

CLINICAL PHARMACOLOGY SUPPLEMENTARY BLA REVIEW
Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
Office of Tissues & Advance Therapies (OTAT)

STN 125683

Applicant: Grifols Therapeutics LLC

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

Indication: Primary Humoral Immunodeficiency

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TABLE OF CONTENTS

Introduction	1
Recommendations	3
Study Title: An Open-label, Multi-center Study to Evaluate the Safety and Pharmacokinetics of IGSC 20% Administered for 6 Months in Subjects with Primary Immunodeficiency.	4

INTRODUCTION

XEMBIFY, immune globulin subcutaneous (human), 20%, is a ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for subcutaneous administration. XEMBIFY consists of 18%-22% protein in 0.16-0.26 M glycine and 10 to 40 mcg/mL polysorbate 80.

XEMBIFY is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. Isotonicity is achieved by the addition of glycine. XEMBIFY is incubated in the final container (at the low pH of 4.1 to 4.8). In the manufacturing process of XEMBIFY, there were several steps taken for virus inactivation or removal. The main steps of the manufacturing process that contributed to the virus clearance capacity were as follows:

- Caprylate precipitation/depth filtration
- Caprylate incubation
- Column chromatography

- Nanofiltration
- Low pH final container incubation

To provide additional assurance of the pathogen safety of the final product, the capacity of the XEMBIFY manufacturing process to remove and/or inactivate viruses has been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

RECOMMENDATION

From clinical pharmacology perspective, the study design, PK analysis, and results are acceptable.

Study Title: An Open-label, Multi-center Study to Evaluate the Safety and Pharmacokinetics of IGSC 20% Administered for 6 Months in Subjects with Primary Immunodeficiency (PI).

This was a prospective, multi-center, open-label, single-sequence, 6-month, pharmacokinetic (PK), safety, and tolerability study of IGSC 20% in subjects with PI (approximately 30 study centers). Approximately 50 subjects were planned to be enrolled in order to have approximately 30 adult subjects and 12 to 18 pediatric subjects (age 2 to 16 years). Pediatric enrollment was stratified by age category for each of the following age groups: 2 to 5 years, >5 to 12 years, and >12 to 16 years of age.

The objectives of the study were as follows:

- To determine a weekly subcutaneous (SC) dose of IGSC 20% that produced steady-state AUC of total IgG that was non-inferior to that of IV dose of IGIV-C 10% in subjects with Primary Immunodeficiency (PI).
- To determine if IGSC 20% replacement therapy maintained mean steady-state trough total IgG levels that were comparable to the mean trough total IgG levels with the IGIV-C 10% replacement therapy in PI subjects.
- To evaluate the safety and tolerability of SC administered IGSC 20%.
- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4).
- Antibody levels for *Streptococcus pneumoniae* (*S. pneumoniae*), *Hemophilus influenzae* (*H. influenzae*), and *Clostridium tetani* (*C. tetani* [tetanus]).

The selection of the dose for SC administration was based on the literature data of the absolute bioavailability of SC administered IgG and prior experience with other products (Gamunex-C, Hizentra, and Gammagard). Generally, the absolute bioavailability of SC administered IgG range from 1.37 to 1.53. In this study, a dose adjustment factor of 1.37 was used for SC administration.

The study consisted of 2 phases: an IV phase followed by a SC phase. The PK study consisted of all subjects who received study medication and had sufficient and valid serum IgG concentration versus time data for either IV or SC phase. The subjects were treated with IGIV-C 10% and IGSC 20%.

IGSC 20%: Grifols Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) is a sterile liquid formulation of immunoglobulin that is purified from human plasma via a multi-step process. IGSC 20% vials were supplied in a 50 mL vial size or smaller containing a 20% solution of immunoglobulin (ie, a concentration of 20 g/100 mL) with a nominal 10 grams immunoglobulin per vial.

IGIV-C 10%: IGIV-C 10% is a sterile liquid formulation of immunoglobulin that is purified from human plasma via a multi-step process. IGIV-C 10% is a licensed product. IGIV-C 10% vials were supplied in the vial sizes of 10, 25, 50, 100, and 200 mL.

