	30.0 (11.2)	37.5
CL (mL/kg/d)	1.97 (0.22)	11.4	1.41 (0.46)	32.8	1.55 (0.48)	30.9

==Please calculate volume of distribution at steady state (Vss) and mean residence time (MRT).==

AUC_{tau} = area under the serum concentration versus time curve, with tau = end of the dosing interval; CL = total body clearance; C_{max} = maximum concentration; CV = coefficient of variation; n = number of subjects; NA = not applicable; SD = standard deviation; T_{max} = time of maximum concentration; $t_{1/2}$ = terminal half-life; ~~Vz = volume of distribution.~~

[a] Median and Range ~~given~~.

The median half-life of BIVIGAM was 30 days for the 21 subjects in the pharmacokinetic subgroup.

RECOMMENDATION

From a pharmacokinetics perspective, this study is acceptable for adult patients.

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STUDY TITLE: TOLERABILITY AND PHARMACOKINETIC COMPARISON OF IMMUNE GLOBULIN INTRAVENOUS (HUMAN), 10% (IGIV, 10%) ADMINISTERED INTRAVENOUSLY OR SUBCUTANEOUSLY IN SUBJECTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PID)

OBJECTIVES

The objectives of the study were to evaluate the safety, efficacy, and pharmacokinetics of Nabi IGIV 10% in patients with PID.

INVESTIGATIONAL PLAN:

This was an open-label study conducted at 15 study centers. A total of 63 subjects were enrolled in the study, similar numbers of men and women with a mean age of 41 years. Most subjects were non-elderly adults (70%) between 18 and 64 years of age, but there were also a number of other age groups: 4 children (between 6 to 11 years of age), 6 adolescents (between 12 and 17 years of age), and 9 elderly subjects (≥65 years of age). The oldest subject was 75 years of age. Although pediatric subjects were enrolled (children, ages 6 – 11 years and adolescents, ages 12-17 years), they declined to participate in the PK phase of the study. The sponsor noted that enrolling pediatric subjects in a study of this nature was difficult, since these are rare conditions. There were 17 subjects with a 3-week cycle and 46 subjects with a 4-week cycle.

The total duration of the study was expected to be 21 to 27 months. The enrollment period was expected to be 6-12 months. Individual subjects were dosed every 3 to 4 weeks for approximately 12 months, with an observation period of approximately 15 months.

TREATMENTS ADMINISTERED

All subjects enrolled in the study received Nabi-IGIV 10% administered by means of an infusion pump for precise infusion rates at a dose of 300-800 mg/kg per infusion. Infusions were administered at 3- or 4-week intervals, depending on the subject's previous IgG replacement schedule. The initial infusion rate was 0.3 mL/kg/hr (30 mg/kg/hr) for 10 minutes. If this rate was well tolerated, the rate could have been increased to 0.5 mL/kg/hr (50 mg/kg/hr) for 20 minutes. If the subject continued to show no signs of intolerance, the rate could have been gradually increased every 20 minutes by 0.5 mL/kg/hr to the typical rate a subject was accustomed to receiving or a maximum tolerated rate up to 3.5 mL/kg/hr (350 mg/kg/hr). In this way, infusion rates were individualized for each subject. Infusion time was not to exceed 8 hours.

Doses were adjusted during the study to maintain trough total IgG concentrations >500 mg/dL. This was accomplished by targeting a trough concentration of ≥600 mg/dL. Proportional changes in the next dose were employed (for example, if a trough was 400 mg/dL, the next dose was 50% higher).

If a non-life-threatening AE occurred during an infusion, the rate could have been adjusted to one-half of the rate at the time of AE onset or to a "keep vein open" rate until symptoms subsided. Following the first infusion, the highest tolerated rate achieved at the first infusion was to be the target for subsequent infusions. Infusion rates higher than this target rate were only allowed under direct supervision and approval of the investigator.

PHARMACOKINETIC ANALYSES

For all subjects, blood samples were collected prior to the start of each infusion and at the final clinical visit for determination of total IgG with IgG subclasses (IgG1, IgG2, IgG3 and IgG4). Additionally samples for all subjects were collected prior to the start and 15 to 30 minutes after the end of infusions 1, 4, 8 and 12 for determination of total IgG with IgG subclasses and specific antibodies against pneumococcal capsular polysaccharide (types 4, 6B, 9V, 14, 18C, 19F, 23F), *H. influenzae* B, and tetanus.

