

# CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology  
Office of Blood Review & Research

STN 125590

Sponsor: ADMA Biologics

Product: Immune Globulin Intravenous (Human), 10% Liquid with standardized, (b) (4)  
(ASCEINIV).

Indication: For the treatment of primary humoral immunodeficiency (PI).

Submission Date: July 31, 2015

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**Study Title:** An open label, multicenter study to evaluate the pharmacokinetics, efficacy and safety of RI-002 (IGIV) in subjects with primary immunodeficiency diseases (PIDD). 6

## INTRODUCTION

ASCENIV is a purified, sterile, ready-to-use preparation of concentrated human immunoglobulin G (IgG) antibodies. The distribution of IgG subclasses is similar to that of normal plasma. The active ingredient is human immunoglobulin purified from source human plasma. ASCENIV contains  $100 \pm 10$  mg/mL protein, of which not less than 96% is human immunoglobulin obtained from source human plasma. It is formulated in water for injection containing 0.1-0.14 M sodium chloride, 0.20-0.29 M glycine, 0.15-0.25% polysorbate 80, and pH 4.0-4.6. ASCENIV contains  $\leq 200$   $\mu$ g/mL of IgA.

The manufacturing process of ASCENIV employs three steps to remove/inactivate adventitious viruses to minimize the risk of virus transmission. The steps are "Precipitation and removal of fraction III" during cold ethanol fractionation, classical "solvent/detergent treatment" and "35 nm virus filtration." Precipitation and removal of fraction III removes both enveloped and non-enveloped viruses, solvent/detergent treatment represents a virus inactivation step for enveloped viruses, and 35 nm virus filtration removes both enveloped and non-enveloped viruses by size exclusion. In addition to the steps above, low pH during several steps of the production process contributes to virus inactivation.

# CLINICAL PHARMACOLOGY COMMENTS

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

ASCENIV is a replacement therapy in patients with primary humoral immunodeficiency (PI) (e.g. agammaglobulinaemia, hypogammaglobulinaemia, CVID, SCID). The broad spectrum of neutralizing IgG antibodies against bacterial and viral pathogens and their toxins helps to avoid recurrent serious opportunistic infections. IgG antibodies are opsonins that increase phagocytosis and elimination of pathogens from the circulation. ~~The product contains various naturally occurring polyclonal antibodies (e.g., Streptococcus pneumoniae, H. influenza type B, CMV, measles, tetanus amongst others) and standardized high levels of (b) (4) derived from human plasma. The mechanism of action has not been fully elucidated in PI.~~

### 12.2 Pharmacokinetics

~~In the Phase 3 pivotal clinical study, efficacy, safety and pharmacokinetics of ASCENIV were evaluated in 59 subjects with PI (See [Clinical Studies \[14\]](#)). Serum concentrations of total IgG were measured. Pharmacokinetics of ASCENIV were assessed in 30 subjects (ages 7 to 74) following the seventh infusion for subjects on a 4-week dosing interval and the ninth infusion for subjects on a 3-week dosing interval. The dose of ASCENIV used in these subjects ranged from 291 mg/kg to 760 mg/kg. After the infusion, Blood samples were taken until day 28 after infusion for the 4-week dosing interval and until day 21 after infusion for the 3-week dosing interval. Table 4 summarizes the total IgG Pharmacokinetic Parameters of ASCENIV, based on serum concentration of total IgG. The mean  $\pm$  SD half-life of ASCENIV was  $28.5 \pm 4.4$  days for on a 3-week dosing interval and  $39.7 \pm 11.6$  days for subjects on a 4-week dosing interval. for the 30 subjects in the pharmacokinetic subgroup. Although no systematic study was conducted to evaluate the effect of gender on the pharmacokinetics of ASCENIV, based on the small sample size (11 males and 19 females) it appears that the total IgG pharmacokinetics of ASCENIV is may be comparable in males and females. In 4 subjects between 7 and 16 (Pediatric) years of age, the Total IgG pharmacokinetics of ASCENIV is comparable to that observed in 26 adult subjects ( $>16$  population) years of age or older.~~