Blood samples for PK analysis (subjects >5 years of age) following IV administration were taken at the following time: prior to infusion (at time 0), 1 h after completion of infusion, 3 to 16 hours post-infusion with a window of 2 hours around the 16-hour time point if required by site, 1 day \pm 2 h post-infusion, 2 days \pm 2 h post-infusion, 3 days \pm 4 h post-infusion, 5 days \pm 4 h post-infusion, 7 days \pm 1 day post-infusion, 14 days \pm 1 day post-infusion, 21 days \pm 1 day post-infusion (last sample for subjects on a 3-week dosing schedule) and 28 days \pm 1 day post-infusion (only for subjects on a 4-week dosing schedule).

Blood samples for PK analysis (subjects \leq 5 years of age) following IV administration were taken at the following time: prior to infusion (at time 0), 1 h after completion of infusion, 3 to 16 hours post-infusion with a window of 2 hours around the 16-hour time point if required by site, 2 days \pm 2 h post-infusion, 7 days \pm 1 day post-infusion, 14 days \pm 1 day post-infusion, 21 days \pm 1 day post-infusion (last sample for subjects on a 3-week dosing schedule) and 28 days \pm 1 day post-infusion (only for subjects on a 4-week dosing schedule).

Blood samples for PK analysis (subjects >5 years of age) following SC administration were taken at the following time: prior to the 13th SC infusion, 1 day \pm 4 h post-infusion, 3 days \pm 4 h post-infusion, 4 days \pm 4 h post-infusion, 5 days \pm 4 h post-infusion, 7 days \pm 1 day post-infusion.

Blood samples for PK analysis (subjects \leq 5 years of age) following SC administration were taken at the following time: prior to the 13th SC infusion, 3 days \pm 4 h post-infusion, 7 days \pm 1 day post-infusion.

The primary PK parameter evaluated was the steady-state AUC of total IgG over a regular dosing interval defined as follows:

- AUC_{0- τ} , SC, the AUC over a weekly dosing interval (τ) at an approximate steady-state condition following weekly SC infusion.
- AUC_{0- τ} , IV, the AUC over a regular dosing interval (τ) at an approximate steady-state condition following the regular IV infusion, either every 3 weeks or every 4 weeks.

The subjects received their IV dose ranging from 300-800 mg/kg. Because the dosing intervals were different between the IV and SC Phases, prior to the statistical comparison, the AUC_{(0-21) days} or AUC_{(0-28) days} from the IV Phase were adjusted to AUC_{(0-7) days} as follows:
AUC_{(0-7) days, IV} = AUC_{(0-21) days, IV} / 3, for subjects on an every-3-week IV dosing schedule
AUC_{(0-7) days, IV} = AUC_{(0-28) days, IV} / 4, for subjects on an every-4-week IV dosing schedule

Non-inferiority of steady-state AUC of total IgG between the final SC dose of IGSC 20% and the IGIV-C 10% was tested based on 90% confidence interval. The Test (SC Phase) was considered non-inferior to Reference (IV Phase) if the lower bound of the 90% CI for the geometric LSM ratio of AUC_{(0-7) days} between the Test and Reference was above 0.80 (80%). The results of the study are summarized in Tables 1-3. The concentration-time profile of total IgG is shown in Figure 1.

The results of the study indicated that AUC₍₀₋₇₎ days was comparable between IV and SC administration but the C_{max} was about 35% lower following SC administration than IV (Table 1). The 90% confidence interval indicated that the AUC₍₀₋₇₎ days following SC administration was bioequivalent to the IgG following IV administration (Table 4). Due to small sample size, the impact of age (children), sex, race, and ethnicity on the PK of IgG could not be evaluated (Tables 2 & 3). AUC and C_{max} following IV and SC administration was higher (10-15%) in males than females (Table 3). The higher AUC and C_{max} values may not be of any clinical significance.

Table 1: PK Parameters of Total IgG at Steady-State in IV and SC Phases

Phase	Statistics	AUC _{0-21 days} (h*mg/dL)	AUC _{0-28 days} (h*mg/dL)	AUC _{0-7 days} (h*mg/dL) ^a	C _{max} (mg/dL)	t _{max} (hour)
IV	n	6	43	49	49	49
	Mean±SD	671958.7±87393.42	841996.2±173255.00	212150.5±41832.11	2153.7±436.90	5.814±8.0194
	CV%	13	21	20	20	137.93
	Min, Max	550176, 749872	424364, 1233619	106091, 308405	1430, 3170	0.75, 48.93
	Geometric Mean	667003.5	823944.3	207921.5	2112.3	
	90% CI for Geometric Mean	596949.2, 745278.9	779831.8, 870552.1	197865.8, 218488.2	2014.7, 2214.6	
SC	n			39	41	41
	Mean±SD			218315.6±48121.25	1395.2±312.32	76.089±35.7163
	CV%			22	22	46.94
	Min, Max			102650, 367496	636, 2320	0.00, 167.72
	Geometric Mean			213141.4	1360.7	
	90% CI for Geometric Mean			200568.6, 226502.3	1280.7, 1445.8	