In a subset of subjects, blood samples were collected for PK profile assessments at the 4th (or 5th for the 3-week schedule) IgG infusion day (or subsequent infusion day). In addition, as per Protocol Amendment 3, at certain study sites, during a PK extension portion of the study conducted on subjects that did not participate in the original PK portion of the study, PK parameters were assessed at infusion 13 for subjects on the 4 week infusion cycle or at Infusion 17 for subjects on the 3-week infusion cycle. Sampling times used for the extensive PK profiling included the following:

- predose sample taken before the start of the infusion
- 15 minutes after the end of infusion
- 1 hour (± 5 minutes) after the end of infusion
- 24 hours (± 1 hour) after the end of infusion
- 3 days (± 6 hours) after the end of infusion
- 7 days (± 1 day) after the end of infusion
- 14 days (±1 day) after the end of infusion
- 21 days (±1 day) after the end of infusion
- 28 days (±1 day) after the end of infusion: for 4-week infusion

These profile samples were assayed to determine the concentrations of total IgG and specific antibodies against pneumococcal capsular polysaccharide (types 4, 6B, 9V, 14, 18C, 19F, 23F), *H. influenzae* B, and tetanus. The serum levels were determined by ------- --------------------------(b)(4)---

All PK parameters were estimated by non-compartmental analysis (------------------------- --------------(b)(4)---------------------), and summary statistics values were determined using SAS version 8.2 or later).

PK parameters based on total serum IgG, anti-pneumococcal capsular polysaccharide (including subtypes), anti-*H. influenzae* B, and anti-tetanus levels, were calculated. The IgG subclass levels were not included in the profile parameter estimates, although trough levels were determined prior to each infusion.

PHARMACOKINETIC EVALUATION

For determination of PK parameters, serial blood sampling over an extended time period was required.   This phase of the study was only conducted with volunteers. This volunteer population included 21 subjects: 5 subjects with the 3-week cycle and 16 subjects with the 4-week cycle. None of the 10 pediatric subjects agreed to participate in the profiling section of the protocol, although peak and trough data were collected for pediatric patients, as well as adult subjects, at infusions 1, 4, 8 and 12.

Actual sampling times were used instead of scheduled sampling times. There was a rapid rise in total IgG during the infusion period for both cycles, attaining similar mean maximum concentrations at the end of the infusion. The concentration-time curves for the 2 cycles were similar, with values returning to pre-infusion at around Days 14 - 21. Variation between the 2 cycles was well within the SD for each population. Linear and semilogarithmic plots of IgG mean serum concentrations over both cycle schedules looked similar over time (see especially the linear plot (below), where differences are more noticeable).

Mean linear and semilogarithmic IgG serum concentration – time plots are illustrated below. Semilogarithmic plot data from the 3 and 4 week cycles were pooled.