**Table 4: Total IgG Pharmacokinetic Parameters Estimates (PK Population) in Subjects with PIDD**

Parameters	3-week cycle (n = 10)		4-week cycle (n = 20)	
	Mean (SD)	CV%	Mean (SD)	CV%
C <sub>max</sub> (mg/dL)	2,427 (452)	18.63	2,227 (584)	26.21

Parameters	3-week cycle (n = 10)		4-week cycle (n = 20)	
	Mean (SD)	CV%	Mean (SD)	CV%
C <sub>min</sub> (mg/dL)	1,152 (308)	26.73	954 (245)	25.65
T <sub>max</sub> (h) <sup>a</sup>	2.93 (1.80, 4.52)	NA	2.78 (1.43, 99.08)	NA
AUC <sub>tau</sub> (d*mg/dL)	32,128 (7,020)	21.85	35,905 (9,351)	26.04
t <sub>1/2</sub> (d)	28.47 (4.38)	15.38	39.70 (11.57)	29.13
CL (mL/d/kg)	1.68 (0.43)	25.42	1.47 (0.50)	33.63
V <sub>ss</sub> (mL/kg)	76.79 (13.45)	17.52	89.57 (26.16)	29.21

AUC<sub>tau</sub> = steady-state area under the plasma concentration versus time curve with tau = dosing interval; CL = total body clearance;

C<sub>max</sub> = maximum concentration; C<sub>min</sub> = minimum concentration; CV = coefficient of variation; n = number of subjects;

NA = not applicable; SD = standard deviation; T<sub>max</sub> = time of maximum concentration; t<sub>1/2</sub> = terminal half-life;

V<sub>ss</sub> = Volume of distribution steady-state; <sup>a</sup> median (range)

Pharmacokinetic Parameters were also assessed (n=30) for specific antibodies to Streptococcus pneumoniae, Haemophilus influenzae type B, Cytomegalovirus (CMV), measles, tetanus and (b) (4). Subjects who received ASCENIV demonstrated a mean 5.47 fold rise in (b) (4) as compared to the level seen after their last dose of commercial immune globulin infused prior to joining this clinical trial. The PK parameters for antibodies to specific antigens are summarized in the [Table 5](#).

**Table 5: PK Parameters (Mean (SD)) for Antibodies to Specific Antigens**

Specific Antigen	3-week cycle (n = 10)				4-week cycle (n = 20)			
	Baseline	Pre-Infusion	‡C <sub>∞</sub>	‡AUC <sub>0-∞</sub>	Baseline	Pre-Infusion	‡C <sub>∞</sub>	‡AUC <sub>0-∞</sub>
Cytomegalovirus	NA	723 (936)	1988 (1732)	22,377 (27,124)	NA	799 (909)	1,828 (1,263)	24,080 (17,637)
H. influenzae type B	3.24 (1.01)	2.67 (0.66)	7.44 (1.45)	79.3 (12.5)	2.25 (1.28)	2.05 (1.18)	6.72 (1.88)	83.7 (32.88)
Measles	NA	2411 (2280)	5,580 (3,556)	69085 (59929)	NA	3259 (4152)	5,765 (4,614)	95,754 (106,564)
(b) (4)	(b) (4)							
S. pneumoniae, Serotype (b) (4)	28.5 (16.8)	16.5 (8.12)	32.5 (12.03)	436 (199.0)	16.9 (10.4)	11.5 (6.29)	26.3 (9.31)	374 (155.9)
S. pneumoniae, Serotype (b) (4)	9.73 (6.74)	9.19 (4.27)	17.9 (5.67)	243 (99.68)	5.67 (9.32)	7.72 (5.39)	17.6 (7.60)	264 (167.5)
S. pneumoniae, Serotype (b) (4)	4.86 (1.98)	6.83 (2.20)	14.2 (3.60)	186 (62.5)	3.62 (1.70)	5.34 (1.55)	12.9 (3.35)	190 (42.56)
S. pneumoniae, Serotype (b) (4)	7.33 (2.41)	6.51 (2.08)	12.9 (4.05)	171 (49.2)	5.42 (2.89)	5.85 (3.16)	12.0 (4.98)	190 (91.83)
S. pneumoniae, Serotype (b) (4)	2.11 (1.67)	2.07 (1.03)	4.14 (1.63)	51.7 (23.76)	1.19 (0.47)	1.61 (0.59)	4.36 (1.95)	54.7 (14.42)
S. pneumoniae, Serotype (b) (4)	3.02 (2.15)	3.04 (1.67)	6.10 (3.29)	77.9 (45.4)	1.22 (0.47)	2.01 (0.91)	4.77 (2.41)	65.8 (27.36)
S. pneumoniae, Serotype (b) (4)	4.24 (2.20)	3.08 (2.67)	5.47 (3.00)	75.0 (43.6)	2.98 (3.48)	2.36 (1.06)	5.30 (2.01)	78.3 (26.74)
S. pneumoniae, Serotype (b) (4)	1.79 (0.64)	2.16 (0.73)	4.87 (2.14)	57.9 (24.19)	1.16 (0.62)	1.63 (0.38)	3.94 (1.45)	55.3 (14.80)