^a AUC_{0-7 days} in the IV Phase is calculated as AUC_{0-21 days}/3 for subjects on an every-3-week IV dosing schedule, and as AUC_{0-28 days}/4 for subjects on an every-4-week IV dosing schedule.

Sources: Post-text Tables 14.2.1/2.1 and 14.2.1/2.2

Table 2: Steady-State AUC in IV and SC Phases as a function of age

Age Group (years) Statistics	Study Phase				AUC Ratio SC/IV AUC _{0-7 days} Ratio, SC/IV
	IV (N = 49)			SC (N=41)	
	AUC _{0-21 days} (h*mg/dL)	AUC _{0-28 days} (h*mg/dL)	AUC _{0-7 days} (h*mg/dL) ^a	AUC _{0-7 days} (h*mg/dL)	
All Subjects (N)	6	43	49	39 ^b	38
Mean±SD	671958.7±87393.42	841996.2±173255.00	212150.5±41832.11	218315.6±48121.25	1.049±0.1269
CV%	13	21	20	22	12.10
Min, Max	550176, 749872	424364, 1233619	106091, 308405	102650, 367496	0.69, 1.45
2 -5 (n)	0	2	2	1	1
Mean±SD	NC	797724.0±273175.15	199431.0±68293.79	183864.0±NC	1.220±NC
CV%	NC	34	34	NC	NC
Min, Max	NC	604560, 990888	151140, 247722	183864, 183864	1.22, 1.22
>5 -12 (n)	0	7	7	5	5
Mean±SD	NC	753285.6±162514.63	188321.3±40628.67	215557.6±27604.33	1.178±0.1878
CV%	NC	22	22	13	15.94
Min, Max	NC	568669, 1029075	142167, 257269	187838, 245614	0.95, 1.45
>12 -16 (n)	2	4	6	4	4
Mean±SD	705206.5±46324.69	902168.8±215633.55	228717.8±42609.51	240008.8±40578.07	1.053±0.0685
CV%	7	24	19	17	6.51
Min, Max	672450, 737963	714202, 1211554	178551, 302889	205646, 298678	0.99, 1.15
>16 (n)	4	30	34	29	28
Mean±SD	655334.8±104444.27	857623.8±166849.67	214881.1±40508.74	216987.0±52388.87	1.019±0.1059
CV%	16	19	19	24	10.40
Min, Max	550176, 749872	424364, 1233619	106091, 308405	102650, 367496	0.69, 1.20

Note: NC = Not calculated.

^a AUC_{0-7 days} in the IV Phase is calculated as AUC_{0-21 days}/3 for subjects on an every-3-week IV dosing schedule, and as AUC_{0-28 days}/4 for subjects on an every-4-week IV dosing schedule.

^b AUC_{0-7 days} was calculable for 39 of 41 subjects in the SC phase PK population due to discrepancies in actual collection time for the last sample and the resulting percentage of AUC due to extrapolation exceeded 40% for 2 subjects.

