CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology Clinical Review

Office of Blood Review & Research

STN 125046/1325 (Supplement)
Sponsor: Grifols Therapeutics Inc
Product: Gamunex-C
Indication: Primary humoral immunodeficiency
Submission Date: February 4, 2015
Reviewer: Iftekhar Mahmood, Ph. D.
RPM: Edward Thomson
Through: Bindu George, M. D.

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INTRODUCTION

GAMUNEX-C is a ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for intravenous and subcutaneous (PI indication only) administration. GAMUNEX-C consists of 9%–11% protein in 0.16–0.24 M glycine.

GAMUNEX-C 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. GAMUNEX-C is incubated in the final container (at the low pH of 4.0–4.3). The product is intended for intravenous administration and may be administered subcutaneously in treatment of PI.

CLINICAL PHARMACOLOGY LABELING COMMENTS

1 Clinical Pharmacology

1.1 Mechanism of Action

PI

GAMUNEX-C supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacterial, viral, parasitic, and mycoplasmal agents, and their toxins. The mechanism of action in PI has not been fully elucidated.

ITP

The mechanism of action of high doses of immunoglobulins in the treatment of ITP has not been fully elucidated.

CIDP

The precise mechanism of action in CIDP has not been fully elucidated.

1.2 Pharmacodynamics

Immunoglobulins are fractionated blood products made from pooled human plasma. Immunoglobulins are endogenous proteins produced by B lymphocyte cells. The main component of GAMUNEX-C is IgG (≥98%) with a sub-class distribution of IgG_1, IgG_2, IgG_3 and IgG_4 of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively.

1.3 Pharmacokinetics

Intravenous Administration

Two randomized pharmacokinetic crossover trials were carried out with GAMUNEX-C in 38 subjects with Primary Humoral Immunodeficiencies given 3 infusions 3 or 4 weeks apart of test product at a dose of 100-600 mg/kg body weight per infusion. ~~One trial compared the pharmacokinetics characteristics of GAMUNEX-C to GAMIMUNE N, 10% and the other trial compared the pharmacokinetics of GAMUNEX-C (10% strength) with a [redacted] concentration of this product. The ratio of the geometric least square means for dose normalized IgG peak levels of GAMUNEX-C and GAMIMUNE N, 10% was 0.996. The corresponding value for the dose normalized area under the curve (AUC) of IgG levels was 0.990. The results of both PK parameters were within the pre-established limits of 0.080 and 1.25. Similar results were obtained in the comparison of GAMUNEX-C 10% to a [redacted] concentration of GAMUNEX-C.~~

The ~~main~~ pharmacokinetic parameters of GAMUNEX-C, measured as total IgG ~~in study 100152 are displayed below:~~ are shown in Table 13.

Table 13: PK Parameters of GAMUNEX®-C ~~and GAMIMUNE® N, 10%~~

In this Table please include the PK parameters as shown in pediatric age groups following IV administration. You can combine the two Tables. Please do not provide GAMIMUNE-N PK information.

	GAMUNEX®-C				~~GAMIMUNE® N, 10%~~			
	N	Mea	SD	Med	~~N~~	~~Mea~~	~~SD~~	~~Med~~

		n		ia n		n		ia n
C_{max} (mg/mL)	17	19.04	3.06	19.71	17	19.31	4.17	19.30
$C_{max-norm}$ (kg/mL)	17	0.047	0.007	0.046	17	0.047	0.008	0.047
AUC $_{(0-tn)}^{*}$ (mg*hr/mL)	17	6746.48	1348.13	6949.47	17	6854.17	1425.08	7119.86
AUC $_{(0-tn)}^{*}$ $_{norm}$ (kg*hr/mL)	17	16.51	1.83	16.95	17	16.69	2.04	16.99
$T_{1/2}^{\ddagger}$ (days)	16	35.74	8.69	33.09	16	34.27	9.28	31.88

* Partial AUC: defined as pre-dose concentration to the last concentration common across both treatment periods in the same patient.

† Only 15 subjects were valid for the analysis of $T_{1/2}$.