Specific Antigen	3-week cycle (n = 10)				4-week cycle (n = 20)			
	Baseline	Pre-Infusion	‡C <sub>max</sub>	‡AUC <sub>0-t<sub>max</sub></sub>	Baseline	Pre-Infusion	‡C <sub>max</sub>	‡AUC <sub>0-t<sub>max</sub></sub>
S. pneumoniae, Serotype (b) (4)	3.22 (2.71)	2.33 (1.82)	4.09 (2.00)	57.8 (39.6)	4.07 (6.97)	3.08 (3.94)	6.05 (6.22)	98.9 (130.9)
S. pneumoniae, Serotype (b) (4)	1.81 (1.17)	2.09 (1.13)	4.68 (2.22)	59.5 (30.82)	1.35 (0.84)	1.81 (0.78)	5.69 (3.10)	65.0 (18.38)
S. pneumoniae, Serotype (b) (4)	0.64 (0.33)	0.68 (0.29)	1.36 (0.44)	18.8 (6.88)	0.48 (0.73)	0.74 (0.75)	1.56 (0.94)	24.0 (18.93)
S. pneumoniae, Serotype (b) (4)	16.0 (6.61)	16.0 (11.3)	27.9 (11.46)	373 (167.0)	10.4 (4.61)	10.3 (3.93)	27.6 (9.91)	375 (125.7)
Tetanus	5.61 (1.76)	6.53 (2.06)	19.5 (5.83)	203 (50.1)	7.42 (6.87)	7.96 (5.10)	22.1 (7.49)	314 (155)

\*Arithmetic mean ± SD (N) except T<sub>max</sub> for which the median [Range] (N) is reported.

†Units are µg/mL for Hib, PEI U/mL for CMV, mIU/mL for measles, titer for (b) (4), and IU/mL for tetanus.

‡Units are days×µg/mL for Hib, days×PEI U/mL for CMV, days×mIU/mL for measles, days×titer for (b) (4), and days×IU/mL for tetanus.

## **RECOMMENDATIONS**

The pharmacokinetic study design and results are acceptable. The applicant should modify the clinical pharmacology labeling as suggested by the FDA.

**Study Title:** An open label, multicenter study to evaluate the pharmacokinetics, efficacy and safety of RI-002 (IGIV) in subjects with primary immunodeficiency diseases (PIDD).

The primary objective of this study was to demonstrate that RI-002 (IGIV) reduces the frequency of serious bacterial infections (SBIs), as defined by the Diagnostic Criteria for Serious Infection Types guideline, in subjects with primary humoral immunodeficiency. The secondary objectives were to evaluate;

1. The incidence of infections (serious and non-serious)
2. The number of days lost from work/school/usual activities per year due to infections and their treatment
3. The number of unscheduled visits to physician/ER due to infection
4. The time to resolution of infections
5. The number of hospitalizations and days of hospitalizations due to infections per subject-year
6. The number of days of antibiotic therapy (prophylactic and treatment)
7. The relationship among dose of RI-002, trough level, and risk of serious and non-serious infections
8. Trough total Immunoglobulin G (IgG) and specific antibody levels at regular intervals
9. The pharmacokinetic (PK) profile of total IgG and specific antibody levels

