

# CLINICAL PHARMACOLOGY REVIEW

Division of Hematology  
Office of Blood Review & Research

## STN 125350/0

Product: Immune Globulin Subcutaneous (Human), 20% Liquid

Sponsor: CSL Behring

Indication: For the treatment of Primary Immunodeficiency (PID)

Date Received: April 30, 2009

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## INTRODUCTION

The objective of the current study was to evaluate the efficacy, tolerability, safety, and pharmacokinetics (PK) of IgPro20 in subjects with Primary Immunodeficiency (PID). IgPro20 is a 20% IgG solution that is being developed as an intended successor to CSL Behring's currently marketed IGSC product Vivaglobin, a 16% IgG solution. IgPro20 has nearly the same formulation as its parent product Privigen (IgPro10, a 10% IgG solution), which is marketed as an IGIV treatment for PID and chronic immune thrombocytopenic purpura (ITP). Use of a 20% IGSC formulation reduces the infusion volume and duration of infusion compared to 10% IGSC preparations used in Europe and elsewhere in the world, and to the 16% IGSC, Vivaglobin, currently used for replacement therapy.

Individual serum IgG levels during IGSC treatment with IgPro20 in the current study were compared to individual target IgG levels derived from IGIV treatment with Privigen in the same subjects participating in preceding studies. In this way, a dose adjustment coefficient (DAC) could be derived to ensure that serum IgG trough levels achieved during treatment with IgPro20

were comparable to the average daily serum IgG levels achieved previously during treatment with Privigen. Based on the experience with Vivaglobin, the initial weekly IgPro20 dose in the current study was set at 1.30 times the subjects' previous weekly equivalent Privigen dose. At the end of a 12-week wash-in/wash-out period, the individual IgPro20 doses were adjusted to achieve the target IgG level for the subsequent 12-month efficacy period of the study, during which the efficacy and safety of IgPro20 were investigated. This review focuses only on the results of the PK sub-study.

## CLINICAL PHARMACOLOGY LABELING COMMENTS

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#### 12.1 Mechanism of Action

IgPro20 supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The mechanism of action in Primary Immunodeficiency (PID) has not been fully elucidated.

#### 12.2 Sponsor: What happened to 12.2?

#### 12.3 Pharmacokinetics

The pharmacokinetics (PK) of IgPro20 was evaluated in a PK sub-study of subjects with PID participating in the 15-month efficacy and safety study (*see Clinical Studies [14]*). All PK subjects were treated previously with Privigen<sup>®</sup>, Immune Globulin Intravenous (Human), 10% Liquid and were switched to weekly subcutaneous treatment with IgPro20. After a 3-month wash-in/wash-out period, doses were adjusted individually with the goal of providing a systemic serum IgG exposure (area under the IgG serum concentration vs time curve; AUC) that was not inferior to the AUC of the previous weekly-equivalent IGIV dose. Table 7 summarizes the PK parameters for 18 subjects in the sub-study ~~including dosing and serum IgG peak and trough levels~~ following treatment with IgPro20 and IGIV.

~~Table 7: Additional PK Parameters~~

**Table 7: Pharmacokinetics parameters of IgPro20 and IGIV**

	<b>IgPro20</b>	<b>IGIV* (Privigen<sup>®</sup>)</b>
Number of subjects	18	18
Dose*		
Mean	228 mg/kg bw	152 mg/kg bw
Range	141-381 mg/kg bw	86-254 mg/kg bw
IgG peak levels		
Mean	1616 mg/dL	2564 mg/dL
Range	1090-2825 mg/dL	2046-3456 mg/dL
IgG trough levels		
Mean	1448 mg/dL	1127 mg/dL
Range	952-2623 mg/dL	702-1810 mg/dL
AUC (day x mg/dL)**	10560 7210-18670	10320 8051-15530

bw, body weight.

\* For IGIV: weekly-equivalent dose.

\*\* AUC standardized to a 7-day period.