Source: Post-text Table 14.2.1/2.3

Table 3: PK Parameters of total IgG as a function of sex, race, and ethnicity

PK Parameter	AUC _{0-7 days} (h*mg/dL)		C _{max} (mg/dL)		T _{max} (h)	
	n Mean (CV%)		n Mean (CV%)		n Mean (CV%)	
Study Phase	IV	SC	IV	SC	IV	SC
IV Dosing Frequency						
Every 3 weeks	6 223986.2 (13)	4 218859.0 (18)	6 2060.0 (23)	6 1420.0 (15)	6 7.083 (123.85)	6 92.723 (29.91)
Every 4 weeks	43 210499.0 (21)	35 218253.5 (23)	43 2166.7 (20)	35 1391.0 (24)	43 5.637 (142.00)	35 73.237 (49.80)
Sex						
Male	24 223218.8 (19)	20 233692.7 (22)	24 2257.1 (19)	20 1485.9 (22)	24 4.569 (117.07)	20 72.691 (56.59)
Female	25 201524.9 (19)	19 202129.2 (20)	25 2054.4 (20)	21 1308.9 (21)	25 7.010 (141.34)	21 79.326 (38.26)
Race						
White	45 210795.1 (20)	35 215844.8 (23)	45 2117.8 (20)	37 1380.4 (23)	45 6.042 (137.97)	37 76.092 (47.20)
Black/African American	1 254014.0 (NC)	1 278220.0 (NC)	1 2690.0 (NC)	1 1740.0 (NC)	1 2.830 (NC)	1 72.720 (NC)
Indian/Alaska Native	3 218527.3 (18)	3 227174.0 (13)	3 2513.3 (25)	3 1463.3 (14)	3 3.390 (9.45)	3 77.180 (61.98)
Ethnicity						
Hispanic/Latino	4 214685.8 (21)	4 217405.5 (15)	4 2330.0 (29)	4 1385.0 (17)	4 3.218 (25.84)	4 75.268 (53.35)
Not Hispanic/Latino	45 211925.2 (20)	35 218419.6 (23)	45 2138.0 (20)	37 1396.3 (23)	45 6.045 (137.85)	37 76.178 (47.02)

Note: NC = Not calculated.

Source: Post-text Table 14.2.1/4

Table 4: Statistical Analysis of Primary PK Endpoint of Steady State AUC_{0-7days} (h*mg/dL) of Total IgG

	Mean±SD	Geometric Mean	Geometric LSM	GLSM Ratio, SC/IV	90% CI, GLSM Ratio, SC/IV
PK Population					
IV Phase ^a (n=49)	212150.5±41832.11	207921.5	207822.8		
SC Phase (n=39)	218315.6±48121.25	213141.4	215829.3	1.04	(1.00, 1.07)
PK Population: Interim 8 Subjects Excluded					
IV Phase ^a (n=41)	212190.7±43625.64	207554.5	207326.8		
SC Phase (n=31)	221905.1±47538.66	216935.3	220783.6	1.06	(1.03, 1.10)
PK Population: Only Subjects with Sufficient and Valid Serial PK Profile in both IV and SC Phases					
IV Phase ^a (n=38)	209425.9±43940.16	204762.0	204762.0		
SC Phase (n=38)	218537.6±48746.97	213227.8	213227.8	1.04	(1.01, 1.08)

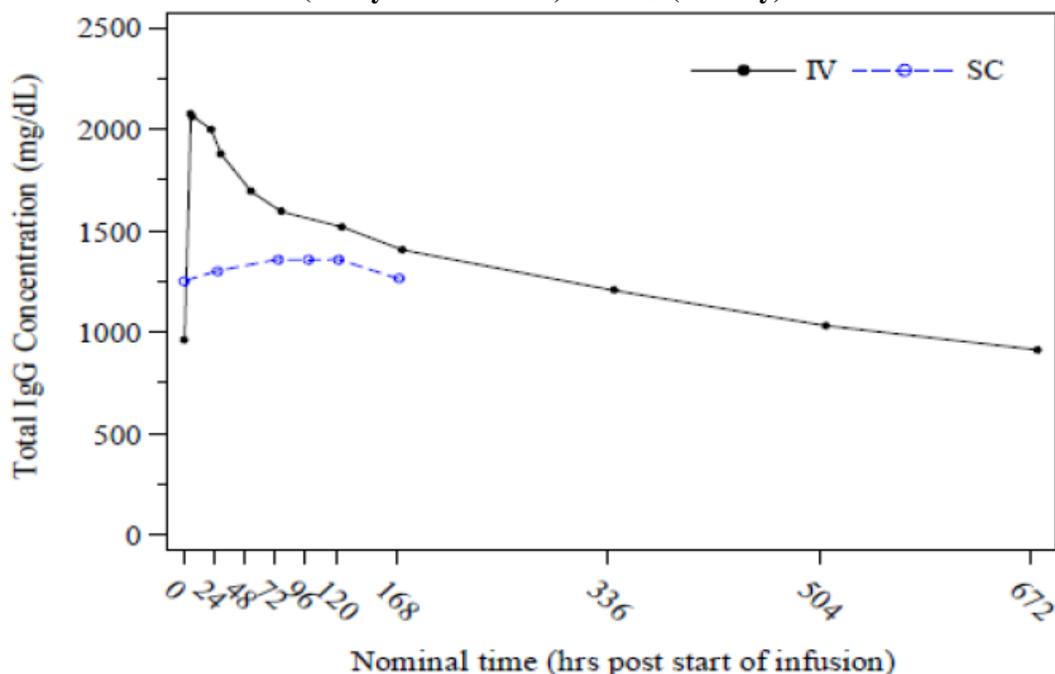
Geometric least-squares means (GLSMs), GLSM ratio, and 90% CI of GLSM ratio are determined from a mixed-effect model for the log-transformed parameter value with study phase as a fixed effect and subject as a random effect.