The two pharmacokinetic trials with GAMUNEX-C show the IgG concentration/time curve follows a biphasic slope with a distribution phase of about 5 days characterized by a fall in serum IgG levels to about 65-75% of the peak levels achieved immediately post-infusion. This phase is followed by the elimination phase with a half-life of approximately 35 days. IgG trough levels were measured over nine months in the therapeutic equivalence trial. Mean trough levels were 7.8 ± 1.9 mg/mL and for GAMUNEX-C trough levels were 7.8 ± 1.9 mg/mL. treatment group and 8.2 ± 2.0 mg/mL for the GAMIMUNE N, 10% control group.

Add PK study results in pediatrics following IV administration and include the following Table. (You can combine it with adult information).

PK parameters following IV administration of Gamunex-C by age

Age Category	Statistics	$t_{1/2}$ (hr)	AUC(0-t) (hr*mg/mL)	AUC(0-tau) (hr*mg/mL)	CL(0-t) (mL/hr/kg)	Vss (mL/kg)
2 – 5 years	N	1	1	1	1	1
	Mean	1038.50	7479.0	7499.0	0.05430	82.040
	SD	N/A	N/A	N/A	N/A	N/A
6 – 11 years	N	5	5	5	5	5
	Mean	758.52	5953.6	6052.6	0.09128	94.784
	SD	137.989	1573.84	1333.59	0.027465	17.6773
12 – 16 years	N	8	8	8	8	8
	Mean	717.90	8131.9	8009.5	0.07029	73.303
	SD	170.141	1173.38	1358.76	0.015912	17.2204
≥ 17 years	N	29	29	29	29	29
	Mean	720.62	7564.9	7524.8	0.06243	65.494
	SD	130.864	1190.68	1183.05	0.015547	18.7172

SD = standard deviation; N/A = not applicable.

PI: Subcutaneous Administration

In a single sequence, open-label, crossover trial in adults and adolescents, the pharmacokinetics, safety, and tolerability of SC administered GAMUNEX-C in subjects with PI were evaluated. A total of 32 and 26 subjects received GAMUNEX-C as IV or SC for PK study, respectively. Subjects received GAMUNEX-C 200-600 mg/kg IV (?) every 3-4 weeks for at least 3 months, at which time they entered the IV phase (?) of the study. Subjects were crossed over to weekly SC infusions. The weekly SC dose was determined by multiplying the total IV dose by 1.37 and dividing the resultant new total dose by 3 or 4 depending on the previous IV interval. The PK endpoint parameter (AUC of total plasma IgG) following IV and SC administration is summarized below in Table 14. The lower bound of the 90% confidence interval for the geometric mean ratio of AUC (SC vs. IV) was 0.861, therefore, meeting the pre-specified non-inferiority margin between the two modes of administration.

~~**Table 14: Summary of PK Endpoint of AUC**~~

~~Trial~~	~~Route of Administration~~	~~Statistics~~	~~$AUC_{0-\tau,IV}$ (mg*h/mL)~~	~~$AUC_{0-\tau,SC}$ (mg*h/mL)~~	~~Adj. $AUC^{*}_{0-\tau,SC}$ (mg*h/mL)~~
~~Adult, Adolescent~~	~~IV (n = 32)~~	~~Mean~~	~~7640~~	~~NA‡~~	~~NA~~
		~~%CV ‡~~	~~15.9~~		
		~~Range~~	~~5616 - 10400~~		
	~~SC~~	~~Mean~~	~~NA~~	~~1947~~	~~6858~~

	(n = 26)	%CV		20.4	18.1
		Range		1300 2758	5169 10364
Child, Adolescent	IV (n = 11)	Mean	6870	NA	NA
		%CV	21.0		
		Range	4868-8754		
	SC (n = 10)	Mean	NA	2308	7317
		%CV		16.5	14.3
		Range		1876-3039	5627-9117

CV, coefficient of variation; NA, not applicable

* Adj. $AUC_{0-\tau,SC}$: Adjusted steady-state area under the concentration vs. time curve following SC administration based on IV dosing schedule, calculated as $AUC_{0-\tau,SC}$ multiplied by 3 or 4 for subjects on every 3-week or every 4-week IV dosing schedule, respectively.