Figure 1. Linear plot of mean total serum IgG concentrations (mg/dL) by treatment cycle
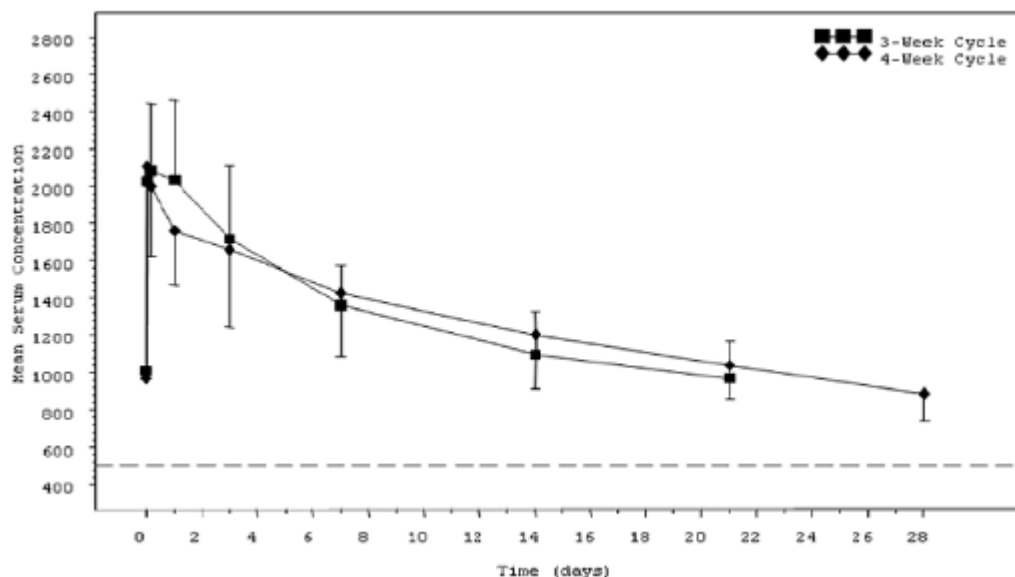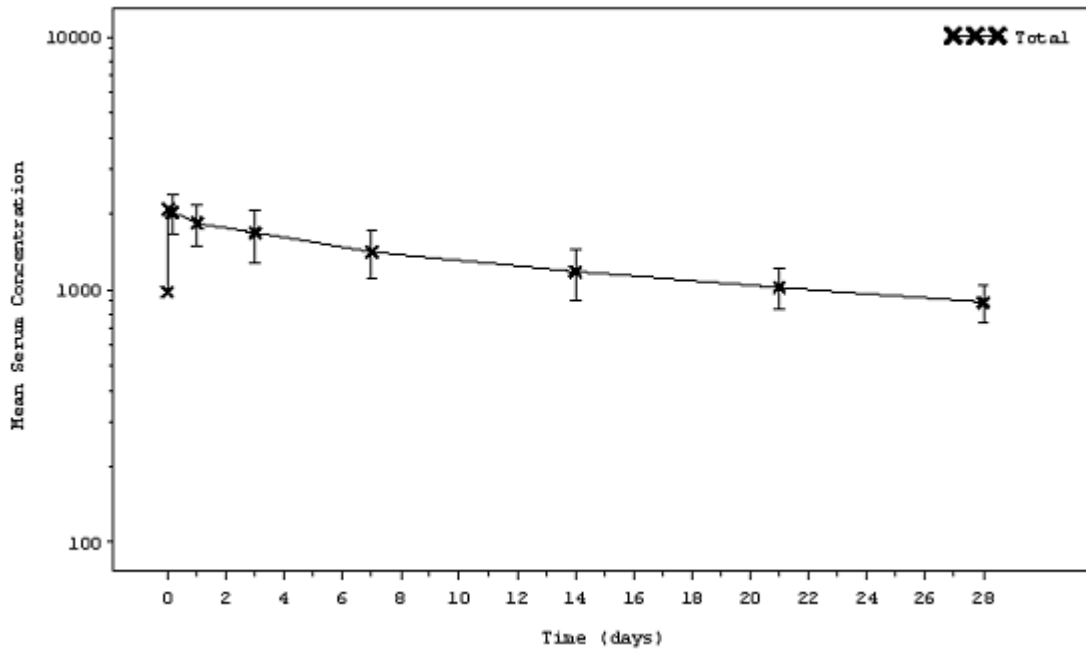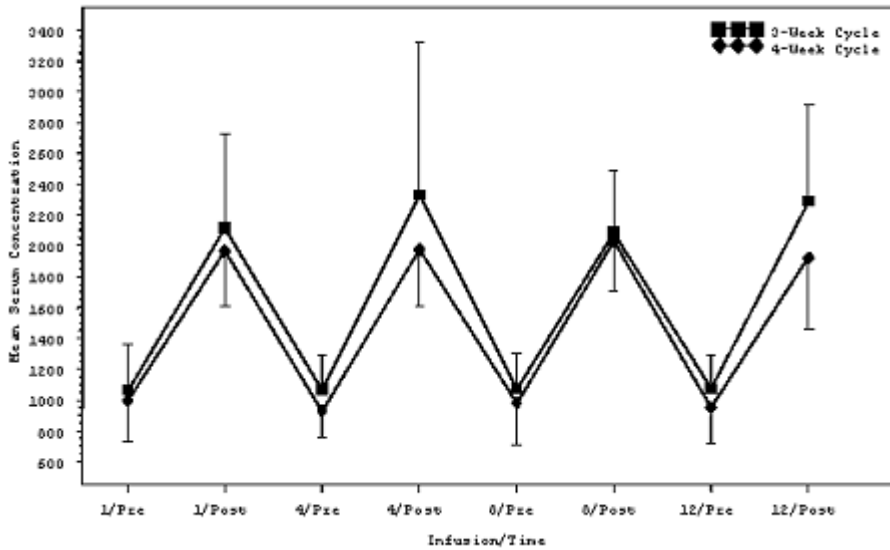
Figure 2. Log-linear plot of overall mean serum concentrations from profiled infusions of total IgG (mg/dL)