This was a Phase III, multicenter, open-label study of RI-002 administered as an intravenous infusion of RI-002 (IGIV) 284-1008 mg/kg every 3 or 4 weeks (21 or 28 days) in 59 subjects with Primary Immunodeficiency Diseases (PIDD). The study was conducted at 9 centers in the United States. In order to be enrolled in the study, a subject (male or female) was to be between 2 and 75 years of age, had a confirmed clinical diagnosis of PIDD including hypogammaglobulinemia or agammaglobulinemia, had received IGIV therapy which was maintained at a steady dose ( $\pm$  50% of the mean dose) for at least 3 months prior to study entry, and have maintained a trough IgG level at least 500 mg/dL prior to receiving RI-002.

Once registered, the subjects received an intravenous infusion of RI-002 on study day 1 (required to be within 28 days of screening) and every 3 or 4 weeks thereafter according to their current interval of IGIV treatment, for 1 year. Subjects were to receive RI-002 at the same dose or higher dose if medically appropriate (300-800 mg/kg), every 3 or 4 weeks for 1 year. Dose increases above 800 mg/kg required approval of the ADMA Medical Director. In addition, a portion of subjects participated in the PK part of the study. The pharmacokinetic part of the study included 31 subjects (30 included in analysis), 27 adults and 4 pediatrics.

Blood samples for PK analysis were obtained beginning after infusion 7 for subjects on the 4-week schedule (visit 9) and after infusion 9 for subjects on the 3-Week schedule (visit 11). Blood samples for PK analysis were obtained at the following time points:

- Prior to infusion ( $\pm$  5 minutes)

- At the end of the infusion ( $\pm 5$  minutes)
- 60 minutes post infusion ( $\pm 5$  minutes)
- 2 hour post infusion ( $\pm 5$  minutes)
- 24 hours post infusion ( $\pm 45$  minutes)
- 48 hours post infusion ( $\pm 45$  minutes)
- 4 days, 7 days, 14 days, and 21 days ( $\pm 1$  day) after the day of the infusion. Those subjects on the 28 day IGIV cycle were to have an additional PK blood draw on day 28.

Pharmacokinetic parameters were assessed for total IgG and specific antibodies (Streptococcus pneumoniae (including serotypes), Haemophilus influenzae type B (HIB), Cytomegalovirus (CMV), measles, Respiratory syncytial virus (RSV), and tetanus).

Among subjects in the PK population (n=30), 26 were adults (>16 years), with 2 children in each group aged 7-11 and 12-16 years. This population included 11 male and 19 female subjects aged 7 to 74 years (mean 42.5 years). There were 20 and 10 subjects in 4-week and 3-week dosing cycle, respectively. PK parameters were estimated by non-compartmental analysis.

Administration of RI-002 with either regimen (3 or 4 week dosing schedule) resulted in increases in IgG and in HIB, CMV, RSV, tetanus, and the Streptococcus pneumoniae serotype antibodies. The PK parameters of total IgG are summarized in Tables 1 and 2.

**Table 1: Pharmacokinetic Parameters of total IgG (baseline uncorrected)**

Statistic	3-Week Cycle (N=10)		4-Week Cycle (N=20)	
	Mean $\pm$ SD (n)	CV%	Mean $\pm$ SD (n)	CV%
C <sub>max</sub> (mg/dL)	2427 $\pm$ 452 (10)	18.63	2227 $\pm$ 584 (20)	26.21
C <sub>min</sub> (mg/dL)	1152 $\pm$ 308 (10)	26.73	954 $\pm$ 245 (20)	25.65
T <sub>max</sub> (h) <sup>a</sup>	2.93 [1.80,4.52] (10)	NA	2.78 [1.43,99.08] (20)	NA
AUC <sub>tau</sub> (day·mg/dL)	32128 $\pm$ 7020 (10)	21.85	35905 $\pm$ 9351 (20)	26.04
t <sub>1/2</sub> (d)	28.47 $\pm$ 4.38 (6)	15.38	39.70 $\pm$ 11.57 (13)	29.13
CL (mL/kg/d)	1.68 $\pm$ 0.43 (10)	25.42	1.47 $\pm$ 0.50 (20)	33.63
V <sub>ss</sub> (dL/kg)	76.79 $\pm$ 13.45 (6)	17.52	89.57 $\pm$ 26.16 (13)	29.21

AUC<sub>tau</sub> = steady-state area under the plasma concentration versus time curve with tau = dosing interval; CL = total body clearance; C<sub>max</sub> = maximum concentration; C<sub>min</sub> = minimum concentration; CV = coefficient of variation; n = number of subjects; NA = not applicable; SD = standard deviation; T<sub>max</sub> = time of maximum concentration; t<sub>1/2</sub> = terminal half-life; V<sub>ss</sub> = Volume of distribution steady-state.