† CV, coefficient of variation; NA, not applicable

Table 14: Summary of AUC of serum total IgG at steady state following IV or SC administration

Route of Administration	IV (N = 11)			SC (N = 10)	AUC Ratio, SC/IV
Statistics	$AUC_{0-\tau,IV}$ (h*mg/dL) (0-21 days)	$AUC_{0-\tau,IV}$ (h*mg/dL) (0-28 days)	Adj._$AUC_{0-\tau,IV}$[a] (h*mg/dL) (0-7 days)	$AUC_{0-\tau,SC}$ (mg*h/mL) (0-7 days)	
All Subjects (N)	9	2	11	10	10
Mean	661851.9	800112.0	216873.7	230830.0	1.05
%CV	22%	9%	21%	17%	-
Range	486832.0 – 875356.0	749868.0 - 850356.0	162277.0 - 291785.0	187577.0 - 303913.0	0.86 – 1.21
Age Group: 2-5 years (N)		1	1	1	1
Mean	NC	749868.0	187467.0	202298.0	1.08
%CV	NC	NC	NC	NC	-
Range	NC	NC	NC	NC	NC
Age Group: 6-11 years (N)	5		5	4	4
Mean	605265.4	NC	201755.0	238921.3	1.14
%CV	22	NC	22	19	-
Range	486832.0 - 830830.0	NC	162277.0 - 276943.0	197074.0 - 303913.0	1.10 - 1.21
Age Group: 12-16 years (N)	4	1	5	5	5
Mean	732585.0	850356.0	237873.8	230063.4	0.98
%CV	20	NC	19	17	-
Range	527066.0 - 875356.0	NC	175689.0 - 291785.0	187577.0 - 267197.0	0.86 - 1.07

[a] Adj._ $AUC_{0-\tau,IV}$: Adjusted weekly IV $AUC_{(0-7\ days)}$ is calculated as $AUC_{(0-21\ days)}/3$ or $AUC_{(0-28\ days)}/4$.

Please convert Table 14 in word format

In a second, single sequence, open-label, crossover trial, the pharmacokinetics, safety, and tolerability of SC administered GAMUNEX-C were evaluated in children and adolescents. The design of the study was essentially the same as above. A total of 11 and 10 subjects (age range 2 to 16 years) received GAMUNEX-C as IV or SC for PK analysis, respectively. The PK parameter (AUC of total IgG) following IV and SC administration is summarized in Table 14. The PK analysis results are consistent to those in the adult and adolescent trial, demonstrating the appropriateness of the conversion factor of 1.37 applied to calculating the SC dose from the IV dose of GAMUNEX-C in pediatric populations.

The mean trough concentrations (mean C_{trough}) of ~~plasma~~ total IgG following IV and SC administration are presented in Table 15 for both studies.

