

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology

Office of Blood Review & Research

STN 125596

Sponsor: BAXALTA US INC.

Product: IMMUNE GLOBULIN SUBCUTANEOUS (HUMAN), 20% SOLUTION (CUVITRU)

Indication: Immune Globulin Subcutaneous (Human), 20% Solution to treat primary immune deficiency disorders associated with defects in humoral immunity

Submission Date: September 14, 2015

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INTRODUCTION

CUVITRU is manufactured from large pools of human plasma. IgG preparations are purified from plasma pools using a modified Cohn-Oncley cold ethanol fractionation process, as well as cation and anion exchange chromatography.

CUVITRU contains 200 milligram/mL protein. The maximum immunoglobulin A (IgA) concentration is (b) (4) . CUVITRU contains a broad spectrum of IgG antibodies against bacterial and viral agents. Glycine (0.25M) serves as a stabilizing and buffering agent, and there

are no added sugars, sodium or preservatives. CUVITRU is a ready-for-use sterile, liquid preparation of highly purified and concentrated immunoglobulin G (IgG) antibodies.

To improve the margin of safety, validated virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent (S/D) treatment, 35 nm nanofiltration, and a low pH incubation at elevated temperature (30°C to 32°C). The S/D process includes treatment with an organic mixture of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80 at 18°C to 25°C for a minimum of 60 minutes. S/D treatment inactivates the lipid-enveloped viruses investigated to below detection limits within minutes. The ethanol fractionation process provides an additional virus clearance capacity.

The following is the clinical pharmacology review of the submission.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

<TRADE NAME> supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. <TRADE NAME> also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in <TRADE NAME> have not been fully elucidated.

12.2 Pharmacodynamic

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma.

Adequate doses of <TRADE NAME> may restore abnormally low immunoglobulin G levels to the normal range.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters of subcutaneously administered <TRADE NAME> were evaluated in 60 subjects with primary immunodeficiency (PI) during a clinical study in North America [see *Clinical Studies* (14)]. Subjects were treated intravenously for 13 weeks with a comparator product [GAMMAGARD LIQUID, Immune Globulin (Human), 10%] and then switched to weekly subcutaneous <TRADE NAME> infusions. Initially, subjects were treated for up to 12 to 16 weeks at a subcutaneous dose that was 145% of the intravenous dose. A comparison of the area under the curve (AUC) for subcutaneous versus intravenous infusions was performed on 15 subjects aged 12 years and older. Subsequently, all subjects were treated with this dose for 12 weeks after which the dose was individualized for all subjects using the trough IgG levels, as described below. After approximately 4 months treatment at this subcutaneous dose, a PK evaluation was conducted on all subjects.

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At this dose adjustment, the geometric mean ratio of the AUC for subcutaneous <TRADE NAME> vs. intravenous administration immune globulin 10% was 109% (~~90% confidence limit 103.94 to 113.36~~). The peak IgG level occurred at a geometric mean of 79 (~~95% CI: 65.37 to 94.70~~) hours after subcutaneous <TRADE NAME> administration.

In part 4 of the study, pharmacokinetic parameters for <TRADE NAME> were assessed for 60 subjects aged 2 years and older. The pharmacokinetic parameters of <TRADE NAME> administered subcutaneously are shown in Table 6. The median peak IgG levels were lower (1809 mg/dL, 95% CI:1745 to 2068 mg/dL) during subcutaneous treatment with <TRADE NAME> compared to IGIV, 10% administration (2602 mg/dL, 95% CI: 2304 to 3043 mg/dL for 3 week intervals and 2521 mg/dL, 95% CI: 2326 to 2666 mg/dL for 4 week intervals), consistent with the lower weekly dose compared to the dose administered every 3 or 4 weeks intravenously. In contrast, the geometric mean trough levels were higher with <TRADE NAME> (1474 mg/dL, 95% CI: 1403 to 1548 mg/dL), compared to those when given intravenously (1158 mg/dL, 95% CI: 1036 to 1294 mg/dL for 3 week intervals and 1019 mg/dL, 95% CI: 955 to 1088 mg/dL for 4 week intervals), a result of both higher monthly dose and more frequent dosing. Pharmacokinetic parameters for <TRADE NAME> did not significantly differ between age groups.

In the Table below or if additional Tables are needed, please provide PK parameters for each age group (from 2-<5 years to >65 years of age) including the sample size. Keep the CI values in the Table. Please also check the number of digits in the Table.

Table 6	
Pharmacokinetic Parameters	
Parameter	Median (95% CI) N=60
AUC [g*days/L]	115.44 (110 to 120)
AUC / (Dose/Weight) [(g*days/L)/(g/kg)]	536.43 (466.83 to 582.14)
Apparent clearance [mL/kg/day]	1.86 (1.80 to 2.17)
C _{max} [mg/dL]	1809 (1745 to 2068)
C _{min} [mg/dL]	1477 (1323 to 1535)
T _{max} [hours]	104 (71 to 119)

Pharmacokinetic Modeling and Simulation

Once Weekly, Biweekly or more Frequent Dosing (2-7 times per week)

Pharmacokinetic characterization of biweekly or more frequent dosing of <TRADE NAME> was undertaken using population PK based modeling and simulation. Serum IgG concentration data consisted of 2056 samples from 102 unique pediatric and adult subjects with PI from two clinical studies conducted in North America and Europe. Compared with weekly administration, PK modeling and simulation predicted that administration of <TRADE NAME> on a biweekly basis at double the weekly dose results in comparable IgG exposure (overlapping IgG average, 5th- and 95th-percentile concentrations across the concentration time profile). In addition, PK modeling

~~and simulation predicted that for the same total weekly dose, <TRADE NAME> infusions given 2-7 times per week (frequent dosing) produce IgG exposures comparable to weekly dosing (overlapping IgG concentrations [average, 5th and 95th percentiles]) across an entire 2-week interval.~~

Dose Adjustment Factor

~~Using data from the pooled analysis of two clinical studies, results of model based simulations demonstrated that weekly or biweekly <TRADE NAME> dosing regimens with an IGIV:IGSC dose adjustment factor of 1:1.30 adequately maintain IgG exposure (median AUC_{0-28 day} ratios of 96.0% for weekly and 95.8% for biweekly) compared to IGIV dosing every 4 weeks.~~

RECOMMENDATIONS

The pharmacokinetic study design and the results of the study are acceptable. The applicant has modified the clinical pharmacology labeling comments as suggested by the FDA and is acceptable.

Study #1

Study Title: A clinical study of immune globulin subcutaneous (human), 20% for the evaluation of efficacy, safety, and pharmacokinetics in subjects with Primary Immunodeficiency Diseases (PID). (Study #170903)

The overall objectives of the study were to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of Immune Globulin Subcutaneous (Human) (IGSC), 20% in subjects with PID.