<sup>a</sup> Units median [Range] (n)

**Table 2: Pharmacokinetic Parameters of total IgG (baseline corrected)**

Antibody	Regimen	Parameter	Units	N	Arithmetic		
					Mean	Standard Deviation	CV (%)
IGG	Q21D	C <sub>MAX</sub>		10	1,223.3000	296.5745	24.24
		T <sub>MAX</sub>	hr	10	3.0433	0.8145	26.76
		AUC(0-t)		10	6,604.1707	2,912.7143	44.10
		Lambda <sub>z</sub>	/hr	5	0.0059	0.0029	48.38
		t <sub>½</sub>	days	5	5.7345	2.3541	41.05
		CL	mL/day/kg	10	9.1830	3.8832	42.29
		V <sub>z</sub>	mL/kg	5	82.4347	62.1649	75.41
	CMIN	mg/dL	10	18.5000	30.7038	165.97	
	Q28D	C <sub>MAX</sub>		20	1,230.5000	453.0645	36.82
		T <sub>MAX</sub>	hr	20	7.6400	21.5352	281.87
		AUC(0-t)		20	7,935.6015	3,482.0345	43.88
		Lambda <sub>z</sub>	/hr	9	0.0041	0.0021	51.68
		t <sub>½</sub>	days	9	10.1487	8.1360	80.17
		CL	mL/day/kg	20	8.0237	4.8867	60.90
V <sub>z</sub>		mL/kg	9	81.6423	35.4422	43.41	
CMIN	mg/dL	20	46.3000	82.2743	177.70		

The half-life (baseline uncorrected) of RI-002 in adult subjects ranged from 28 to 39 days which follows the observation of other immunoglobulins. However, it should be noted that the reported half-lives of immunoglobulins are based on either 21-day or 28-day blood sampling schemes. Therefore, the reported half-life of RI-002 should be interpreted with caution. On the other hand, baseline corrected half-life ranged from 6 to 10 days which reconciles with the blood sampling scheme.

In this study, the sample size did not allow the evaluation of impact of age on the PK of RI-002 (Table 3). There are two subjects each in >65 or <16 years of age groups. There appears to be no difference in the AUC and clearance values across age groups, but due to small sample size it is difficult to draw any conclusion.

The impact of gender on the PK of RI-002 remains inconclusive (Table 4). In 21-day dosing schedule, there were 3 males and 7 females. The mean clearance of RI-002 in 3 males and 7 females were 1.2 and 1.9 mL/hour per kg, respectively. The mean half-life in 1 male and 5 females were 25 and 29 days, respectively. In 28-day dosing schedule, there were 8 males and 12 females. The mean clearance of RI-002 in 8 males and 12 females were 1.8 and 1.3 mL/hour per kg, respectively. The mean half-life in 7 males and 6 females were 39 and 42 days, respectively. Although half-life of RI-002 is comparable between males and females, the clearance of RI-002 does not follow a clear pattern. In 21-day dosing schedule, the females have higher clearance than males but lower in 28-day dosing schedule.