Pre- and post-infusion concentrations were determined at infusions 1, 4, 8 and 12 for all subjects, and mean plots are illustrated below:
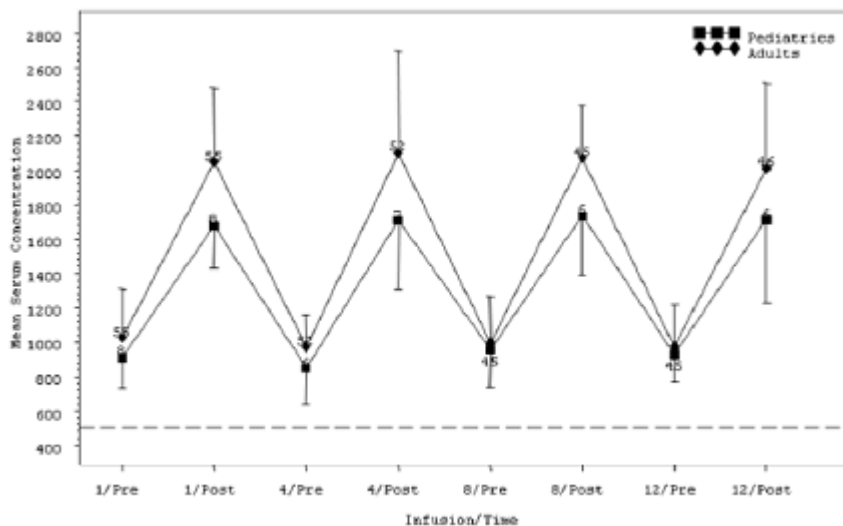
Figure 3. Mean trough/peak (pre-/post infusion) serum IgG concentrations (mg/dL) for infusions 1, 4, 8 and 12 by treatment cycle

The trough (pre-) and peak (post) serum IgG concentrations were similar for the 2 treatment cycles, and any variation was well within the standard deviation for each population. Mean trough concentrations were well above the minimum acceptable trough concentration of 500 mg/dL.
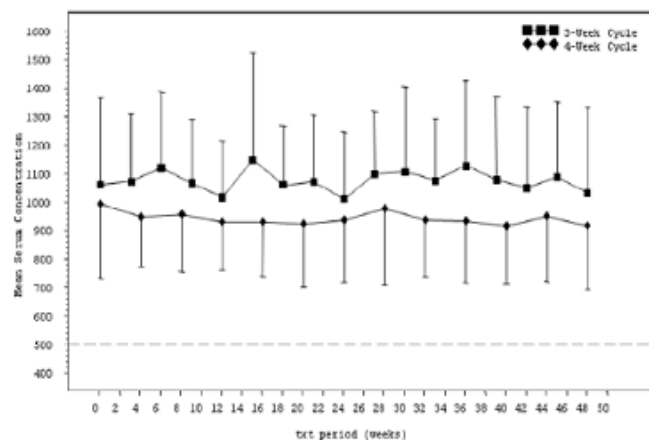
Immediately below are plots of mean trough/peak (pre/post) serum IgG concentrations for infusions 1, 4, 8, and 12 in pediatric and adults patients:

Figure 4. Mean trough/peak (pre-/post infusion) serum IgG concentrations (mg/dL) for infusions 1, 4, 8 and 12 in pediatric and adult subjects

Mean trough (pre-infusion) concentrations for total IgG were determined throughout the study. See the figure immediately below for mean concentrations:

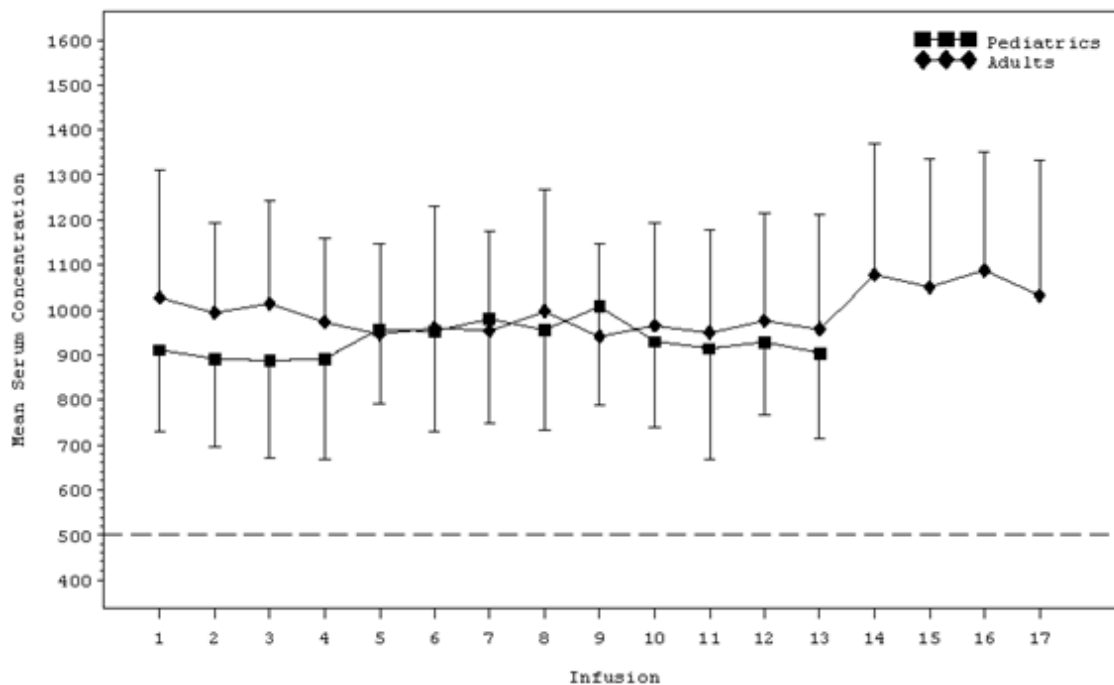Figure 5. Mean serum trough concentrations of total IgG (mg/dL) by treatment cycle

Although the mean trough values for the 3-week cycle were generally higher than the 4-week cycle (about 10-15%, based upon visual inspection), these differences were accompanied by large standard deviations for both groups.

Trough concentrations were reasonably consistent throughout the study for both treatment cycles, and mean trough concentrations were well above 500 mg/dL for both treatment cycles as well. This included both pediatric and adult subjects at all time points. Only a single trough concentration below the target value of 500 mg/dL was measured (487 mg/dL) at infusion with the 4-week cycle.

There was no indication for the PK parameters of any clinically relevant differences between the 3 and 4-week treatment cycles. The Cmax and Tmax were similar for the 2 treatment groups, while the AUC(tau) and T-1/2 were somewhat higher for the 4-week group, as expected.

The figure below illustrates mean serum trough concentrations for total IgG (mg/dL) in pediatric and adult subjects.

Figure 6. Mean serum trough concentrations of total IgG (mg/dL) in pediatric and adult subjects

None of the 10 pediatric subjects (children, ages 6 – 11 years) and adolescents (ages 12 – 18 years) agreed to participate in the "PK population," i.e., for the full PK serial profiling. Consequently, Table 1 shown below does not include data from the pediatric population