This was a Phase 2/3, prospective, open-label, non-controlled, multi-center study using IGSC, 20% to evaluate efficacy, safety, tolerability, and PK parameters of IGSC, 20%. The study was planned for approximately 47 subjects with PID, at least 2 years of age at the time of screening, including a minimum of 20 subjects aged 2 to <18 years (at least 6 aged 12 to <18 years) in the European region.

The study consisted of 2 epochs; Epoch 1, which included 12 weeks treatment with SUBCUVIA (IGSC, 16%), or 13 weeks intravenous treatment with KIOVIG (IGIV, 10%), and Epoch 2, which included 51 weeks of IGSC 20% administered SC. Study design is summarized in Figure 1.

The study consisted of 2 study epochs.

Study Epoch 1:

Duration: Twelve weeks for treatment with IGSC, 16%, or 13 weeks for treatment with IGIV, 10%. Administration, dosage frequency, and dose for Epoch 1 depended on the pre-study treatment (IGIV or IGSC). However, the dose range was required to be within 0.3-1.0 g/kg body weight/4 weeks. One week after the last IGIV, 10% infusion (after infusion number 4 for the 4 week treatment interval or infusion number 5 for the 3 week treatment interval), Study Epoch 2 began. For subjects receiving IGSC, 16% during Epoch 1, subjects on a weekly treatment schedule began Epoch 2 one week after the last infusion, and subjects on a biweekly schedule began Epoch 2 two weeks after the last infusion.

PK assessments were performed in subjects aged ≥ 12 years starting at the second to last IGIV, 10% infusion for subjects on IGIV, or starting at the last IGSC, 16% infusion in subjects on SC pre-treatment.

Study Epoch 2

Duration: 51 weeks

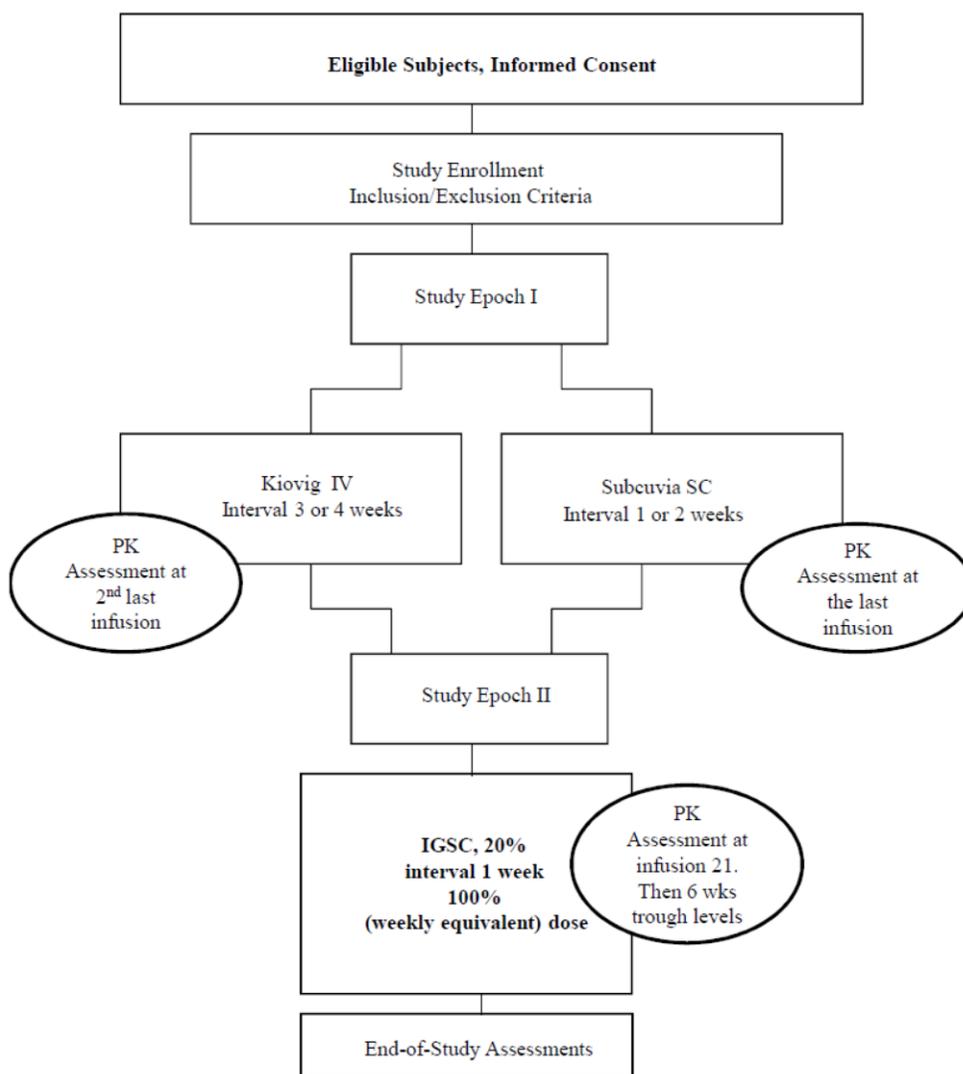
Administration: IGSC, 20%

Dosage frequency: once every week.

Dose: the same dose as used during Study Epoch 1, adjusted to a weekly equivalent dose if necessary. After approximately 5 months in this study epoch, a PK assessment was performed in subjects aged 12 years and older.

Pharmacokinetic assessments were performed in subjects aged ≥ 12 years, starting at the second to last IGIV or starting at the last IGSC, 16% infusion during Epoch1, and after approximately 5 months in Epoch 2.

Figure 1: Study Design



CRITERIA FOR EVALUATION:

Primary Endpoint:

Acute serious bacterial infection (ASBI) rate defined as the mean number of ASBIs per subject per year in the intent-to-treat (ITT) population. ASBIs included bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognized bacterial pathogen.

Secondary Endpoints: Safety, efficacy, and PK.

Pharmacokinetics:

a. Trough levels

- Immunoglobulin G (IgG) trough levels during approximately 3 months treatment with IGSC, 16% or IGIV, 10% (Study Epoch 1) and IgG trough levels after SC administration of IGSC, 20% (Study Epoch 2).
- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae and Hepatitis B Virus) during approximately 3 months treatment with IGSC, 16% or IGIV, 10% (Study Epoch 1) and trough levels of these specific antibodies after SC administration of IGSC, 20% (Study Epoch 2)

b. Assessment of PK parameters assessed for IgG such as area under the curve (AUC), clearance (CL) for IV and apparent clearance (CL/F) for SC administration, maximum concentration (C_{max}), and minimum concentration (C_{min}).

Study Epoch 1:

IV treatment: PK assessment was started at IV infusion 4 (for 3-week treatment interval) or starting at IV Infusion 3 (for 4-week treatment interval). Blood samples were collected at the following time points:

Pre-infusion (trough level of previous infusion, within 1 hour of infusion start time, day 0 of PK)

30 minutes (± 3 minutes) after completion of the infusion (day 0 of PK)

Day 1 (± 6 hours from infusion start time of day 0)

Day 4 (± 6 hours from infusion start time of day 0)

Day 9 (± 1 day)

Day 14 (± 2 days)

Day 21 (± 2 days, = trough level blood draw before next infusion and end of PK assessment for 3-week treatment interval) and

Day 28 (± 2 days, = trough level blood draw before next infusion and end of PK assessment for 4-week treatment interval).