For the 19 subjects completing the wash-in/wash-out period, the average dose adjustment for IgPro20 was 153% (range: 126% to 187%) of the previous weekly-equivalent IGIV dose. After 12 weeks of treatment with IgPro20 at this individually adjusted dose, the final steady-state AUC determinations were made in 18 of the 19 subjects. The geometric mean ratio of the steady-state AUCs, standardized to a weekly treatment period, for IgPro20 vs IGIV treatment was 1.002 (range: 0.77 to 1.20) with a lower-90% confidence limit interval of 0.951-1.055 for the 18 subjects.

~~An additional assessment of the PK sub-study was to determine the ratio of serum IgG trough levels with IgPro20 (IGSC) compared to the previous trough levels with IGIV that were associated with matching AUCs.~~

In an additional PK sub-study, the ratio of serum IgG trough levels with IgPro20 (IGSC) compared to the previous trough levels with IGIV that were associated with matching AUCs was determined. It was found that the IgG trough levels during treatment with IgPro20 were 1.3 times higher than the preceding trough levels during treatment with IGIV (Privigen<sup>®</sup>). This calculated IGSC: IGIV ratio of 1.3 ( $\pm 15\%$  of this value, or  $\pm 0.2$ ) can be used to assess ~~adequate~~ dosing with IgPro20 by providing a target IgG trough level based on previous trough levels with IGIV treatment. To confirm ~~adequate~~ appropriate dosing, the target trough level following steady-state IgPro20 treatment should be within the range of 1.1 to 1.5 times the previous steady-state trough levels with IGIV.

With IgPro20, peak serum levels are lower (1616 vs 2564 mg/dL) than those achieved with IGIV while trough levels are generally higher (1448 vs 1127 mg/dL). Subcutaneous administration results in relatively stable steady-state serum IgG levels when the product is dosed on a weekly basis.<sup>13,14</sup> After the subjects had reached steady-state with weekly administration of IgPro20, peak serum IgG levels were observed after a mean of 2.9 days (range: 0 to 7 days) in 18 subjects.

~~The serum IgG levels in subjects receiving weekly subcutaneous therapy with IgPro20 were relatively stable in contrast to serum IgG levels observed with monthly IGIV treatment (rapid peaks followed by a slow decline).~~

## **RECOMMENDATION**

The pharmacokinetic study design and analysis of IgPro20 is acceptable. The sponsor should incorporate the clinical pharmacology labeling of IgPro20 as suggested by the FDA.

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**Study Title:** A Phase III, Open-Label, Prospective, Multicenter Study of the Efficacy, Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20 in Subjects with Primary Immunodeficiency (PID).

The primary objective of the study was to evaluate whether the chosen subcutaneous (SC) dose regimen for IgPro20 was associated with steady-state area under the concentration-time curves (AUCs) for serum immunoglobulin (IgG) that were not inferior to those obtained with the previous intravenous (IV) dose regimen. The secondary objective was to determine the PK parameters AUC, maximum concentration ( $C_{max}$ ), time to reach maximum concentration ( $T_{max}$ ) for total serum IgG and serum concentrations of IgG subclasses, specific IgGs, and L-proline following the administration of IgPro20.

This was a prospective, open-label, multicenter, single-arm, Phase III study of IgPro20 in subjects with PID. The entire study consisted of a 12-week wash-in/wash-out period, followed by a 12-month efficacy period during which the efficacy and safety of IgPro20 were evaluated. A 2-part PK study was conducted in a subset of subjects. Of the 21 subjects who were included in the PK study, 19 subjects were included in Part I and 18 subjects were included in part II of the PK study. There were 11 males and 8 females in the study (10-60 years of age; four subjects were children between 6 and 16 years). During Part I of the PK study, 2 subjects were excluded due to protocol deviations of having been administered the wrong planned starting dose. One of the 19 subjects who completed Part I was excluded from Part II due to a protocol deviation of failure to measure the AUC of IgG at week  $28 \pm 1$ . Subjects had to have previously received IGIV therapy with Privigen at regular 3- or 4-week intervals for at least 3 months prior to starting treatment with IgPro20 in the current study, and to have had at least 3 documented serum  $C_{trough}$  measurements of  $\geq 5$  g/L during the previous 3 months on IGIV replacement therapy.