**Table 3: Pharmacokinetic Parameters of total IgG (baseline uncorrected)  
(As a function of age)**

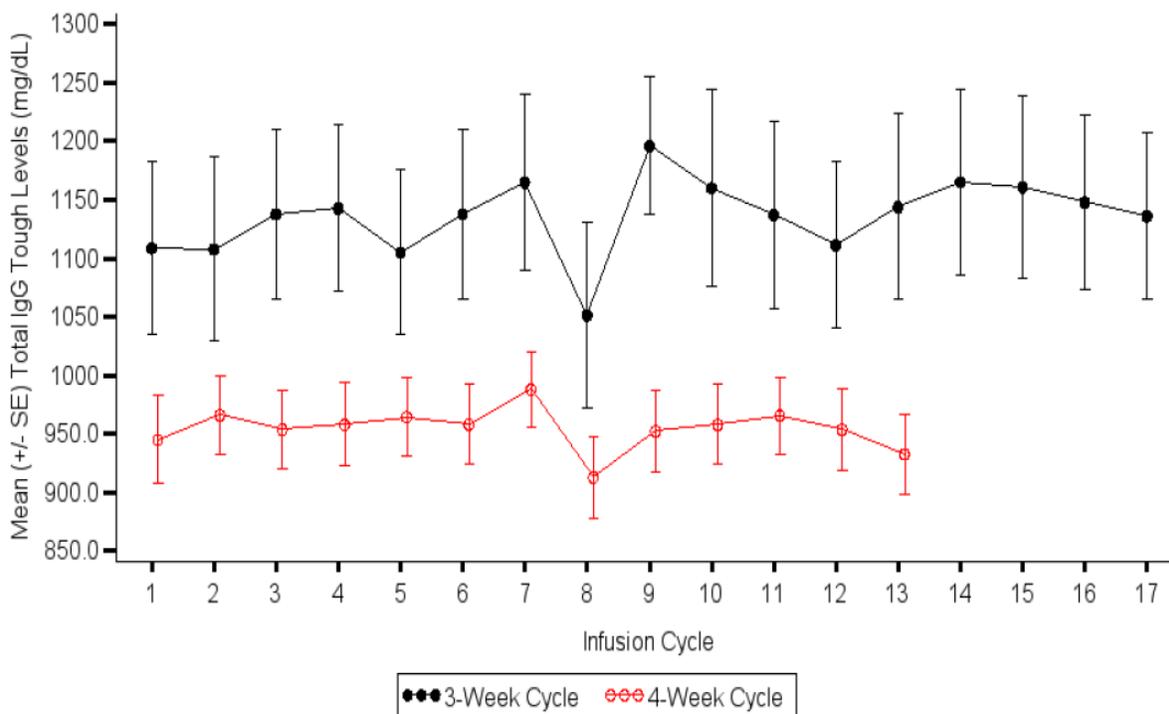
Regimen	Age Group	Parameter	Units	N	Arithmetic		
					Mean	Standard Deviation	CV (%)
Q21D	>=17 & <= 64	C <sub>MAX</sub>	mg/dL	6	2,503.1667	485.1744	19.38
		T <sub>MAX</sub>	hr	6	3.2444	0.9719	29.96
		AUC (0-t)	daysxmg/dL	6	33,447.9336	7,806.5571	23.34
		Lambda <sub>z</sub>	/hr	4	0.0009	0.0001	5.42
		t <sub>½</sub>	days	4	31.0525	1.7685	5.70
		CL	mL/day/kg	6	1.6293	0.4430	27.19
		V <sub>z</sub>	mL/kg	4	84.2530	6.6195	7.86
		C <sub>MIN</sub>	mg/dL	6	1,192.0000	315.3024	26.45
	>= 65	C <sub>MAX</sub>	mg/dL	2	2,578.0000	159.8061	6.20
		T <sub>MAX</sub>	hr	2	3.0500	0.2828	9.27
		AUC (0-t)	daysxmg/dL	2	30,719.5814	2,986.1515	9.72
		Lambda <sub>z</sub>	/hr	2	0.0012	0.0001	11.04
t <sub>½</sub>		days	2	23.3149	2.5740	11.04	
CL		mL/day/kg	2	1.8679	0.5121	27.42	
V <sub>z</sub>		mL/kg	2	61.8773	10.2898	16.63	
C <sub>MIN</sub>		mg/dL	2	1,011.5000	177.4838	17.55	
<=16	C <sub>MAX</sub>	mg/dL	2	2,048.0000	520.4306	25.41	
	T <sub>MAX</sub>	hr	2	2.4333	0.4243	17.44	
	AUC (0-t)	daysxmg/dL	2	29,577.7094	10,119.9109	34.21	
	Lambda <sub>z</sub>	/hr	0	.	.	.	
	t <sub>½</sub>	days	0	.	.	.	
	CL	mL/day/kg	2	1.6232	0.5456	33.61	
	V <sub>z</sub>	mL/kg	0	.	.	.	
	C <sub>MIN</sub>	mg/dL	2	1,171.5000	523.9661	44.73	