SC treatment: PK assessment was started at SC infusion 12 (for 1-week treatment interval) or starting at SC Infusion 6 (for 2-week treatment interval). Blood samples were collected at the following time points (for 1-week treatment interval)

Pre-infusion (trough level of previous infusion within 1 hour of infusion start time) (day 0 of PK)
Day 1 (\pm 6 hours from infusion start time of day 0)
Day 3 (\pm 6 hours from infusion start time of day 0)
Day 5 (\pm 6 hours from infusion start time of day 0)
Day 7 (\pm 6 hours from infusion start time of day 0), blood draw before next infusion and end of
Day 10 (\pm 1 day) subjects on 2-week treatment interval only
Day 14 (\pm 2 days), blood draw before next infusion and end of PK assessment for 2-week
treatment interval

Study Epoch 2:

PK assessment was started at SC infusion 21 (numbered from the beginning of Epoch 2). Blood samples were collected at the following time points:

Pre-infusion (trough level of previous infusion within 1 hour of infusion, day 0 of PK)
Day 1 (\pm 6 hours from infusion start time of day 0)
Day 3 (\pm 6 hours from infusion start time of day 0)
Day 5 (\pm 6 hours from infusion start time of day 0)
Day 7 (\pm 6 hours from infusion start time of day 0, pre-infusion to the next SC infusion)

Blood samples for children <12 years of age were taken at time 0, and days 3 and 7. The PK parameters in subjects >12 years of age were estimated by extensive sampling using non-compartmental analysis. Since children <12 years of age had only 3 blood samples, in order to compare PK parameters between subjects >12 years and <12 years of age, PK parameters were recalculated using only three blood samples. The results of the PK study are summarized in Tables 1- 13.

Following IGIV administration (18-<65 years of age), the clearance and C_{\min} of IgG were 1.01 mL/day per kg (range = 0.97-1.05) and 11.7 g/L (10.5-13.0), respectively, for subjects on a 3-week schedule (n = 2). For subjects on a 4-week schedule (n = 9), the clearance and C_{\min} of IgG were 1.44 mL/day per kg (range = 1.04-1.89) and 7.0 g/L (range = 5-11.7), respectively. In adolescents (12-<18 years of age; on a 4-week schedule; n = 7), the clearance and C_{\min} of IGIV were comparable with subjects >18 years of age.

Following IGSC (16%) administration (18-<65 years of age), the clearance and C_{\min} of IgG were 1.62 mL/day per kg (range = 1.4-2.5) and 11.7 g/L (range = 6.9-11.9), respectively, for subjects on a 1-week schedule (n = 9). In adolescents (12-<18 years of age; on a 1-week schedule; n = 1), the clearance and C_{\min} of IgG (16%) were 2.1 mL/day per kg and 10.4 g/L, respectively.

Following IGSC (20%) administration (18-<65 years of age), the clearance and C_{\min} of IgG were 1.7 mL/day per kg (range = 1.27-2.85) and 8.05 g/L (range = 5.5-10.4), respectively, for subjects on a 1-week schedule (n = 18). In adolescents (12-<18 years of age; on a 1-week schedule; n = 11), the clearance and C_{\min} of IgG (16%) were 1.9 mL/day per kg (range = 1.1-3.2)

and 8.6 g/L (5.4-16.3), respectively. In adolescents (12-<18 years of age; on a 1-week schedule; n = 11), the clearance and C_{min} of IGSC were comparable with subjects >18 years of age.

In children, 2-5 years of age (n = 1) and 6-11 years of age (n =10), the clearance, C_{max}, and C_{min} were comparable with adolescents and adults (Tables 10-13).

Comments: The pharmacokinetics of IGSC 16% and IGSC 20% are comparable from children to adults. However, the sample size for 2-5 years of age is very small (n =1) which hinders the comparison of PK in this age group with older children and adults. This is the age group in which the differences in PK parameters are anticipated from older children, adolescents, and adults.

Table 1

Analyte=IgG Total [g/L], Age Group=Subjects aged 18 to <65 years, Treatment=IV, Interval=3 Weeks

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	2	290.81 (NA)	293.78 (NA)	252.10;335.46	83.36 (252.10;335.46)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	2	989.32 (NA)	990.02 (NA)	952.72;1027.33	74.61 (952.72;1027.33)
Clearance [mL/kg/days]	2	1.01 (NA)	1.01 (NA)	0.97;1.05	0.08 (0.97;1.05)
Cmax [g/L]	2	17.62 (NA)	17.82 (NA)	15.17;20.47	5.30 (15.17;20.47)
Tmax [h]	2	26.01 (NA)	26.07 (NA)	24.33;27.80	3.47 (24.33;27.80)
Cmin [g/L]	2	11.67 (NA)	11.74 (NA)	10.50;12.98	2.48 (10.50;12.98)

Table 2

Analyte=IgG Total [g/L], Age Group=Subjects aged 18 to <65 years, Treatment=IV, Interval=4 Weeks

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	9	270.85 (224.72 to 326.44)	264.59 (235.20 to 353.12)	168.63;393.35	41.08 (252.39;293.47)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	9	693.13 (589.02 to 815.64)	701.16 (546.84 to 912.58)	529.68;958.67	179.66 (564.91;744.57)
Clearance [mL/kg/days]	9	1.44 (1.23 to 1.70)	1.43 (1.10 to 1.83)	1.04;1.89	0.43 (1.34;1.77)
Cmax [g/L]	9	15.99 (14.18 to 18.03)	15.17 (14.07 to 20.18)	13.50;21.24	1.57 (14.78;16.35)
Tmax [h]	9	8.62 (2.87 to 25.93)	5.33 (2.02 to 26.53)	1.97;93.90	23.82 (2.10;25.92)
Cmin [g/L]	9	7.00 (5.85 to 8.38)	6.73 (5.98 to 7.90)	5.00;11.66	1.26 (6.34;7.60)

Table 3

Analyte=IgG Total [g/L], Age Group=Subjects aged 18 to <65 years, Treatment=SC, Interval=1 Week

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	9	68.66 (60.47 to 77.95)	69.06 (58.07 to 83.08)	52.18;86.99	13.42 (61.41;74.84)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	9	617.94 (540.35 to 706.68)	651.03 (586.98 to 688.99)	402.26;728.57	77.87 (595.83;673.71)
Apparent Clearance [mL/kg/days]	9	1.62 (1.42 to 1.85)	1.54 (1.45 to 1.70)	1.37;2.49	0.19 (1.48;1.68)
Cmax [g/L]	9	10.84 (9.52 to 12.35)	11.62 (8.87 to 12.62)	8.03;13.18	2.26 (10.12;12.38)
Tmax [h]	9	30.81 (21.23 to 44.72)	23.58 (23.13 to 71.25)	22.98;72.00	6.33 (23.33;29.67)
Cmin [g/L]	9	8.96 (7.79 to 10.29)	8.87 (7.55 to 11.05)	6.89;11.89	2.07 (7.59;9.66)