In Part I of the PK, at the end of the wash-in/wash-out period, serum IgG trough levels ( $C_{trough}$ ) were measured at weeks 9 to 12 of IgPro20 treatment and compared to the same individual's target IgG trough level ( $C_{target}$ ) determined during previous IGIV treatment with Privigen at steady-state, and an individual dose adjustment coefficient (DAC) was derived for adjusting the Immune Globulin Subcutaneous (Human) (IGSC, IgPro20) dose administered during the subsequent efficacy period. The weekly SC dose of IgPro20 for use in the efficacy period was adjusted based on individual DACs for subjects participating in the PK sub-study. Blood samples were taken at 30 to 10 minutes pre-infusion at weeks 9 to 12 (i.e., 4 samples).

$C_{target}$  was used for comparison with  $C_{trough}$  values obtained with IgPro20 treatment at the end of the wash-in/wash-out period and was derived from the AUC associated with Privigen infusion (AUCIV) in the following way:

$$C_{target} = (AUCIV / T_{period}) = (sAUC / 7)$$

Where  $T_{period}$  is the respective sampling period in which the AUC was estimated (time of last sample minus time of first sample).

In Part II of the PK study, after at least 12 weeks of treatment with the adjusted dose of IgPro20 in the efficacy period (at week  $28 \pm 1$ ), total serum IgG was measured at appropriate time points during one 7-day dosing interval to determine PK parameters, including the AUC standardized to 7 days (sAUC), to evaluate whether the adjusted dose of IgPro20 provided a non-inferior sAUC compared to the sAUC obtained with the previous IGIV dose, i.e., whether the systemic IgG exposure with IgPro20 was comparable to the previous systemic exposure with Privigen. Serum concentrations of IgG subclasses, specific IgGs, and L-proline were also determined at week  $28 \pm 1$ . The following PK parameters were measured in part II PK study:

Serum total IgG AUC,  $C_{\max}$ ,  $T_{\max}$ , and minimum concentration ( $C_{\min}$ )

Serum concentration of IgG subclasses: IgG1, IgG2, IgG3, IgG4

Serum concentration of specific IgGs: anti-measles, anti-CMV, anti-*Hemophilus influenzae* type B, anti-tetanus, and anti-*Streptococcus pneumoniae* (antibodies against 23 polysaccharides isolated from *S. pneumoniae*; the antigens are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F following Danish nomenclature), and serum concentrations of L-proline.

A total of 8 blood samples were taken within 7 days at the following time points: 30 to 10 minutes pre-infusion, 10  $\pm$  5 minutes before end of infusion, and 2  $\pm$  1 h, 1 day  $\pm$  8 h, 2 days  $\pm$  8 h, 3 days  $\pm$  8 h, 4 days  $\pm$  8 h, and 7 days  $\pm$  8 h post-infusion (before the next infusion). This series of blood samples was drawn once beginning at the infusions for weeks 27, 28, or 29 and ended one week later, before the next infusion.

IgPro20 was administered as an SC infusion at weekly intervals for approximately 15 months. During the initial 12-week wash-in/wash-out period, subjects received an individualized dose regimen of 1.30 times their weekly equivalent IGIV dose received in preceding studies with Privigen. In the 12-month efficacy period, the dose was adjusted on the basis of steady-state  $C_{\text{trough}}$  values at weeks 9 to 12, aiming to attain the individual  $C_{\text{target}}$  levels in serum that had been determined during previous IGIV treatment with Privigen.

The reference (historical) therapy was IGIV treatment with Privigen in preceding studies. Data obtained during earlier treatment with Privigen were used for calculating the initial IgPro20 dose during the wash-in/wash-out period as well as the  $C_{\text{target}}$  for IgPro20, and for evaluating the non-inferiority of systemic IgG exposure during treatment with the adjusted dose of IgPro20 in Part II of the PK study. Privigen is a marketed liquid IGIV at a concentration of 10%. In the preceding studies, Privigen was administered IV every 3 or 4 weeks using an individualized dose regimen of 200 to 800 mg IgG/kg body weight.

Standard validated methods were used for analyzing total IgG and IgG subclasses, specific IgGs and L-proline.