IgG trough concentrations were obtained prior to all study infusions for therapeutic dose monitoring. All subjects' doses were adjusted during the course of the study with a target threshold of maintaining trough IgG concentrations >500 mg/dL. Trough IgG concentrations were consistently maintained above the 500 mg/dL threshold during the study. Only three values were reported below 500 mg/dL after the screening visit, with two occurring prior to the first infusion of RI-002 (406 and 483 mg/dL), and one occurring prior to infusion 8 in a subject on a 3-week treatment cycle (490 mg/dL). Mean trough IgG concentrations were consistently higher in subjects receiving RI-002 on a 3-week treatment cycle (range 1052 to 1195 mg/dL) compared to subjects on a 4-week treatment cycle (range 913 to 978 mg/dL). Mean total IgG trough levels by infusion number are shown in Figure 1.

**Table 4: Pharmacokinetic Parameters of total IgG (baseline uncorrected)  
(as a function of gender)**

Regi- men	Sex	Parameter	Units	N	Arithmetic		
					Mean	Standard Deviation	CV (%)
Q21D	Male	C <sub>MAX</sub>	mg/dL	3	2,499.0000	104.2449	4.17
		T <sub>MAX</sub>	hr	3	2.5944	0.4001	15.42
		AUC (0-t)	daysxmg/dL	3	36,249.7321	3,204.2204	8.84
		Lambda_z	/hr	1	0.0011	.	.
		t <sub>½</sub>	days	1	25.1350	.	.
		CL	mL/day/kg	3	1.1939	0.3357	28.12
		V <sub>z</sub>	mL/kg	1	54.6014	.	.
		C <sub>MIN</sub>	mg/dL	3	1,414.6667	240.7412	17.02
	Female	C <sub>MAX</sub>	mg/dL	7	2,396.2857	547.2902	22.84
		T <sub>MAX</sub>	hr	7	3.2357	0.8932	27.60
		AUC (0-t)	daysxmg/dL	7	30,361.8553	7,639.0992	25.16
		Lambda_z	/hr	5	0.0010	0.0002	18.64
		t <sub>½</sub>	days	5	29.1410	4.5404	15.58
		CL	mL/day/kg	7	1.8823	0.2624	13.94
V <sub>z</sub>		mL/kg	5	81.2331	8.8580	10.90	
C <sub>MIN</sub>		mg/dL	7	1,039.1429	271.0808	26.09	
Q28D	Male	C <sub>MAX</sub>	mg/dL	8	2,293.3750	687.2381	29.97
		T <sub>MAX</sub>	hr	8	15.0146	33.9746	226.28
		AUC (0-t)	daysxmg/dL	8	35,951.7016	9,610.7289	26.73
		Lambda_z	/hr	7	0.0008	0.0003	33.25
		t <sub>½</sub>	days	7	39.4948	15.7032	39.76
		CL	mL/day/kg	8	1.7564	0.4616	26.28
		V <sub>z</sub>	mL/kg	7	96.9828	29.7296	30.65
		C <sub>MIN</sub>	mg/dL	8	952.1250	289.6340	30.42
	Female	C <sub>MAX</sub>	mg/dL	12	2,182.8333	531.6157	24.35
		T <sub>MAX</sub>	hr	12	2.7236	0.7679	28.19
		AUC (0-t)	daysxmg/dL	12	35,873.1012	9,605.1434	26.78
		Lambda_z	/hr	6	0.0007	0.0001	18.42
		t <sub>½</sub>	days	6	42.2419	8.6030	20.37
		CL	mL/day/kg	12	1.2854	0.4383	34.09
V <sub>z</sub>		mL/kg	6	84.5260	19.3801	22.93	
C <sub>MIN</sub>		mg/dL	12	955.9167	223.8090	23.41	

**Figure 1: Mean ( $\pm$ SE) total IgG trough levels by infusion number**



In addition to total IgG concentrations, pharmacokinetics were assessed for the following antibodies: Haemophilus Influenzae Type b (HIB), Cytomegalovirus (CMV), Measles, Respiratory syncytial virus (RSV), and Tetanus. The PK of these antibodies are summarized in Table 5. At the moment the clinical application of these antibodies is not known.