SC = 16%

Table 4

Analyte=IgG Total [g/L], Age Group=Subjects aged 18 to <65 years, Treatment=SC, Interval=2 Weeks

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	1	113.52 (NA)	113.52 (NA)	113.52;113.52	0.00 (113.52;113.52)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	1	588.47 (NA)	588.47 (NA)	588.47;588.47	0.00 (588.47;588.47)
Apparent Clearance [mL/kg/days]	1	1.70 (NA)	1.70 (NA)	1.70;1.70	0.00 (1.70;1.70)
Cmax [g/L]	1	8.42 (NA)	8.42 (NA)	8.42;8.42	0.00 (8.42;8.42)
Tmax [h]	1	121.75 (NA)	121.75 (NA)	121.75;121.75	0.00 (121.75;121.75)
Cmin [g/L]	1	7.42 (NA)	7.42 (NA)	7.42;7.42	0.00 (7.42;7.42)

SC = 16%

Table 5

Analyte=IgG Total [g/L], Age Group=Subjects aged 18 to <65 years, Treatment=SC 20%, Interval=1 Week

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	18	62.45 (57.05 to 68.37)	63.49 (56.53 to 70.91)	40.55;87.05	14.38 (56.53;70.91)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	18	587.16 (523.31 to 658.81)	629.12 (498.15 to 699.83)	350.54;787.85	201.68 (498.15;699.83)
Apparent Clearance [mL/kg/days]	18	1.70 (1.52 to 1.91)	1.59 (1.43 to 2.01)	1.27;2.85	0.58 (1.43;2.01)
Cmax [g/L]	18	9.86 (8.87 to 10.96)	9.91 (9.45 to 11.22)	5.90;15.79	1.77 (9.45;11.22)
Tmax [h]	18	66.57 (45.77 to 96.83)	72.48 (24.98 to 121.17)	19.78;192.33	96.18 (24.98;121.17)
Cmin [g/L]	18	8.05 (7.34 to 8.83)	8.27 (6.74 to 9.48)	5.52;10.36	2.74 (6.74;9.48)

Table 6

Analyte=IgG Total [g/L], Age Group=Subjects aged 12 to <18 years, Treatment=IV, Interval=4 Weeks

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	7	279.26 (235.52 to 331.11)	292.90 (209.26 to 338.26)	209.26;338.26	99.49 (227.54;327.03)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	7	622.22 (472.92 to 818.65)	706.12 (418.84 to 879.47)	418.84;879.47	335.93 (470.25;806.18)
Clearance [mL/kg/days]	7	1.61 (1.22 to 2.11)	1.42 (1.14 to 2.39)	1.14;2.39	0.89 (1.24;2.13)
Cmax [g/L]	7	15.61 (13.74 to 17.73)	16.44 (11.70 to 17.45)	11.70;17.45	2.05 (15.19;17.24)
Tmax [h]	7	8.26 (1.97 to 34.60)	3.55 (2.23 to 101.83)	2.23;101.83	24.62 (2.27;26.88)
Cmin [g/L]	7	6.39 (5.01 to 8.14)	6.28 (4.27 to 9.37)	4.27;9.37	2.35 (5.21;7.56)

Table 7

Analyte=IgG Total [g/L], Age Group=Subjects aged 12 to <18 years, Treatment=SC, Interval=1 Week

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	1	73.03 (NA)	73.03 (NA)	73.03;73.03	0.00 (73.03;73.03)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	1	475.84 (NA)	475.84 (NA)	475.84;475.84	0.00 (475.84;475.84)
Apparent Clearance [mL/kg/days]	1	2.10 (NA)	2.10 (NA)	2.10;2.10	0.00 (2.10;2.10)
Cmax [g/L]	1	11.89 (NA)	11.89 (NA)	11.89;11.89	0.00 (11.89;11.89)
Tmax [h]	1	170.85 (NA)	170.85 (NA)	170.85;170.85	0.00 (170.85;170.85)
Cmin [g/L]	1	10.37 (NA)	10.37 (NA)	10.37;10.37	0.00 (10.37;10.37)

Table 8

Analyte=IgG Total [g/L], Age Group=Subjects aged 12 to <18 years, Treatment=SC, Interval=2 Weeks

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	1	151.85 (NA)	151.85 (NA)	151.85;151.85	0.00 (151.85;151.85)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	1	648.53 (NA)	648.53 (NA)	648.53;648.53	0.00 (648.53;648.53)
Apparent Clearance [mL/kg/days]	1	1.54 (NA)	1.54 (NA)	1.54;1.54	0.00 (1.54;1.54)
Cmax [g/L]	1	11.92 (NA)	11.92 (NA)	11.92;11.92	0.00 (11.92;11.92)
Tmax [h]	1	213.00 (NA)	213.00 (NA)	213.00;213.00	0.00 (213.00;213.00)
Cmin [g/L]	1	10.09 (NA)	10.09 (NA)	10.09;10.09	0.00 (10.09;10.09)

Table 9

Analyte=IgG Total [g/L], Age Group=Subjects aged 12 to <18 years, Treatment=SC 20%, Interval=1 Week

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
AUC [g*days/L]	11	66.25 (54.08 to 81.17)	61.42 (55.04 to 81.91)	43.64;137.32	21.41 (55.04;76.46)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	11	521.66 (426.91 to 637.44)	528.36 (443.23 to 687.47)	308.43;889.30	195.58 (443.23;638.81)
Apparent Clearance [mL/kg/days]	11	1.92 (1.57 to 2.34)	1.89 (1.57 to 2.64)	1.12;3.24	0.69 (1.57;2.26)
Cmax [g/L]	11	10.15 (8.37 to 12.32)	9.41 (8.31 to 11.95)	6.86;20.69	3.33 (8.31;11.64)
Tmax [h]	11	88.00 (56.16 to 137.89)	116.83 (71.72 to 170.37)	24.50;172.92	92.25 (71.72;163.97)
Cmin [g/L]	11	8.59 (7.07 to 10.45)	8.17 (7.30 to 11.25)	5.36;16.33	2.34 (7.30;9.64)

Table 10

**Comparison of Pharmacokinetic Parameters of IgG Total in Epoch 4 (SC 20% individualized) by Age Group
(Study 170904: Safety Analysis Set)**

PK Parameter=AUC [g*days/L]

Age Group	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
Aged 2-5 Years	1	106.23 (NA)	106.23 (NA)	106.23;106.23	0.00 (106.23;106.23)
Aged 6-11 Years	10	108.70 (96.66 to 122.24)	113.20 (86.85 to 124.92)	84.05;141.96	22.69 (97.97;120.66)
Aged 12 Years and Older	48	114.26 (106.27 to 122.85)	114.94 (100.30 to 120.97)	60.59;190.48	39.62 (96.51;136.13)