Table 1. Total IgG pharmacokinetic parameter estimates – PK population

Statistic	3-week cycle (N = 5)		4-week cycle (N = 16)		Total (N = 21)	
	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%
C_{max} (mg/dL)	2184.00 (293.309)	13.4	2121.88 (425.256)	20.0	2136.67 (391.884)	18.3
T_{max} [a] (h)	4.050 (2.67 – 26.13)	NA	3.475 (2.58 – 78.58)	NA	3.500 (2.58 – 78.58)	NA
AUC_{tau} (h*mg/dL)	668,173.6 (118,197.53)	17.7	852,213.4 (155,333.93)	18.2	806,203.4 (165,545.09)	20.5
$t_{½}$ (day)	19.596 (4.1390)	21.1	33.484 (10.7244)	32.0	30.012 (11.2437)	37.5
CL (mL/kg/day)	1.97096 (0.224191)	11.4	1.41088 (0.462731)	32.8	1.55090 (0.479861)	30.9
Vz (L/kg)	0.05587 (0.013922)	24.9	0.06402 (0.015180)	23.7	0.06198 (0.014956)	24.1

AUC = area under the plasma concentration versus time curve; CL = total body clearance; C_{max} = maximum concentration; CV = coefficient of variation; NA = not applicable; SD = standard deviation; T_{max} = time of maximum concentration; $t_{½}$ = terminal half-life; Vz = volume of distribution.
[a] Median and range, calculated from start of infusion.

The Cmax and the Tmax values were similar for the 2 treatment cycles. The t½ for the total population was estimated at about 30 days. The AUCtau and t½ values were slightly higher for the 4-week compared to the 3-week treatment cycle, as expected. The AUCtau of the 4-week cycle measured AUC to 28 days whereas the 3-week cycle up to 21 days, so the 4-week cycle should have a higher AUC. Despite the smaller number of subjects in the 3-week treatment cycle group, the variability within the groups was generally lower in the 3-week group, probably a reflection of the much broader age range in the 4-week cycle group.

There was a rapid rise in total IgG during the infusion period for both cycles, attaining similar mean maximum concentrations at the end of the infusion. The concentration-time curves for the 2 cycles were similar with values returning to pre-infusion at around Days 14 - 21. Variation between the 2 cycles was well within the standard deviation for each population.

Trough concentrations were maintained throughout the study for both treatment cycles, and mean trough concentrations were well above the minimum acceptable trough concentration of 500 mg/dL for both treatment cycles and pediatric as well as adult subjects at all time points. There was no indication from the PK parameters of any clinically relevant difference between the 3-week and 4-week treatment cycles. The Cmax and the Tmax were similar for the 2 treatment cycles while the AUC(tau) and T-1/2, were slightly higher for the 4-week compared to the 3-week treatment cycle.

Below are average trough concentrations (and standard deviations) of total IgG and its subclasses, calculated from the 4th dose for the 4-week dosing cycle, and the 5th dose for the 3 week dosing cycle. These trough times (doses) correspond to those used for characterization of the full PK profile (see Table 1) above.

Table 2. Trough total IgG and subclasses (IgG1, IgG2, IgG3 and IgG4) concentrations for patients on 3 and 4 week dosing. Troughs are those prior to the 4th dose for 4 week dosing, and prior to the 5th dose in 3 week dosing

Entity	Serum Conc (mg/dL) ± SD 4-Week Dosing: Baseline	Serum Conc (mg/dL) ± SD 4-Week Dosing: 4th Dose	Serum Conc (mg/dL) ± SD 3-Week Dosing: Baseline	Serum Conc (mg/dL) ± SD 3-Week Dosing: 5th Dose
Total IgG	1001 ± 262	927 ± 171	1062 ± 304	1018 ± 197
IgG1	620 ± 178	570 ± 138	637 ± 181	618 ± 129
IgG2	301 ± 107	265 ± 63.3	332 ± 151	286 ± 56.5
IgG3	27.7 ± 25.6	27.9 ± 27.2	26.8 ± 9.96	26.6 ± 9.36
IgG3	23.8 ± 19.8	20.0 ± 14.9	28.9 ± 22.8	30.2 ± 27.2

Trough (baseline) serum concentrations following 3 and 4 week dosing were quite similar.

