

Clinical Pharmacology BLA Review
Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissues and Advanced Therapy

BLA	125613
Product	KEDRAB [®] [Kamada-HRIG (Human Rabies Immune Globulin)]
Sponsor	Kamada Limited
Indication	Passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with a rabies vaccine.
Date Received	08/29/2016
Reviewer	Xiaofei Wang, Ph.D.
RPM	Jiahua Qian, Ph.D.
Through	Lei Xu, M.D., Ph.D. Ilan Irony, M.D.

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Executive Summary

Kamada human rabies immune globulin (KEDRAB, Kamada-HRIG, KamRAB,) is a human rabies immune globulin product indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possible rabid animal and in combination with a rabies vaccine. The proposed dose is a single intramuscular (IM) injection at the dose of 20 IU per kilogram of body weight in combination of rabies vaccines.

The pharmacokinetic profile of KEDRAB was compared with a comparator HRIG that is currently on the market, in 26 healthy subjects. In a single dose, two-way crossover study comparing KEDRAB to the corresponding reference comparator HRIG product, at the dose of 20 IU/kg in healthy subjects, KEDRAB showed lower C_{max} and AUC of rabies virus neutralizing antibody (RVNA) than the comparator HRIG. Single dose IM injection of KEDRAB resulted in

maximum plasma RVNA levels of 0.25 IU/mL. The median Tmax was 7 days (range: 3 – 14 days). The elimination half-life was approximately 17.9 days. The bioequivalence (BE) assessment results did not meet bioequivalence criteria. The point estimate of the ratios of ln-transformed, Cmax, AUC_T, and AUC_I for RVNA were within the acceptable bioequivalence limits of 80- 125% (81.71%, 82.35%, and 84.44% for Cmax, AUC_T, and AUC_I respectively). However, the 90% confidence interval (CI) of Cmax, AUC_T, and AUC_I were out of the bioequivalence limit of 80-125% (75.34 – 88.62%, 77.39 - 87.63%, and 78.63 – 90.68% for Cmax, AUC_T, and AUC_I respectively). HRIGs are recommended to be co-administered with active rabies vaccine. Therefore, it is difficult to assess the clinical impact of above bioequivalence assessment results of single dose of HRIGs without co-administration of active rabies vaccines.

HRIGs have the potential to attenuate the vaccinee's immune response to rabies vaccine. In a double-blind, randomized study, 16 healthy subjects were administered either KEDRAB (20IU/kg IM) or saline placebo followed by three doses of a rabies vaccine on Days 0, 7 and 28. None of the subjects in either group developed a RVNA ≥ 0.5 IU/mL until Day 14. Compared to the placebo + vaccine group, subjects in KEDRAB + vaccine group had lower RVNA titers on Day 14. This observation confirmed that KEDRAB had similar effect in interfering with the host immune response to rabies vaccine.

The pharmacokinetic profile of KEDRAB was also compared with the comparator HRIG in a single dose, parallel study when co-administered with five doses of a rabies vaccine on Day 0, 3, 7, 14, and 28 in 118 healthy subjects. The peak plasma RVNA was 71.9 IU/mL and 53.9 IU/mL for KEDRAB and comparator HRIG, respectively. For both treatment groups, the median Tmax was 14 days (range: 14 – 49 days). The half-lives were 48.6 hours and 52.7 hours for KEDRAB and comparator HRIG, respectively. KEDRAB was not bioequivalent to the comparator HRIG when co-administered with a five-dose rabies vaccine regimen: the 90% confidence interval (CI) of Cmax, AUC_T, and AUC_I were out of the bioequivalence limit of 80-125% (90.62 – 171.28%, 79.03 – 134.98%, and 80.48 – 141.54% for Cmax, AUC_T, and AUC_I respectively). The mean RVNA titer on Day 3 was lower in the KEDRAB with rabies vaccine group than that in the comparator HRIG with vaccine group (0.188 ± 0.051 vs 0.229 ± 0.054 , $P=0.0005$). However, these pharmacokinetic differences are not expected to affect clinical outcomes. Please refer to the review by Dr. Winson Tang for details.

Based on above information, the clinical pharmacology reviewer recommends approval for this biological license application from clinical pharmacology perspective.

Introduction

On August 29, 2016, Kamada Limited submitted BLA 125613 seeking approval for its Human Rabies Immune Globulin, KEDRAB (Kamada-HRIG).

Rabies is a preventable viral disease of mammals most often transmitted through the bite of a rabid animal. Rabies is caused by RNA viruses in the Family *Rhabdoviridae*, Genus *Lyssavirus*. Rabies infection is almost universally fatal once symptoms appear.