Table 11

PK Parameter=Apparent Clearance [mL/kg/days]

Age Group	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
Aged 2-5 Years	1	1.86 (NA)	1.86 (NA)	1.86;1.86	0.00 (1.86;1.86)
Aged 6-11 Years	10	1.74 (1.45 to 2.09)	1.71 (1.31 to 2.34)	1.23;2.53	0.86 (1.38;2.25)
Aged 12 Years and Older	48	1.91 (1.75 to 2.08)	1.91 (1.82 to 2.15)	0.91;3.81	0.70 (1.64;2.34)

Table 12

PK Parameter=Cmax [g/L]

Age Group	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
Aged 2-5 Years	1	16.19 (NA)	16.19 (NA)	16.19;16.19	0.00 (16.19;16.19)
Aged 6-11 Years	10	16.79 (15.17 to 18.58)	17.25 (15.18 to 18.92)	12.62;21.12	2.70 (15.54;18.24)
Aged 12 Years and Older	48	17.27 (15.83 to 18.83)	16.79 (15.42 to 17.88)	7.19;32.01	6.48 (14.56;21.04)

Table 13

PK Parameter=Cmin [g/L]

Age Group	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
Aged 2-5 Years	1	15.27 (NA)	15.27 (NA)	15.27;15.27	0.00 (15.27;15.27)
Aged 6-11 Years	10	14.54 (12.63 to 16.73)	15.45 (11.30 to 16.54)	10.87;20.24	3.90 (12.45;16.35)
Aged 12 Years and Older	48	14.64 (13.50 to 15.88)	15.11 (12.90 to 15.55)	6.78;28.55	4.56 (12.26;16.82)

Study #2

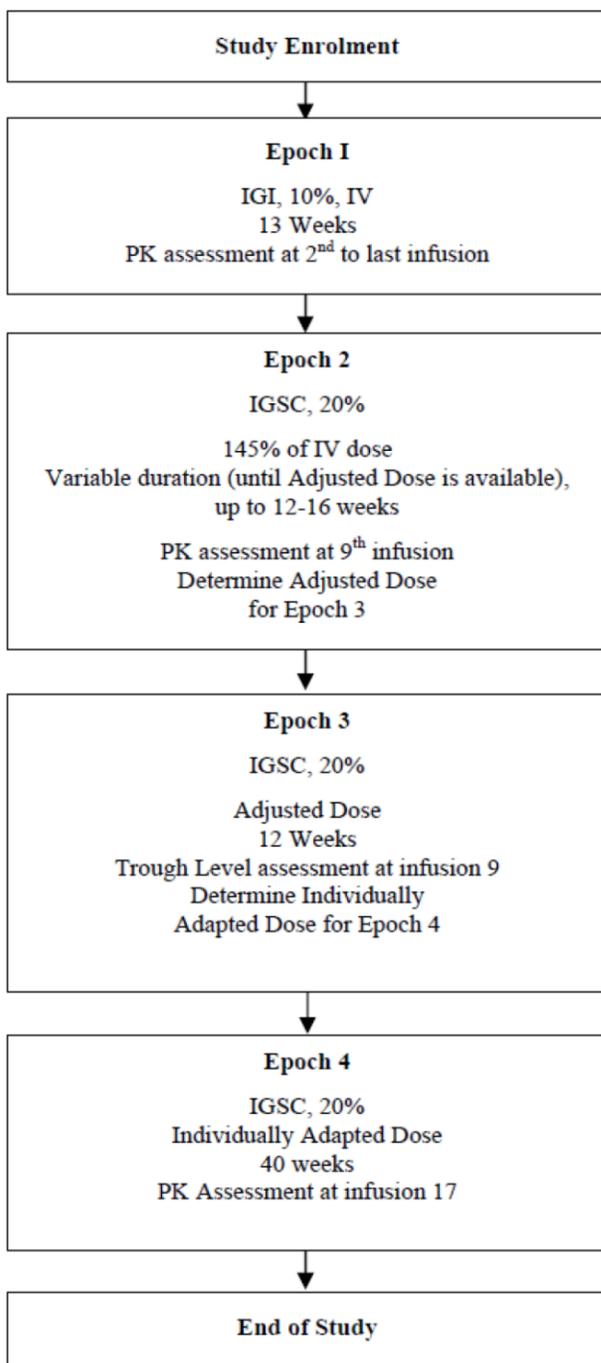
Study Title: A clinical study of immune globulin subcutaneous (Human), 20% solution (IGSC, 20%) for the evaluation of efficacy, safety, tolerability, and pharmacokinetics in subjects with primary immunodeficiency diseases”. (Study # 170904)

This was a phase 2/3, prospective, open-label, non-controlled, multicenter, global study to evaluate efficacy, safety, tolerability, and PK of IGSC, 20%. The study population was to consist of approximately 70 subjects, at least 2 years of age at the time of screening, males and females of any ethnic group and race, who had a diagnosis of PIDD associated with antibody deficiency. The planned enrollment target of 70 subjects was to consist of at least 30 SC-naive and approximately 40 SC-experienced subjects. All subjects were to be on a stable IgG dose for at least 12 weeks prior to enrollment. Additionally, 16-20 of the 70 subjects were to be between 2 and < 16 years of age, of these, approximately 6-8 were to be adolescents between 12 and <16 years, and approximately 4-6, each, were to be between 2 to <5 years and between 5 and <12 years. The study consisted of 4 epochs:

- In Epoch 1 subjects received IGIV, 10% intravenously (IGIV, 10%). All subjects aged ≥ 12 years completed a PK assessment. Dose was 0.3-1.0 g/kg body weight/4 weeks. One week after the last IGIV, 10% infusion, Study Epoch 2 began.
- In Epoch 2, subjects received IGSC, 20% subcutaneously weekly at a dose adjusted to 145% of the IGIV, 10% dose. The first 15 subjects aged ≥ 12 years completed a PK assessment. Based on the PK data from Epoch 1 and Epoch 2, the IGSC, 20% dose that would, on average, provide equivalent IgG exposure as IGIV, 10% administration (“Adjusted Dose”) was calculated.
- In Epoch 3, subjects were treated with IGSC, 20% weekly for 3 months at the “Adjusted Dose”. Since this Adjusted Dose represented the average dose-response of only 15 subjects, the possibility that some subjects could be over- or under-dosed, could not be excluded. Thus, for each subject’s an “Individually Adapted Dose” of IGSC, 20% dose was determined by comparing the trough level attained in Epoch 3 to the expected trough level increase calculated from the PK comparison of Epochs 1 and 2.
- In Epoch 4, subjects were infused with IGSC, 20% weekly at the “Individually Adapted Dose”. Efficacy, safety and tolerability were determined throughout Epochs 2 to 4 (12 months). Of note, treatment in Epoch 3 started as soon as the Adjusted Dose became available. Consequently, later enrolling subjects who completed Epoch 1 after the Adjusted Dose was available, directly went into treatment with the Adjusted Dose (Epoch 3). The study design is summarized in Figure 1.