## Results

### Pharmacokinetics Part I:

The mean PK parameters for serum IgG at steady-state obtained during IGIV treatment with Privigen in the preceding studies are summarized in Table 1. For each subject, the serum IgG target trough level ( $C_{\text{target}}$ ) was derived by calculating the average daily IgG level from the AUC

measured during Privigen treatment. The mean  $C_{\text{trough}}$  value (measured as  $C_{\text{last}}$ ) during steady-state Privigen treatment was 11.37 g/L, and the mean  $C_{\text{target}}$  based on the average daily IgG level from the AUC measurement was 15.00 g/L.

**Table 1**  
**Summary of pharmacokinetic parameters for serum IgG at steady-state during IGIV treatment with Privigen during preceding studies ZLB03\_002CR and ZLB05 006CR (comparison of PK IGIV and PK Part I populations)**

Parameter	Mean (SD); median (range)	
	PK IGIV (N = 38)	PK Part I (N = 19)
$C_{\text{min}}$ (g/L)	10.58 (2.439) 10.28 (5.79-18.10)	11.35 (2.517) 10.95 (7.30-18.10)
$C_{\text{max}}$ (g/L)	24.21 (5.011) 24.20 (10.44-34.56)	26.03 (4.077) 24.97 (20.46-34.56)
sAUC (day × g/L)	98.72 (20.64) 95.24 (49.28-155.3)	105.0 (20.87) 94.70 (80.51-155.3)
$C_{\text{target}}$ (g/L)	14.10 (2.948) 13.61 (7.04-22.18)	15.00 (2.982) 13.53 (11.50-22.18)
$C_{\text{last}}$ (g/L)	10.68 (2.427) 10.32 (5.85-18.10)	11.37 (2.546) 11.93 (7.02-18.10)

$C_{\text{last}}$  = Last measured concentration;  $C_{\text{max}}$  = Maximum concentration;  $C_{\text{min}}$  = Minimum concentration;  $C_{\text{target}}$  = Target trough concentration; IGIV = Immune Globulin Intravenous (Human); N = Total number of subjects in population; PK = Pharmacokinetic; sAUC = Area under the concentration-time curve standardized to a 7-day period; SD = Standard deviation.

Before the infusions at weeks 9 to 12 during the wash-in/wash-out period, IgG  $C_{\text{trough}}$  values were measured and used to calculate the mean steady-state (actual) trough level for IGSC treatment with IgPro20. Comparing the target ( $C_{\text{target}}$ ) and actual ( $C_{\text{actual}}$ ) trough levels, the dose adjustment coefficient (DAC) was calculated individually for each subject in the PK Part I study. The mean trough level ( $C_{\text{actual}}$ ) determined at weeks 9 to 12 was 13.17 g/L, while the mean target trough level ( $C_{\text{target}}$ ) was 15.00 g/L (Table 2). On the basis of these data, to derive the adjusted dose for use during the efficacy period, the weekly dose adjustment increment was calculated for each subject using the following formula:

$$D \text{ (mg/kg)} = (C_{\text{target}} - C_{\text{actual}}) / 5.5 \text{ mg/dL}$$

Where  $C_{\text{target}}$  and  $C_{\text{actual}}$  are target and actual  $C_{\text{trough}}$  values of IgG (mg/dL) obtained after IGIV with Privigen and IGSC treatment with IgPro20.

The above formula for dose adjustment was based on the trough level response of 5.5 mg/dL to a dose of 1 mg/kg/week (or 550 mg/dL for 100 mg/kg/week) observed in a case collection of PID subjects with at least 3 months of continuous treatment with IGSC.

**Table 2**  
**Dose adjustment (PK part I)**

Parameter	PK Part I (N = 19)	
	Mean (SD)	Median (range)
IV weekly dose <sup>a</sup> (mg/kg bw)	156.1 (52.22)	152.5 (86-254)
$C_{\text{target}}$ (g/L)	15.00 (2.982)	13.53 (11.50-22.18)
$C_{\text{actual}}$ (g/L)	13.17 (2.715)	12.07 (8.51-19.69)
Dose adjustment increment (mg/kg bw)	33.21 (20.89)	30.27 (-7.70-66.23)
SC adjusted dose (mg/kg bw)	234.4 (74.16)	205.2 (141.1-381.5)
SC : IV ratio (DAC)	1.531 (0.156)	1.508 (1.26-1.87)

$C_{\text{actual}}$  = Average of 4 trough levels during Weeks 9 to 12;  $C_{\text{target}}$  = Target trough concentration; DAC = Dose adjustment coefficient; IV = Intravenous; N = total number of subjects; SC = Subcutaneous; SD = Standard deviation.