### Conclusions

The pharmacokinetics of RI-002 follows the same pattern as other immunoglobulins. Half-life (uncorrected baseline) of RI-002 which is equal to or longer than the sampling scheme should be interpreted with caution. Due to small sample size, the impact of age could not be evaluated on the PK of RI-002. Similarly, the impact of gender on the PK of RI-002 is difficult to assess due to unbalanced sample size in the 21-day dosing schedule and inconsistency between the two dosing schedules (in 21-day dosing schedule, the females have higher clearance than males but lower in 28-day dosing schedule).

**Table 5: Summary of Pharmacokinetic Parameters for Antibodies to Hib, CMV, Measles, RSV, and Tetanus**

Parameter*	Hib	CMV	Measles	RSV	Tetanus
3-Week Cycle (Q21)					
$C_{max}^{\dagger}$	7.44±1.45 (10)	1988±1732 (10)	5580±3556 (10)	4299±2271 (10)	19.5±5.83 (10)
$T_{max}$ (h)	2.89 [1.73,4.52] (10)	3.30 [1.82,338.67] (10)	3.38 [1.82,167.97] (10)	2.14 [1.73,4.25] (10)	2.54 [1.73,4.52] (10)
$AUC_{(0-\infty)}^{\ddagger}$	79.3±12.5 (10)	22377±27124 (10)	69085±59929 (10)	43769±19398 (10)	203±50.1 (10)
$\lambda_z$ (1/h)	0.0015±0.0007 (8)	0.0018±0.0011 (6)	0.0017±0.0013 (4)	0.0021±0.0000 (2)	0.0012±0.0004 (7)
$t_{1/2}$ (h)	23.4±9.89 (8)	24.30±19.45 (6)	23.0±13.15 (4)	13.9±0.052 (2)	24.9±6.41 (7)
Baseline <sup>†</sup>	3.24 (1.01)	NA	NA	1001 (640)	5.61 (1.76)
Pre-Infusion <sup>†</sup>	2.67 (0.66)	723 (936)	2411 (2280)	1198 (642)	6.53 (2.06)
4-Week Cycle (Q28)					
$C_{max}^{\dagger}$	6.72±1.88 (20)	1828±1263 (20)	5765±4614 (20)	5006±2102 (20)	22.1±7.49 (20)
$T_{max}$ (h)	2.71 [1.48,189.58] (20)	3.53 [1.43,189.58] (20)	3.27 [0.73,67] (20)	2.13 [1.48,362.08] (20)	2.94 [1.48,189.58] (20)
$AUC_{(0-\infty)}^{\ddagger}$	83.7±32.88 (20)	24080±17637 (20)	95754±106564 (20)	65672±45086 (20)	314±155 (20)
$\lambda_z$ (1/h)	0.0015±0.0005 (8)	0.0010±0.0001 (2)	0.0013±0.0003 (10)	0.0025±0.0013 (5)	0.0011±0.0003 (10)
$t_{1/2}$ (h)	20.5±6.97 (8)	30.1±4.42 (2)	22.6±5.70 (10)	13.7±5.81 (5)	27.8±7.31 (10)
Baseline <sup>†</sup>	2.25 (1.28)	NA	NA	1377 (1722)	7.42 (6.87)
Pre-Infusion <sup>†</sup>	2.05 (1.18)	799 (909)	3259 (4152)	1291 (1052)	7.96 (5.10)

\*Arithmetic mean ± SD (N) except  $T_{max}$  for which the median [Range] (N) is reported.

<sup>†</sup>Units are µg/mL for Hib, PEI-U/mL for CMV, mIU/mL for measles, titer for RSV, and IU/mL for tetanus.

<sup>‡</sup>Units are days×µg/mL for Hib, days×PEI-U/mL for CMV, days×mIU/mL for measles, days×titer for RSV, and days×IU/mL for tetanus.