Of the 77 treated subjects (51.9% male, 48.1% female), the majority were white/Caucasian (90.9%) and not of Hispanic or Latino ethnicity (93.5%). The median age of treated subjects was 36.0 years (range: 3-83 years). The median weight was 68.20 kg (range: 13.20-161.80 kg).

Figure 1
Study Design for Clinical Study 170904



Pharmacokinetic Datasets:

- PK data set for IGIV, 10% administered every 3 weeks (N= 16), or every 4 weeks (N= 38) (subjects aged 12 years and older).
- PK dataset for IGSC, 20% at 145% of IV dose (N= 18) (subjects aged 12 years and older).
- PK dataset for IGSC, 20% at the individualized dose (N= 60) (subjects aged 2 years and older).

Blood samples for children 2 to <5 years (SC 20%, weekly treatment) was obtained at time zero (60 minutes before drug administration and on days 3 and 7.

Blood samples for children 5 to <12 years (SC 20%, weekly treatment) was obtained at time zero (60 minutes before drug administration and on days 1, 3, 5, and 7.

Blood samples for children 12 to <16 years (IV 10%) was obtained at time zero (60 minutes before drug administration and 30 minutes post-infusion, and on days 1, 4, 9, 14, and 21 (on 3-week dosing schedule) and extended to day 28 on 4-week dosing schedule. For SC treatment the blood sampling scheme was time zero, and on days 1, 3, 5, and 7. Blood sampling scheme for <16 years of age was similar as described for children 12 to <16 years of age.

Pharmacokinetic Results:

Bioavailability:

The bioavailability of IGSC, 20% estimated from the ratio of the geometric means of AUC/week for total IgG during weekly IGSC, 20% treatment in Epoch 4 (once every week) versus IGIV, 10% treatment (3 or 4-week interval standardized to 1 week) was 1.0855 (90% CI: 1.0394 to 1.1336, N = 49).

Bioavailability: Ratios of Geometric Means of the AUC/Week for IgG Under Individualized SC 20% Treatment Versus IV 10% Treatment in Subjects Aged 12 Years and Older (Study 170904: Safety Analysis Set)

Comparison	N	Ratio of Geometric Means	
		Ratio	90% CI of the Ratio
Analyte=IgG [g/L]			
SC 20% individualized/IV 10% 3 weekly	16	1.1013	1.0199 to 1.1893
SC 20% individualized/IV 10% 4 weekly	33	1.0779	1.0204 to 1.1387
SC 20% individualized/IV 10% 3 or 4 weekly	49	1.0855	1.0394 to 1.1336

Subjects aged 12 years and older in Epoch 1 and in Epoch 2:

In subjects who received IGIV, 10% every 3 weeks, (N=16), the median area under the curve (AUC) for total IgG was 360 g*days/L. The median clearance (CL) was 1.75 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 26 g/L and 13 g/L, respectively.

In subjects who received IGIV, 10% every 4 weeks, (N=38), the median area under the curve (AUC) for total IgG was 408*days/L. The median clearance (CL) was 1.28 mL/day per kg. The

median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 25 g/L and 10 g/L, respectively.

During weekly administration of IGSC, 20% at 145% of the IGIV, 10% dose (N=18), the median area under the curve (AUC) for total IgG was 108*days/L. The median clearance (CL) was 1.94 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 17 g/L and 15 g/L, respectively.

Subjects aged 12 years and older in Epoch 4:

12 to <16 years:

During weekly administration of IGSC, 20% at the individualized dose, (N=3), the median AUC for total IgG was 116 g*days/L. The median clearance (CL) was 1.80 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 17 g/L and 16 g/L, respectively.

16 to <65 years:

During weekly administration of IGSC, 20% at the individualized dose (N=37), the median AUC for total IgG was 114 g*days/L. The median clearance (CL) was 1.98 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 19 g/L and 14 g/L, respectively.

>65 years:

During weekly administration of IGSC, 20% at the individualized dose (N=7), the median AUC for total IgG was 139 g*days/L. The median clearance (CL) was 1.72 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 24 g/L and 16 g/L, respectively.

Subjects aged 2 to < 12 years in Epoch 4:

For subjects in this age range, PK assessments were performed only during Epoch 4, between infusion 17 and infusion 18 of IGSC, 20% at the individualized dose.

2 to <5 years:

There was only one subject in this study. The median AUC for total IgG was 106 g*days/L. The median clearance (CL) was 1.86 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 16 g/L and 15 g/L, respectively.

5 to <12 years:

For subjects aged 5 < 12 years receiving weekly infusions of IGSC, 20% at the individualized dose (N=10), the median AUC for total IgG was 110 g*days/L. The median clearance (CL) was

1.85 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 17 g/L and 14 g/L, respectively.

Comments: The pharmacokinetics of IGSC 20% are comparable from children to adults. Like the previous study (study 170903) the sample size for 2-5 years of age is very small (n =1) which hinders the comparison of PK in this age group with older children and adults. This is the age group in which the differences in PK parameters are anticipated from older children, adolescents, and adults.

The following Tables summarize the overall pharmacokinetic results across different age groups and route of administrations.

**Pharmacokinetic Parameters by Treatment
(Study 170904: Safety Analysis Set)**

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min:Max	IQR (Q1:Q3)
Analyte=IgG [g/L], Age Group=Subjects aged 2 to <5 years, Treatment=SC 20% individualized, Interval=1 Week					
AUC [g*days/L]	1	106.23 (NA)	106.23 (NA)	106.23;106.23	0.00 (106.23;106.23)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	1	538.49 (NA)	538.49 (NA)	538.49;538.49	0.00 (538.49;538.49)
Apparent Clearance [mL/kg/days]	1	1.86 (NA)	1.86 (NA)	1.86;1.86	0.00 (1.86;1.86)
C_{max} [g/L]	1	16.19 (NA)	16.19 (NA)	16.19;16.19	0.00 (16.19;16.19)
T_{max} [h]	1	70.42 (NA)	70.42 (NA)	70.42;70.42	0.00 (70.42;70.42)
C_{min} [g/L]	1	15.27 (NA)	15.27 (NA)	15.27;15.27	0.00 (15.27;15.27)
Analyte=IgG [g/L], Age Group=Subjects aged 5 to <12 years, Treatment=SC 20% individualized, Interval=1 Week					
AUC [g*days/L]	10	106.33 (96.28 to 117.42)	110.13 (86.85 to 120.66)	84.05;124.92	22.30 (97.97;120.27)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	10	561.68 (465.67 to 677.47)	540.11 (421.38 to 765.60)	395.76;810.49	295.12 (427.32;722.44)
Apparent Clearance [mL/kg/days]	10	1.78 (1.48 to 2.15)	1.85 (1.31 to 2.37)	1.23;2.53	0.96 (1.38;2.34)
C_{max} [g/L]	10	16.79 (15.17 to 18.58)	17.25 (15.18 to 18.92)	12.62;21.12	2.70 (15.54;18.24)
T_{max} [h]	10	116.39 (83.00 to 163.19)	164.43 (70.17 to 167.48)	57.75;174.47	95.45 (71.27;166.72)
C_{min} [g/L]	10	13.72 (12.31 to 15.29)	13.51 (11.30 to 16.35)	10.87;16.54	3.82 (12.45;16.27)