Note: IV Phase is the reference phase. SC Phase is the test phase being compared to the reference.

^a AUC_{0-7 days} in the IV Phase is calculated as AUC_{0-21 days}/3 for subjects on an every-3-week IV dosing schedule and as AUC_{0-28 days}/4 for subjects on an every-4-week IV dosing schedule.

Sources: Post-text Tables 14.2.1/3.1, 14.2.1/3.2, and 14.2.1/3.3

Figure 1: Mean Steady-State Serum Total IgG Concentration vs. Time Following IV (Every 3 or 4 Weeks) and SC (Weekly) Administration



Trough Serum Concentrations of Total IgG:

The mean serum trough concentration of total IgG measured in subjects at IV or SC phases are summarized in Table 5 and Figure 2. The average of the steady-state mean trough concentrations of total IgG for all subjects during the IV phase was approximately 957 mg/dL.

Table 5: Trough Total IgG during IV and SC Phases

	Trough (mg/dL)								Mean Trough Ratio SC/IV
	IV Phase			SC Phase					
	IV#1	IV#2	Mean Trough ^a	SC#13	SC#14	SC#17	SC#21	Mean Trough ^b	
n	51	49	51	41	38	41	38	44	43
Mean	997.4	923.9	957.13	1247.8	1264.6	1232.0	1227.2	1244.84	1.333
CV%	37	20	25.3	23	24	23	24	21.9	15.68
Range (min, max)	335, 2740	367, 1300	351.0, 1920.0	580, 2220	588, 1930	761, 2090	601, 1950	651.5, 2047.5	0.78, 1.86

^a Mean Trough in the IV Phase is calculated as the average of the trough concentrations at the IV#1 and IV#2 visits.

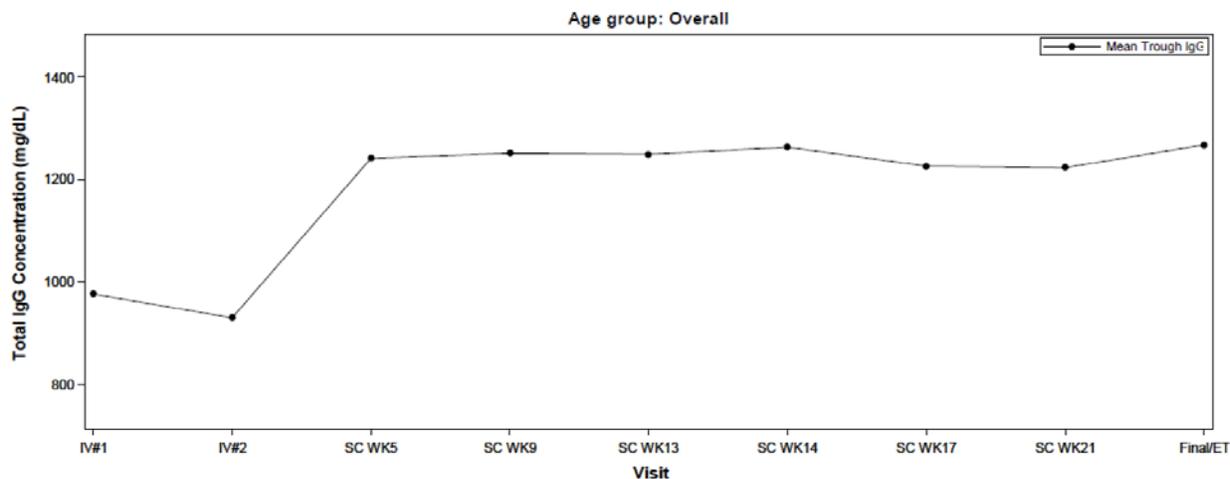
^b Mean Trough in the SC Phase is calculated as the average of the trough concentrations at the SC#13, SC#14, SC#17, and SC#21 visits.