<sup>a</sup> Weekly equivalent dose.

### Pharmacokinetics Part II:

The mean total serum IgG levels in PK part II study measured during one dosing interval at steady-state (week 28 ± 1) are shown in Figure 1. Maximum mean concentrations were achieved at 2 to 4 days after dosing. The PK parameters for serum IgG at steady-state after treatment with the adjusted dose of IgPro20 (week 28 ± 1) are summarized in Table 3.

The mean  $C_{\text{min}}$  of serum IgG during IGSC treatment with IgPro20 (13.70 g/L) was higher than during IGIV treatment with Privigen in the preceding studies (11.24 g/L). The mean  $C_{\text{max}}$  for serum IgG was lower during IgPro20 treatment (16.16 g/L) than during Privigen treatment (25.64 g/L). The mean IgG  $C_{\text{trough}}$  value ( $C_{\text{last}}$ ) during steady-state IGSC treatment with IgPro20 (14.48 g/L) was 29% higher than after IGIV treatment with Privigen in the preceding studies ( $C_{\text{last}}$  = 11.27 g/L).

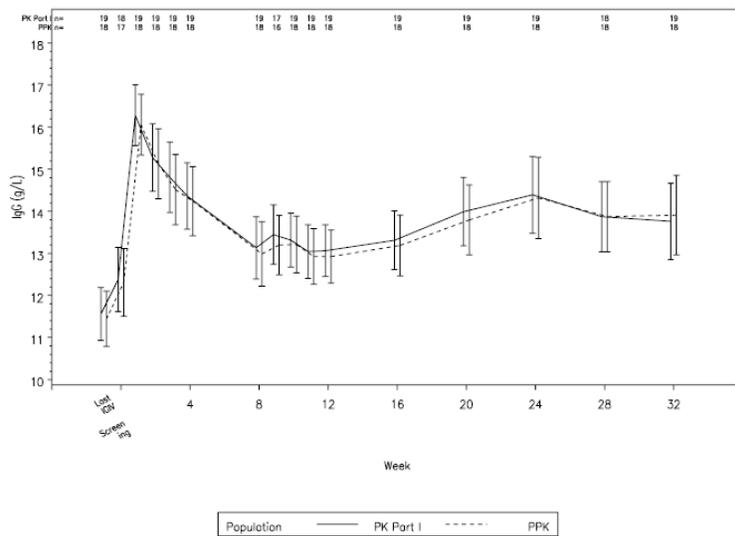
**Table 3**  
**Steady-state pharmacokinetics of serum IgG after treatment with IGSC (current study) and IGIV (studies ZLB03\_002CR and ZLB05\_006CR) (PPK population)**

Parameter	Mean (SD); median (range)	
	IGSC (IgPro20) (N = 18)	IGIV (Privigen) (N = 18)
$C_{min}$ (g/L)	13.70 (4.388)	11.24 (2.543)
	12.05 (9.31-24.86)	10.66 (7.30-18.10)
$C_{max}$ (g/L)	16.16 (4.930)	25.64 (3.825)
	14.02 (10.90-28.25)	24.73 (20.46-34.56)
$C_{last}$ (g/L)	14.48 (4.278)	11.27 (2.582)
	12.89 (9.52-26.23)	11.50 (7.02-18.10)
$T_{max}$ (day)	2.933 (1.773)	ND
	3.118 (0-6.97)	
sAUC (day × g/L)	105.6 (31.56)	103.2 (20.00)
	92.06 (72.10-186.7)	94.42 (80.51-155.3)