**Pharmacokinetic Parameters by Treatment
(Study 170904: Safety Analysis Set)**

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
Analyte=IgG [g/L], Age Group=Subjects aged 12 to <16 years, Treatment=IV 10%, Interval=3 Weeks					
AUC [g*days/L]	3	329.11 (NA)	290.61 (NA)	287.47;426.71	139.24 (287.47;426.71)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	3	595.51 (NA)	447.55 (NA)	383.29;1231.13	847.84 (383.29;1231.13)
Clearance [mL/kg/days]	3	1.68 (NA)	2.23 (NA)	0.81;2.61	1.80 (0.81;2.61)
Cmax [g/L]	3	25.95 (NA)	25.93 (NA)	20.94;32.19	11.25 (20.94;32.19)
Tmax [h]	3	2.45 (NA)	2.53 (NA)	2.00;2.92	0.92 (2.00;2.92)
Cmin [g/L]	3	10.59 (NA)	9.09 (NA)	8.86;14.73	5.87 (8.86;14.73)
Analyte=IgG [g/L], Age Group=Subjects aged 12 to <16 years, Treatment=IV 10%, Interval=4 Weeks					
AUC [g*days/L]	2	399.18 (NA)	399.20 (NA)	395.33;403.07	7.73 (395.33;403.07)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	2	915.80 (NA)	927.10 (NA)	782.76;1071.44	288.68 (782.76;1071.44)
Clearance [mL/kg/days]	2	1.09 (NA)	1.11 (NA)	0.93;1.28	0.34 (0.93;1.28)
Cmax [g/L]	2	22.38 (NA)	23.12 (NA)	17.32;28.92	11.60 (17.32;28.92)
Tmax [h]	2	8.92 (NA)	13.13 (NA)	3.50;22.75	19.25 (3.50;22.75)
Cmin [g/L]	2	9.90 (NA)	9.91 (NA)	9.70;10.11	0.41 (9.70;10.11)

**Pharmacokinetic Parameters by Treatment
(Study 170904: Safety Analysis Set)**

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min;Max	IQR (Q1;Q3)
Analyte=IgG [g/L], Age Group=Subjects aged 12 to <16 years, Treatment=SC 20% 145% IV, Interval=1 Week					
AUC [g*days/L]	1	110.28 (NA)	110.28 (NA)	110.28;110.28	0.00 (110.28;110.28)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	1	345.13 (NA)	345.13 (NA)	345.13;345.13	0.00 (345.13;345.13)
Apparent Clearance [mL/kg/days]	1	2.90 (NA)	2.90 (NA)	2.90;2.90	0.00 (2.90;2.90)
Cmax [g/L]	1	22.80 (NA)	22.80 (NA)	22.80;22.80	0.00 (22.80;22.80)
Tmax [h]	1	23.70 (NA)	23.70 (NA)	23.70;23.70	0.00 (23.70;23.70)
Cmin [g/L]	1	12.41 (NA)	12.41 (NA)	12.41;12.41	0.00 (12.41;12.41)
Analyte=IgG [g/L], Age Group=Subjects aged 12 to <16 years, Treatment=SC 20% individualized, Interval=1 Week					
AUC [g*days/L]	5	113.30 (104.35 to 123.03)	115.89 (NA)	105.14;122.60	11.07 (106.40;117.48)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	5	503.21 (290.49 to 871.69)	556.48 (NA)	311.18;783.18	416.56 (322.10;738.66)
Apparent Clearance [mL/kg/days]	5	1.99 (1.15 to 3.44)	1.80 (NA)	1.28;3.21	1.75 (1.35;3.10)
Cmax [g/L]	5	17.04 (15.74 to 18.45)	17.32 (NA)	15.30;18.04	0.63 (17.03;17.66)
Tmax [h]	5	77.18 (47.91 to 124.32)	68.25 (NA)	47.80;114.57	50.25 (64.08;114.33)
Cmin [g/L]	5	15.06 (13.30 to 17.04)	15.54 (NA)	12.81;16.56	1.20 (14.73;15.93)

**Pharmacokinetic Parameters by Treatment
(Study 170904: Safety Analysis Set)**

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min:Max	IQR (Q1;Q3)
Analyte=IgG [g/L], Age Group=Subjects aged 16 to <65 years, Treatment=IV 10%, Interval=3 Weeks					
AUC [g*days/L]	11	359.00 (315.51 to 408.49)	384.28 (296.16 to 437.33)	265.93;445.95	132.49 (296.16;428.65)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	11	575.09 (482.39 to 685.59)	597.62 (505.26 to 748.32)	331.62;873.52	200.82 (505.26;706.08)
Clearance [mL/kg/days]	11	1.74 (1.46 to 2.07)	1.67 (1.42 to 2.21)	1.14;3.02	0.56 (1.42;1.98)
Cmax [g/L]	11	27.44 (23.54 to 31.98)	25.29 (23.00 to 32.44)	21.99;48.08	7.43 (23.00;30.43)
Tmax [h]	11	9.79 (4.73 to 20.23)	21.98 (3.27 to 26.50)	2.83;28.83	22.82 (3.27;26.08)
Cmin [g/L]	11	12.32 (10.50 to 14.46)	13.09 (10.67 to 15.28)	8.19;17.04	4.25 (10.67;14.92)
Analyte=IgG [g/L], Age Group=Subjects aged 16 to <65 years, Treatment=IV 10%, Interval=4 Weeks					
AUC [g*days/L]	29	407.22 (371.93 to 445.86)	409.31 (381.10 to 462.30)	224.86;632.86	122.58 (352.79;475.38)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	29	791.95 (691.48 to 907.02)	772.96 (735.15 to 964.47)	299.82;1598.49	319.59 (687.06;1006.65)
Clearance [mL/kg/days]	29	1.26 (1.10 to 1.45)	1.29 (1.06 to 1.43)	0.63;3.34	0.46 (0.99;1.46)
Cmax [g/L]	29	24.97 (23.16 to 26.92)	25.33 (23.82 to 27.96)	13.90;34.67	5.95 (22.18;28.13)
Tmax [h]	29	5.54 (3.14 to 9.78)	2.72 (2.50 to 4.17)	2.08;671.92	1.95 (2.38;4.33)
Cmin [g/L]	29	10.33 (9.27 to 11.52)	9.92 (9.23 to 12.78)	5.47;16.18	4.00 (8.79;12.79)