The combination of human rabies immune globulin (HRIG) and active rabies vaccine is recommended for post-exposure prophylaxis (PEP) against rabies infection in previously-unvaccinated patients with possible exposure to the virus. Administration of human rabies immune globulin (HRIG) via intramuscular (IM) injection provides immediate passive antibodies for a short period of time. This protects the patient until the patient can produce antibodies in response to rabies vaccine, which elicits an active immune response that includes the production of rabies virus neutralizing antibodies (RVNA). The Advisory Committee on Immunization Practices (ACIP) of the United States (US) Public Health Service recommends the IM administration of HRIG through infiltration around the wound resulting from the exposure to a rabid animal on Day 0 of exposure. The recommended dose of HRIG for all ages is 20 international units (IU) per kilogram (kg) of body weight; HRIG is not indicated in previously vaccinated persons with documented adequate RVNA titers.

Kamada-HRIG is derived from the plasma of healthy human donors who have been immunized with rabies vaccine and developed high titers of rabies antibody. Kamada-HRIG drug product is a sterile, nonpyrogenic liquid preparation enriched with anti-rabies immunoglobulins (not less than 95% protein as IgG). It has a labeled potency of 150 IU/mL. The product is stabilized with 0.3 M Glycine at a pH range of 5.0-6.0 and does not contain preservatives. Kamada-HRIG is supplied in 2 mL and 10 mL (b) (4) glass vials as a ready-to-use solution.

The clinical pharmacology of Kamada's HRIG (KEDRAB, or KamRAB) was assessed in 3 submitted studies evaluating the pharmacokinetic, pharmacodynamics, safety, and tolerability profile of Kamada-HRIG in healthy adult subjects:

Study 1: A Phase 1 balanced, randomized, single dose, double blind, two-period crossover study to evaluate the safety and efficacy of KamRAB[®] (Kamada human rabies immune globulin) in healthy male and female volunteers (Study No. RD 154/23630).

Study 2: A Phase 1 balanced, randomized, single-dose KamRAB[®] (Kamada human rabies immune globulin) with three doses of rabies vaccine (Rabipur[®]) administration, double blind, one-period, parallel study to evaluate the safety and efficacy of KEDRAB[®] coadministered with active vaccine in healthy male and female volunteers (Study No. RD 154/24061).

Study 3: A Phase 2/3 prospective, randomized, double-blind, non-inferiority study of the safety and effectiveness of simulated post-exposure prophylaxis with Kamada human rabies immune globulin (KEDRAB[®]) with co-administration of active rabies vaccine in healthy subjects (Study No. KamRAB-003).

Study #1

Study Title: A clinical trial to evaluate the safety and efficacy of KamRAB (rabies immune globulin) in healthy male and female volunteers (Study No. RD 154/23630).

Objectives:

1. To monitor the subjects for safety and adverse events after the administration of an intramuscular injection of KEDRAB (KamRAB), with and without an active rabies vaccine.
2. To compare the pharmacokinetic profile of rabies antibody in the blood of healthy subjects receiving KEDRAB (KamRAB) and a positive control in a double-blind crossover mode.

Study Design:

This was a Phase 1 balanced, randomized, single dose, double blind, two-period crossover study to evaluate the safety and efficacy of KEDRAB (KamRAB) (Kamada human rabies immune globulin) in healthy male and female volunteers.

Subjects were randomized to receive a single intramuscular (IM) injection of 20 IU/kg RIG on two separate occasions. Subjects received one of the following treatments (A or B). Following the 42 day test period and 21 day washout period subjects received the second treatment. A total of 26 subjects were enrolled in the study and 23 subjects completed both periods.

Admin 1 (A): Inj. KEDRAB (KamRAB, Kamada-HRIG) 20 IU/kg IM (Kamada, Israel; Test)

Admin 2 (B): Inj. BayRab[®] 20 IU/kg (Bayer Corp, Reference)

Blood samples for pharmacokinetic analysis were collected pre-dose, and at 3, 7, 14, 28, 35, and 42 days post dose in each period. Plasma levels of rabies virus neutralizing antibody (RVNA) were assessed by measuring rabies antibody neutralization activity using the Rapid Focus Fluorescence Inhibition Test (RFFIT). Pharmacokinetic parameters were calculated using non-compartmental analysis.