Source: Post-text Table 14.2.1/5.1

The mean serum trough concentrations of total IgG during the SC phase of the study were relatively constant across week #13 to week #21, with a mean value of 1245 mg/dL ranging from

1227 to 1264 mg/dL in all subjects at each visit. Weekly SC administration of IGSC 20% resulted in relatively constant serum concentrations of total IgG that were 33% higher than the mean serum trough concentrations of total IgG following IV administration.

Figure 2: Mean Trough Total IgG Concentrations (mg/dL) vs. Visit during the IV and SC Phases



Source: Post-text Figure 14.2.4/2

Trough Concentrations of IgG Subclasses in Serum:

The serum trough concentrations of IgG subclasses (IgG1, IgG2, IgG 3 and IgG4) were measured in both the IV and SC phases. The results for both study phases are summarized in Table 6. After the subjects switched from the IV administration to SC administration, the levels of all subclasses (IgG1, IgG2, IgG 3 and IgG4) showed an increase at SC week 9 (the first measurement in the SC phase). The increases were maintained throughout the SC phase. Increases after switching from the IV infusion to the SC infusion in mean trough comparing IV#2 to SC week #9 were 32% for IgG1, 35% for IgG2, 21% for IgG3, and 41% for IgG4.

Serum Trough Levels of Antibodies for Streptococcus pneumoniae, Hemophilus influenzae, and Clostridium tetani:

Trough titers of antibodies against H. influenza, C. tetani, and 23 separate serotypes of S. pneumonia were also measured and compared across study phases. After the subjects switched from the IV administration of IGIV-C 10% to the SC administration of IGSC 20%, there was an increase in these specific antibody titers, which was maintained throughout the SC phase.

Table 6: Trough Concentrations of IgG Subclasses During IV and SC Phases

IgG Subclasses	Statistics	IV#1 (N = 50)	IV#2 (N = 51)	SC Week 9 (N = 44)	SC Week 17 (N = 41)	Final/Early Termination Visit (N = 50)	Change from IV to SC ^a
IgG1	Mean (mg/dL) [Range]	601.4 [246, 1160]	608.2 [278, 1270]	805.4 [348, 1420]	794.2 [501, 1420]	828.6 [365, 1620]	32.4%
IgG2	Mean (mg/dL) [Range]	270.87 [73.3,477.0]	271.31 [84.9, 420.0]	365.57 [120.0, 652.0]	360.98 [169.0, 621.0]	366.94 [132.0, 550.0]	34.7%
IgG3	Mean (mg/dL) [Range]	22.770 [3.34, 78.10]	23.484 [3.43, 81.40]	28.456 [8.54, 149.00]	25.357 [7.08, 61.30]	27.588 [4.90, 133.00]	21.2%
IgG4	Mean (mg/dL) [Range]	27.401 [2.44, 98.80]	27.701 [8.26, 86.20]	39.025 [17.60, 96.30]	38.124 [19.40, 82.80]	38.068 [13.00, 93.70]	40.9%

^a Change from IV to SC (%) = (mean trough concentration in SC Week 9 - mean trough concentration in IV#2) ÷ mean trough concentration in IV#2 × 100.

Sources: [Post-text Tables 14.2.2/1](#), [14.2.2/2](#), [14.2.2/3](#), and [14.2.2/4](#).

Conclusions: The results of the study indicated that IGSC 20% (1.37 times IV dose) was bioequivalent to IGIV10%. Under steady-state conditions, the mean trough concentration following weekly SC administration was 1245 mg/dL whereas, following IV administration, the mean trough concentration was 957 mg/dL. The steady-state trough levels of IgG following SC infusions of IGSC 20% were 33% higher than those from IV infusion of IGIV-C 10%. In addition, serum trough levels of the 4 IgG subclasses were constant across each study phase with increases similar in extent (range: 21-41%) to those for total IgG observed following the switch from IGIV-C 10% to SC administration of IGSC 20%. Due to small sample size, the impact of age (children), sex, race, and ethnicity on the PK of IgG could not be evaluated.