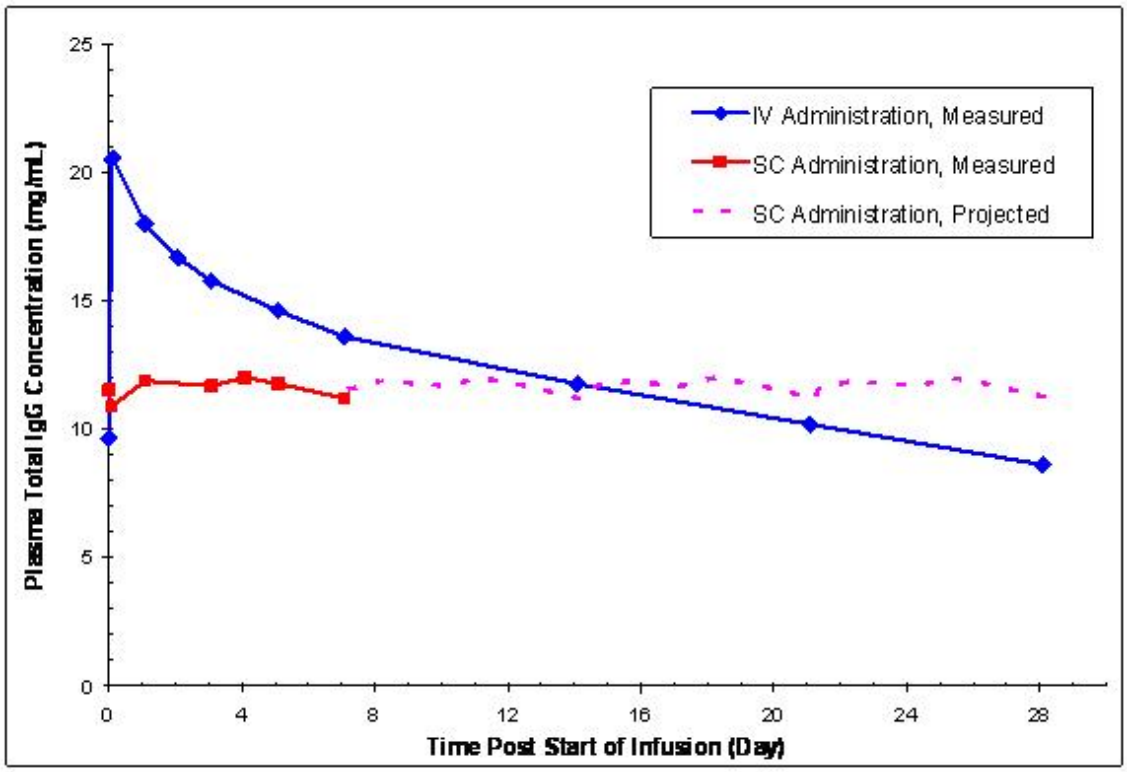
Table 15: Mean ~~Plasma~~ Trough Concentrations of Total IgG (mg/mL) ~~in Plasma~~

	Adult, Adolescent*		Child, Adolescent†	
	IV Mean C_{trough}	SC Mean C_{trough}	IV Mean C_{trough}	SC Mean C_{trough}
n	32	28	11	10
Mean (mg/mL)	9.58	11.4	9.97	13.25
%CV	22.3	20.4	19	14
Range	6.66-14.0	8.10-16.2	7.84-13.20	10.77-16.90

* Measured in plasma; † Measured in serum

In contrast to plasma total IgG levels observed with monthly IV GAMUNEX-C treatment (rapid peaks followed by a slow decline), the plasma IgG levels in subjects receiving weekly SC GAMUNEX-C therapy were relatively stable (Figure 7, adult and adolescent trial).

Figure 7: Mean Steady-state Plasma Total IgG Concentration vs. Time Curves Following IV Administration or Weekly SC Administration in Adult and Adolescents ~~Trial~~



RECOMMENDATIONS

The Pharmacokinetic study design, results, and interpretation of data are acceptable. The applicant should modify the clinical pharmacology labeling section as suggested by the FDA.

The applicant has now revised the clinical pharmacology labeling section as suggested by the FDA and is acceptable.

Study Title: An Open-label, Single-sequence, Crossover Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Subcutaneous GAMUNEX®-C in Pediatric Subjects with Primary Immunodeficiency (study # T5004-401).

This was a multi-center, open-label, single-sequence, crossover study to evaluate the pharmacokinetics (PK), safety and tolerability of SC-administered GAMUNEX-C in pediatrics (2-16 years of age) with primary immunodeficiency (PI) disease. The objectives of the study were as follows:

- Evaluate the steady-state AUC (area under curve) and mean trough of serum total IgG for subcutaneously administered GAMUNEX-C compared to that of the regular IV administered dose in pediatrics.
- Evaluate the safety and tolerability of subcutaneously administered GAMUNEX-C in pediatrics

A total of 14 subjects during the IV phase and 10 subjects during the SC phase were included in the PK analysis for total IgG. There was 1 subject in 2-5 years of age, 5 subjects in 6-11 years of age and 8 subjects in 12-16 years of age. Schema of the study is shown in Figure 1.

The GAMUNEX-C IV dose (200-600 mg/kg per infusion) and dosing interval (every 3-4 weeks) used for each subject were based on each subject's previous IgG treatment regimen and the investigator's best clinical judgment. All subjects switched to the SC Phase upon completion of the IV Phase; approximately one week (7 to 10 days) after the IV #2 visit. Dosing in the SC Phase continued for 12 weeks. The SC dose was 1.37 times of the IV dose to adjust for bioavailability.