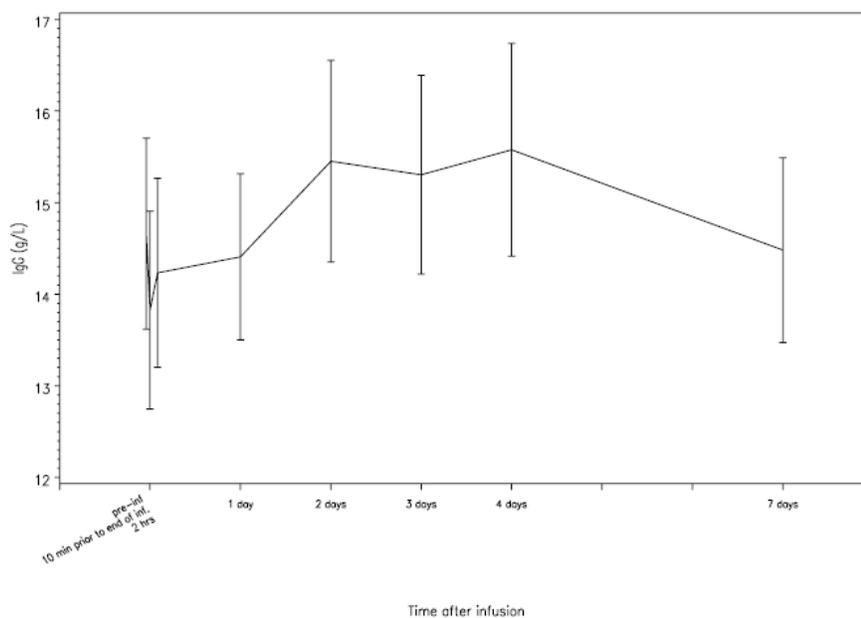
$C_{last}$  = Last measured concentration;  $C_{max}$  = Maximum concentration;  $C_{min}$  = Minimum concentration; IGIV = Immune Globulin Intravenous (Human); IGSC = Immune Globulin Subcutaneous (Human); N = Total number of subjects in population; ND = Not determined; sAUC = Area under the concentration-time curve standardized to a 7-day period; SD = Standard deviation;  $T_{max}$  = Timepoint of maximum concentration.

The 90% confidence interval on AUC (adjusted to a 7-day period) indicated that IGSC (IgPro20) and IGIV (Privigen) are pharmacokinetically equivalent (90% CI = 0.951 – 1.055).

**Figure 1**  
**Serum IgG trough levels over time (PK Part I and Part II or PPK population)**



**Figure 2**  
**Mean serum IgG levels (n = 18; Part II) across one dosing interval at Week 28 ± 1**



**Pharmacokinetics of serum IgG subclasses at steady-state:**

The PK of serum IgG subclasses at steady-state after treatment with the adjusted dose of IgPro20 (Week 28 ± 1) are summarized in Table 4. Overall, in terms of mean  $C_{min}$ ,  $C_{max}$ , and sAUC, the ratios of the individual IgG subclasses contributing to the total IgG were comparable to physiological ratios of IgG subclasses reported in the literature (Table 5). The median  $T_{max}$  for

each subclass of IgG was generally comparable to the median  $T_{max}$  for total IgG (reached at approximately 3 days post infusion (Table 3)).

**Table 4**  
**Steady-state PK of serum IgG subclasses after IGSC treatment IgPro20 (Part II)**

Parameter	Mean (SD); median (range)			
	IgG1 (N = 18)	IgG2 (N = 18)	IgG3 (N = 18)	IgG4 (N = 18)
$C_{min}$ (mg/dL)	748.0 (221.7)	496.9 (179.6)	45.92 (30.33)	18.13 (17.02)
	648.8 (465.3-1294)	466.1 (246.3-931.6)	36.90 (12.20-109.2)	11.00 (3.20-58.80)
$C_{max}$ (mg/dL)	889.5 (235.4)	585.2 (190.5)	54.11 (34.13)	21.35 (18.75)
	812.7 (617.7-1450)	555.9 (353.9-1090)	41.95 (17.20-129.5)	12.60 (4.20-66.70)
$T_{max}$ (day)	3.22 (1.61)	3.05 (1.67)	2.79 (1.18)	2.88 (1.66)
	3.53 (0-6.97)	3.04 (0-6.97)	2.99 (0-4.23)	2.97 (0-6.87)
sAUC (day × mg/dL)	5816 (1566)	3832 (1234)	348.4 (218.2)	141.7 (128.0)
	5373 (4114-9699)	3710 (2350-6850)	273.6 (101.9-787.6)	85.12 (28.51-441.6)