**Pharmacokinetic Parameters by Treatment
(Study 170904: Safety Analysis Set)**

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min:Max	IQR (Q1;Q3)
Analyte=IgG [g/L], Age Group=Subjects aged 16 to <65 years, Treatment=SC 20% 145% IV, Interval=1 Week					
AUC [g*days/L]	15	106.93 (94.29 to 121.26)	104.87 (83.49 to 139.47)	78.54;150.02	55.98 (83.49;139.47)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	15	486.66 (416.32 to 568.88)	523.19 (382.59 to 592.02)	262.99;738.86	209.43 (382.59;592.02)
Apparent Clearance [mL/kg/days]	15	2.05 (1.76 to 2.40)	1.91 (1.69 to 2.61)	1.35;3.80	0.92 (1.69;2.61)
Cmax [g/L]	15	16.90 (14.40 to 19.84)	15.65 (12.84 to 22.04)	11.31;27.26	9.20 (12.84;22.04)
Tmax [h]	15	51.95 (33.35 to 80.91)	71.85 (23.13 to 117.73)	20.30;167.85	94.60 (23.13;117.73)
Cmin [g/L]	15	13.70 (12.28 to 15.28)	14.58 (11.44 to 15.48)	10.24;18.34	4.04 (11.44;15.48)
Analyte=IgG [g/L], Age Group=Subjects aged 16 to <65 years, Treatment=SC 20% individualized, Interval=1 Week					
AUC [g*days/L]	37	115.11 (106.69 to 124.18)	114.28 (103.42 to 126.60)	73.26;168.19	41.52 (97.76;139.28)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	37	525.32 (474.77 to 581.27)	504.07 (448.47 to 552.51)	317.46;1141.54	236.58 (425.03;661.61)
Apparent Clearance [mL/kg/days]	37	1.90 (1.72 to 2.11)	1.98 (1.81 to 2.23)	0.88;3.15	0.84 (1.51;2.35)
Cmax [g/L]	37	19.82 (18.20 to 21.58)	19.40 (17.78 to 22.20)	12.16;31.79	7.61 (16.68;24.29)
Tmax [h]	37	68.84 (52.82 to 89.72)	74.33 (68.35 to 118.75)	18.77;173.32	99.33 (25.98;125.32)
Cmin [g/L]	37	13.61 (12.40 to 14.94)	14.23 (12.31 to 15.24)	5.15;20.91	3.48 (11.97;15.45)

**Pharmacokinetic Parameters by Treatment
(Study 170904: Safety Analysis Set)**

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min:Max	IQR (Q1;Q3)
Analyte=IgG [g/L], Age Group=Subjects aged 65 years and older, Treatment=IV 10%, Interval=3 Weeks					
AUC [g*days/L]	2	349.81 (NA)	349.89 (NA)	342.09;357.70	15.61 (342.09;357.70)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	2	840.55 (NA)	937.32 (NA)	522.54;1352.10	829.56 (522.54;1352.10)
Clearance [mL/kg/days]	2	1.19 (NA)	1.33 (NA)	0.74;1.91	1.17 (0.74;1.91)
Cmax [g/L]	2	26.91 (NA)	26.92 (NA)	26.10;27.74	1.64 (26.10;27.74)
Tmax [h]	2	5.00 (NA)	5.18 (NA)	3.83;6.53	2.70 (3.83;6.53)
Cmin [g/L]	2	12.76 (NA)	12.77 (NA)	12.61;12.92	0.31 (12.61;12.92)
Analyte=IgG [g/L], Age Group=Subjects aged 65 years and older, Treatment=IV 10%, Interval=4 Weeks					
AUC [g*days/L]	7	427.23 (353.01 to 517.06)	413.19 (329.34 to 583.85)	329.34;583.85	142.68 (350.65;493.32)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	7	782.65 (640.48 to 956.38)	784.22 (563.37 to 1058.53)	563.37;1058.53	262.18 (670.94;933.12)
Clearance [mL/kg/days]	7	1.28 (1.05 to 1.56)	1.28 (0.94 to 1.78)	0.94;1.78	0.42 (1.07;1.49)
Cmax [g/L]	7	25.10 (19.72 to 31.94)	23.86 (19.42 to 42.60)	19.42;42.60	6.01 (20.65;26.66)
Tmax [h]	7	6.40 (1.61 to 25.35)	2.70 (1.92 to 95.85)	1.92;95.85	24.33 (2.58;26.92)
Cmin [g/L]	7	10.69 (8.55 to 13.36)	11.34 (8.04 to 13.71)	8.04;13.71	5.30 (8.05;13.35)

**Pharmacokinetic Parameters by Treatment
(Study 170904: Safety Analysis Set)**

Parameter [unit]	N	Geometric Mean (95% CI)	Median (95% CI)	Min:Max	IQR (Q1;Q3)
Analyte=IgG [g/L], Age Group=Subjects aged 65 years and older, Treatment=SC 20% 145% IV, Interval=1 Week					
AUC [g*days/L]	2	118.41 (NA)	118.62 (NA)	111.65;125.59	13.94 (111.65;125.59)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	2	443.00 (NA)	454.17 (NA)	354.03;554.32	200.29 (354.03;554.32)
Apparent Clearance [mL/kg/days]	2	2.26 (NA)	2.31 (NA)	1.80;2.82	1.02 (1.80;2.82)
Cmax [g/L]	2	18.00 (NA)	18.01 (NA)	17.51;18.51	1.00 (17.51;18.51)
Tmax [h]	2	112.44 (NA)	121.53 (NA)	75.42;167.63	92.22 (75.42;167.63)
Cmin [g/L]	2	15.89 (NA)	15.92 (NA)	15.06;16.77	1.71 (15.06;16.77)
Analyte=IgG [g/L], Age Group=Subjects aged 65 years and older, Treatment=SC 20% individualized, Interval=1 Week					
AUC [g*days/L]	7	132.92 (110.39 to 160.04)	139.02 (89.46 to 157.81)	89.46;157.81	35.59 (118.26;153.85)
AUC / (Dose / Weight) [(g*days/L)/(g/kg)]	7	583.39 (433.02 to 785.99)	582.14 (424.59 to 1106.33)	424.59;1106.33	191.45 (460.15;651.60)
Apparent Clearance [mL/kg/days]	7	1.71 (1.27 to 2.31)	1.72 (0.90 to 2.36)	0.90;2.36	0.64 (1.53;2.17)
Cmax [g/L]	7	23.06 (17.97 to 29.60)	24.19 (14.80 to 32.01)	14.80;32.01	10.27 (17.45;27.72)
Tmax [h]	7	93.85 (50.94 to 172.91)	119.02 (23.62 to 163.63)	23.62;163.63	69.00 (70.67;139.67)
Cmin [g/L]	7	15.64 (12.64 to 19.37)	15.85 (9.76 to 20.00)	9.76;20.00	3.45 (15.26;18.71)