SC phase: Weekly SC administration of GAMUNEX-C

For subjects on an every-4-week IV dosing - 1/4 of the IV dose multiplied by 1.37

For subjects on an every-3-week IV dosing - 1/3 of the IV dose multiplied by 1.37

For PK analysis, blood samples were taken as described below.

Steady-state AUC and PK parameters following IV administration GAMUNEX-C was determined from five serial blood samples for total serum IgG concentration taken at the following time points:

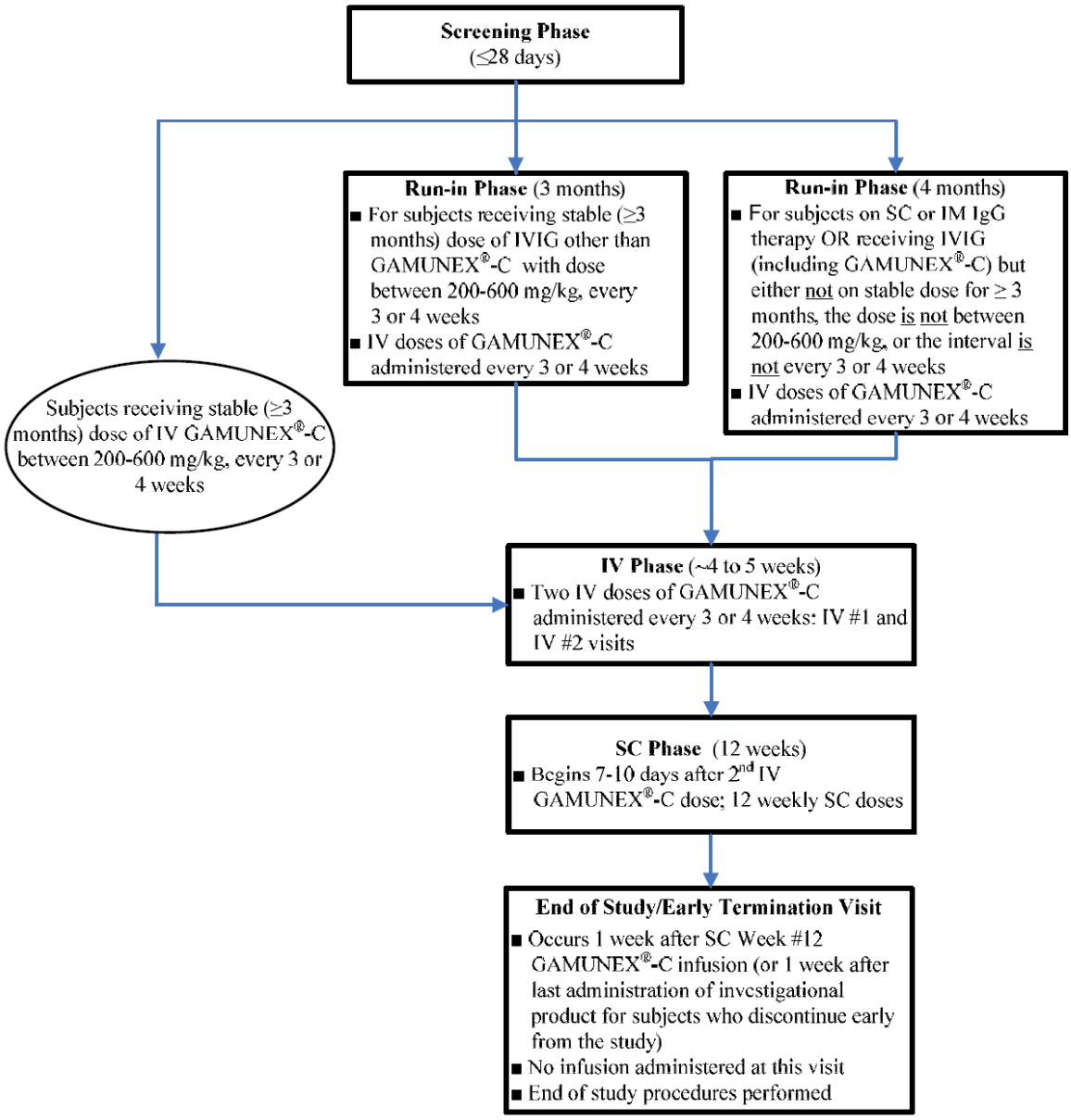
- Immediately prior to the infusion at the IV #1 visit
- 1 hour post infusion at the IV #1 visit
- 2 days post infusion at the IV #1 Day 2 visit
- 7 days post infusion at the IV #1 Day 7 visit
- 3 or 4 weeks post infusion at the IV #2 visit (immediately prior to the IV #2 infusion)