Results:

After single dose IM injection of rabies immune globulin, plasma RVNA reached peak levels around 3 to 14 days. KEDRAB showed lower C_{max} and AUC than the comparator HRIG, BayRab. The mean RVNA titer C_{max} were 0.249 ± 0.063 IU/mL (median T_{max}: 7 days) and 0.302 ± 0.068 IU/mL (median T_{max}: 3 days) for KEDRAB and BayRab respectively. The mean RVNA titer AUC_T for the IM injection of KEDRAB 20 IU/kg and for the IM injection BayRab were 5.222 ± 1.297 Day*IU/mL and 6.266 ± 1.236 Day*IU/mL, respectively. The mean RVNA titer AUC_I were 6.734 ± 1.274 Day*IU/mL and 7.972 ± 1.362 Day*IU/mL for KEDRAB and BayRab respectively (Table 1).

Table 1 Arithmetic Mean Pharmacokinetic Parameters of Rabies Virus Neutralizing Antibody (RVNA) Titers (IU), Study 23630 PK Population

Treatment	C _{max} (IU/mL)	T _{max} [#] (Day)	AUC _T (Day*IU/mL)	AUC _I (Day*IU/mL)	t _{1/2} (Day)
IM Inj. KamRAB 20 IU/kg	0.249 (SD 0.063)	7.000 (3 – 14)*	5.222 (SD 1.297)	6.734 (SD 1.274)	17.87 (SD 6.370)
IM Inj. BayRab [®] 20 IU/kg	0.302 (SD 0.068)	3.000 (3 – 14)*	6.266 (SD 1.236)	7.972 (SD 1.362)	17.79 (SD 6.741)

* T_{max} is expressed as days not as hours as stated in protocol.

Median (range)

Table 2 Geometric Means and 90% Confidence Intervals of Pharmacokinetic Parameters of Rabies Virus Neutralizing Antibody (RVNA) Titers (IU), Study 23630 PK Population

	Test, Kamada	Reference, Bayer	Ratio (%) Test / Reference	90% C.I.s
Geometric LSmeans				
C _{max} (IU/mL)	0.241	0.295	81.71	75.34 – 88.62
AUC _T (IU/mL.day)	5.081	6.170	82.35	77.39 – 87.63
AUC _I (IU/mL.day)	6.639	7.862	84.44	78.63 – 90.68
Median				
T _{max} (day)	7	3	n/a	(p=0.4491) *

* Wilcoxon Rank Sum Test

As shown in Table 2, for bioequivalence assessment, the point estimate of the ratios of ln-transformed C_{max}, AUC_{0-t}, and AUC_∞ were within the acceptable bioequivalence limits of 80-125% (81.71%, 82.35%, and 84.44% for C_{max}, AUC_T, and AUC_I respectively). However, the 90% confidence interval (CI) of C_{max}, AUC_T, and AUC_I were out of the bioequivalence limit of 80-125% (75.34 – 88.62%, 77.39 - 87.63%, and 78.63 – 90.68% for C_{max}, AUC_T, and AUC_I respectively). The results did not meet bioequivalence criteria.

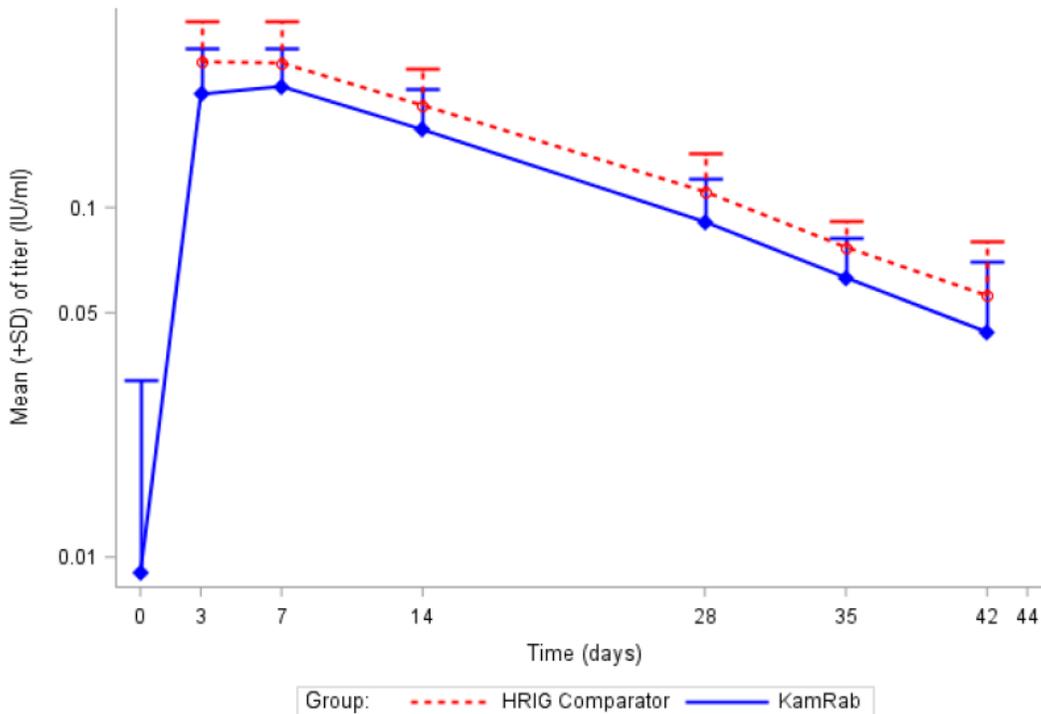
HRIGs are recommended to be co-administered with active rabies vaccine. Therefore, it is difficult to assess the clinical impact of above bioequivalence assessment results of single dose of HRIGs without co-administration of active rabies vaccines.