$C_{max}$  = Maximum concentration;  $C_{min}$  = Minimum concentration; IgG = Immunoglobulin G; N = Total number of subjects in population; sAUC = Area under the concentration-time curve standardized to a 7-day period; SD = Standard deviation;  $T_{max}$  = Timepoint of maximum concentration.

**Table 5**  
**Distribution of IgG subclasses vs. physiological ratio (Part II)**

IgG subclass	Mean (% of total)			Physiological ratio <sup>a</sup> (% of total IgG)
	$C_{min}$ (mg/dL)	$C_{max}$ (mg/dL)	sAUC (day × mg/dL)	
IgG1 (N = 18)	748.0 (57.1%)	889.5 (57.4%)	5816 (57.4%)	43% to 75%
IgG2 (N = 18)	496.9 (38.0%)	585.2 (37.7%)	3832 (37.8%)	16% to 48%
IgG3 (N = 18)	45.9 (3.5%)	54.1 (3.5%)	348.4 (3.4%)	1.7% to 7.5%
IgG4 (N = 18)	18.1 (1.4%)	21.4 (1.4%)	141.7 (1.4%)	0.8% to 11.7%
Total	1308.9 (100%)	1550.2 (100%)	10138.1 (100%)	

$C_{max}$  = Maximum concentration;  $C_{min}$  = Minimum concentration; IgG = Immunoglobulin G; N = Total number of subjects in population; sAUC = Area under the concentration-time curve standardized to a 7-day period.

**Pharmacokinetics of specific serum IgGs at steady-state:**

The changes in serum concentrations of specific IgGs over time, as measured during one dosing interval at week 28 ± 1 (anti-measles, anti-CMV, anti-H. influenzae, anti-tetanus, and anti-S. pneumoniae) were generally similar to those of total serum IgG and IgG subclasses (IgG1, IgG2, IgG3, IgG4). The maximum mean serum concentration was reached 2 days post infusion for anti-measles and anti-CMV IgG, and 4 days after infusion for anti-H. influenzae, anti-tetanus, and anti-S. pneumoniae IgG.

The PK of specific serum IgGs at steady-state after treatment with the adjusted dose of IgPro20 (week 28 ± 1) are summarized in Table 6. Mean C<sub>min</sub> for anti-measles IgG, analyzed by a functional Plaque Reduction Neutralization Test (PRNT), was more than 10 times higher than the minimal protective level of 240 mIU/mL for subjects with PID. The median T<sub>max</sub> for specific IgGs was generally comparable to the median T<sub>max</sub> for total IgG; median T<sub>max</sub> was approximately 3 days for total IgG, anti-CMV, anti-tetanus, and anti-S. pneumoniae, anti-measles and anti-H. influenzae IgG reached their peak levels after approximately 2 and 1 days, respectively.