Steady-state AUC for SC-administered GAMUNEX-C was determined by collection of three serial blood samples for total serum IgG concentration obtained at the following times:

- SC Week #5 (pre-infusion)
- SC Week #9 (pre-infusion)
- SC Week #12 (pre-infusion)
- SC #12 Day 3 (three days post SC #12 infusion)

In addition, two blood samples for determination of trough serum total IgG concentration were drawn prior to SC infusions #5 and #9 at the SC week #5 and SC week #9 visits, respectively.

Figure 1: Study Schema



The PK parameters of Gammunex-C following IV administration are shown in Table 1. In Table 2, a comparison between $AUC_{(0\text{-}tau)}$ and $AUC_{(0\text{-}7)}$ following SC and IV administration of Gammunex-C is shown. In Figure 1, mean steady-state serum total IgG concentration-time curves following IV administration or weekly SC administration are shown.

Table 1: PK parameters following IV administration of Gamunex-C by age

Age Category	Statistics	$t_{1/2}$ (hr)	AUC(0-t) (hr*mg/mL)	AUC(0-tau) (hr*mg/mL)	CL(0-t) (mL/hr/kg)	Vss (mL/kg)
2 – 5 years	N	1	1	1	1	1
	Mean	1038.50	7479.0	7499.0	0.05430	82.040
	SD	N/A	N/A	N/A	N/A	N/A
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	SD	130.864	1190.68	1183.05	0.015547	18.7172

SD = standard deviation; N/A = not applicable.

Conclusions

- The study indicates that PK of Gammunex-C is comparable between adults and children 6 years and older. No conclusion can be drawn for children 2-5 years of age due to small sample size (n =1).
- Weekly SC administration of GAMUNEX-C in pediatric subjects resulted in relatively constant steady-state trough serum concentration of total IgG (1325 mg/dL), which averaged 31% higher than the steady-state trough concentration of total IgG (997 mg/dL) after IV administration of GAMUNEX-C.
- The AUC ratio of IV and SC administration is similar across 2-16 years of age groups.

Table 2: Summary of AUC of serum total IgG at steady state following IV or SC administration

Route of Administration	IV (N = 11)			SC (N = 10)	AUC Ratio, SC/IV
Statistics	$AUC_{0-\tau,IV}$ (h*mg/dL) (0-21 days)	$AUC_{0-\tau,IV}$ (h*mg/dL) (0-28 days)	Adj._$AUC_{0-\tau,IV}$[a] (h*mg/dL) (0-7 days)	$AUC_{0-\tau,SC}$ (mg*h/mL) (0-7 days)	
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Range	486832.0 – 875356.0	749868.0 - 850356.0	162277.0 - 291785.0	187577.0 - 303913.0	0.86 – 1.21
Age Group: 2-5 years (N)		1	1	1	1
Mean	NC	749868.0	187467.0	202298.0	1.08
%CV	NC	NC	NC	NC	-
Range	NC	NC	NC	NC	NC
Age Group: 6-11 years (N)	5		5	4	4
Mean	605265.4	NC	201755.0	238921.3	1.14
%CV	22	NC	22	19	-
Range	486832.0 - 830830.0	NC	162277.0 - 276943.0	197074.0 - 303913.0	1.10 - 1.21
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[a] Adj._ $AUC_{0-\tau,IV}$: Adjusted weekly IV $AUC_{(0\text{-}7\ days)}$ is calculated as $AUC_{(0\text{-}21\ days)}/3$ or $AUC_{(0\text{-}28\ days)}/4$.

Figure 1: Mean steady-state serum total IgG concentration-time curves following IV administration or weekly SC administration