Below are listed antibody concentrations following IgG administration:

Table 3. Antibody parameters (± SD) (* indicates a median value and
** = Not Reliable, since reported T-1/2 was several hundred years)

Parameters	3-week cycle	4-week cycle
S. pneumoniae IgG		
Serotype 1		
Cmax (µg/mL)	5.3 ± 0.8	5.9 ± 3.3
Tmax (hrs)	5.4*	3.4*
AUC(0-t) (IU x hr/mL)	1448 ± 413	2414 ± 2173
Half-life (days)	16 ± 3	84 ± 180
Serotype 2		
Cmax (µg/mL)	3.2 ± 0.5	5.9 ± 6.8
Tmax (hrs)	5.4*	3.5*
AUC(0-t) (IU x hr/mL)	899 ± 158	1714 ± 975
Half-life (days)	16 ± 5	36 ± 25
Serotype 3		
Cmax (µg/mL)	3.6 ± 1.0	4.0 ± 1.5
Tmax (hrs)	5*	4*
AUC(0-t) (IU x hr/mL)	982 ± 166	1596 ± 747
Half-life (days)	19 ± 4	39 ± 28
Serotype 4		
Cmax (µg/mL)	1.2 ± 0.2	1.7 ± 0.7
Tmax (hrs)	4*	3*
AUC(0-t) (IU x hr/mL)	341 ± 45	701 ± 277
Half-life (days)	18 ± 1	29 ± 14
Serotype 5		
Cmax (µg/mL)	14 ± 3	17 ± 7
Tmax (hrs)	4*	3*
AUC(0-t) (IU x hr/mL)	4093 ± 739	7121 ± 4219
Half-life (days)	16 ± 3	35 ± 23
Serotype 6B		
Cmax (µg/mL)	10.1 ± 1.8	11.0 ± 5.2
Tmax (hrs)	26*	3*
AUC(0-t) (µg x hr/mL)	2664 ± 601	4028 ± 1501
Half-life (days)	18 ± 6	32 ± 23
Serotype 7F		
Cmax (µg/mL)	13.8 ± 4.3	17.5 ± 8.0
Tmax (hrs)	4	3
AUC(0-t) (µg x hr/mL)	3424 ± 829	6855 ± 2679
Half-life (days)	14 ± 2	38 ± 22
Serotype 8		
Cmax (µg/mL)	8.5 ± 2.4	9.3 ± 4.1
Tmax (hrs)	5*	3*
AUC(0-t) (IU x hr/mL)	2235 ± 549	3326 ± 1707
Half-life (days)	16 ± 4	28 ± 26

Table 3 (continued) Parameters (± SD) for antibodies (* indicates a median value)

Parameters (continued)	3-week cycle	4-week cycle
S. pneumoniae IgG		
Serotype 9N		
Cmax (µg/mL)	8.1 ± 2.7	8.8 ± 4.1
Tmax (hrs)	4*	3*
AUC(0-t) (IU x hr/mL)	1959 ± 480	3161 ± 1515
Half-life (days)	14 ± 2	27 ± 19
Serotype 9V		
Cmax (µg/mL)	7.1 ± 1.4	7.3 ± 2.2
Tmax (hrs)	4*	4*
AUC(0-t) (IU x hr/mL)	1966 ± 262	2714 ± 992
Half-life (days)	15 ± 3	33 ± 19
Haemophilus Influenzae B		
Cmax (µg/mL)	6.1 ± 1.3	6.8 ± 1.65
Tmax (hrs)	26*	3*
AUC(0-t) (IU x hr/mL)	1820 ± 467	2535 ± 1132
Half-life (days)	17 ± 5	NR
Tetanus Toxoid IgG		
Cmax (IU/mL)	7.0 ± 0.01	7.0 ± 0.1
Tmax (hrs)	3	3
AUC(0-t) (IU x hr/mL)	2804 ± 895	3420 ± 686
Half-life (days)	NR**	NR**

Conclusions:

There was a rapid rise in total IgG during the infusion period for both cycles attaining similar mean maximum concentrations at the end of the infusion. The concentration-time curves for the 2 cycles were similar, with values returning to pre-infusion at around Days 14 to 21. Variation between the 2 cycles was well within the standard deviation for each population. The IgG subclass, trough concentrations for the 3 and 4 week cycles were similar.

Trough concentrations were maintained throughout the study for both treatment cycles, and mean trough concentrations were well above the minimum acceptable trough concentration of 500 mg/dL for both treatment cycles and pediatric as well as adult subjects at all time points. Only a single trough concentration below the target value of 500 mg/dL was measured (487mg/dL) at Infusion 6 with the 4-week cycle.