**Table 6**  
**Steady-state pharmacokinetics of specific serum IgGs after IGSC**  
**Treatment with IgPro20 (Part II)**

Parameter	Mean (SD); median (range)				
	Anti-measles (mIU/mL) (N = 18)	Anti-CMV (IU/mL) (N = 18)	Anti- <i>H. influenzae</i> (mg/L) (N = 18)	Anti-tetanus (IU/mL) (N = 18)	Anti- <i>S. pneumoniae</i> (mg/L) (N = 18)
C <sub>min</sub> (mIU/mL)	2857	10.71	2.964	4.217	126.3
or (IU/mL)	(1216)	(12.38)	(0.853)	(2.263)	(75.41)
or (mg/L)	2868	6.27	2.825	3.610	97.34
	(759.0-4951)	(1.97-55.20)	(1.75-5.23)	(1.40-10.89)	(53.37-323.2)
C <sub>max</sub> (mIU/mL)	4697	14.63	3.771	5.093	159.3
or (IU/mL)	(2417)	(16.40)	(1.100)	(2.398)	(92.46)
or (mg/L)	4408	8.125	3.565	4.670	127.2
	(1299-10497)	(3.95-72.80)	(1.91-6.20)	(2.06-11.93)	(72.70-415.3)
T <sub>max</sub> (day)	2.27	2.58	2.07	2.39	2.56
	(1.72)	(1.49)	(1.90)	(1.73)	(1.58)
	2.13	3.01	1.24	2.65	3.12
	(0-6.95)	(0-4.14)	(0-6.87)	(0-4.20)	(0-4.12)
sAUC	26748	88.06	24.07	33.29	1009
(day × mIU/mL)	(12400)	(96.58)	(7.155)	(16.55)	(589.9)
or (day × IU/mL)	26681	52.86	22.08	29.83	777.7
or (day × mg/L)	(8157-51974)	(20.40-424.7)	(12.54-41.21)	(12.91-82.03)	(451.2-2470)

**Pharmacokinetics of serum L-proline at steady-state:**

The time course of serum L-proline at steady-state, as measured during one dosing interval at Week 28 ± 1, reached to a maximum at 10 minutes prior to the end of infusion. One day after

infusion, the serum L-proline concentrations returned to approximately the same level as before the infusion, indicating a rapid elimination of L-proline. The PK parameters of serum L-proline are summarized in Table 7.

**Table 7**  
**Steady-state pharmacokinetics of serum L-proline after IGSC**  
**treatment with IgPro20 (Part II)**

<b>Parameter</b>	<b>Mean (SD)</b> <b>(N = 18)</b>	<b>Median (range)</b> <b>(N = 18)</b>
$C_{\min}$ ( $\mu\text{mol/L}$ )	186.7 (42.42)	190.0 (111.0-268.0)
$C_{\max}$ ( $\mu\text{mol/L}$ )	449.7 (102.5)	436 (334.0-789.0)
$T_{\max}$ (day)	0.117 (0.049)	0.116 (0.04-0.23)
sAUC (day $\times$ $\mu\text{mol /L}$ )	1653 (329.1)	1669 (1077-2266)

### Conclusions

The following conclusions can be drawn from this study:

- The mean DAC (PK Part I population) for IgPro20 treatment (compared to the previous Privigen dose) was calculated as being needed to attain  $C_{\text{target}}$  was 1.53 (range: 1.26 to 1.87). This corresponded to a mean weekly IgPro20 dose of 234 mg/kg bw (range: 141 to 382 mg/kg bw).
- At steady-state during the efficacy period, after at least 12 weeks of IgPro20 treatment (at week  $28 \pm 1$ ) with the adjusted dose of IgPro20, the mean  $C_{\text{trough}}$  value (measured as  $C_{\text{last}}$ ) of 14.48 g/L (range: 9.52 to 26.23 g/L) was 29% higher than the mean  $C_{\text{trough}}$  of 11.27 g/L during the preceding IGIV treatment (range: 7.02 to 18.10 g/L).
- The changes in serum concentrations of specific IgGs over time were generally comparable to those for total serum IgG and IgG subclasses. Mean  $C_{\min}$  for anti-measles IgG indicated effective protection throughout the dosing intervals (>10 times higher than the minimal protective level of 240 mIU/mL).
- The Trough level ratio (TLR) of serum IgG for IGSC (IgPro20) vs. IGIV (Privigen) at steady-state, based on data from the PK subjects in the PK sub-study, was 1.29.
- After applying the dose adjustment of between 1.26 and 1.87 (mean of 1.53) times the previous IGIV dose with Privigen to the IGSC dose with IgPro20, the geometric mean ratio of sAUC values for IgPro20 vs. Privigen was 1.002, with a lower limit of 90% confidence interval of 0.951. Thus, the criterion for non-inferiority of systemic IgG exposure during IgPro20 treatment compared to the preceding IGIV treatment with Privigen (i.e., the primary objective of the PK sub-study) was met. The IGSC vs. IGIV

- Concentrations of serum L-proline over time demonstrated its rapid elimination from the circulation, with no accumulation, confirming previous results for IgPro20's parent product Privigen.