The mean plasma rabies virus neutralizing antibody (RVNA) concentration of KEDRAB and the comparator HRIG are listed in Table 3 and Figure 1.

Table 3 Mean Plasma Rabies Virus Neutralizing Antibody Titers (IU), Study 23630 PK Population

Study No. RD 154/23630									
Analyte: Rabies Virus Neutralizing Antibody									
Time (day)	KEDRAB (n=23)				Comparator HRIG (n=23)				T/R
	Mean (IU/mL)	%CV	Min (IU/mL)	Max (IU/mL)	Mean (IU/mL)	%CV	Min (IU/mL)	Max (IU/mL)	
0	0.009	270.78	0	0.077	0.000	-	0	0	-
3	0.211	35.92	0.081	0.337	0.261	30.66	0.102	0.406	0.81
7	0.222	29.16	0.112	0.372	0.259	31.93	0.135	0.369	0.86
14	0.167	30.41	0.076	0.282	0.196	27.08	0.137	0.313	0.85
28	0.091	33.19	0.042	0.158	0.111	29.13	0.066	0.191	0.82
35	0.063	30.57	0	0.092	0.077	19.78	0.044	0.105	0.82
42	0.044	59.40	0	0.079	0.056	43.29	0	0.080	0.78

Figure 1. Arithmetic Mean Plasma Rabies Virus Neutralizing Antibody Titer Versus Time Profile (Semi-log Plot), Study 23630 PK Population



Abbreviations: HRIG: human rabies immune globulin; IU: international units; KamRab: Kamada-HRIG; mL: milliliter; PK: pharmacokinetic; RVNA: rabies virus neutralizing antibody; SD: standard deviation

Study # 2

Study Title: A clinical trial to evaluate the safety and efficacy of KamRAB (Rabies Immune Globulin) coadministered with active vaccine in healthy male and female volunteers (Study No. RD 154/24061).

Objectives:

1. To monitor the subjects for safety and adverse events after the co-administration of a single intramuscular injection of KEDRAB (KamRAB) and repeated injections of an active rabies vaccine (Rabipur®).
2. To assess whether KEDRAB (KamRAB) interferes with the development of active antibodies when given simultaneously with the active rabies vaccine.

Study Design:

This was a Phase 1 balanced, randomized, single-dose KEDRAB® (Kamada human rabies immune globulin) with three doses of rabies vaccine (Rabipur®) administration, double blind, one-period, parallel study to evaluate the safety and efficacy of KEDRAB® coadministered with active vaccine in 16 healthy male and female volunteers.

Subjects were randomly assigned to either KEDRAB or placebo administration and received either KEDRAB 20 IU/kg plus three doses of Rabipur® rabies vaccine or placebo (0.9% NaCL 0.133mL/kg) plus three doses of Rabipur® rabies vaccine. The three intramuscular injections (IM Inj) of active vaccine (Rabipur®) were administered on days 0, 7 and 28 to study subjects.

Admin 1 (A): IM Inj. KEDRAB (KEDRAB) 20 IU/kg (Kamada, Israel; Test)

Admin 2 (B): IM Inj. NaCL 0.9% 0.133 ml/kg (Placebo)

Admin 3 (C): 3 x IM Inj. Rabipur® Rabies Vaccine 1.0 ml IM (Days 0, 7 and 28).

Blood samples for pharmacokinetic analysis were collected pre-dose, and at 3, 7, 14, 28, 35, and 42 days post dose. Plasma levels of rabies virus neutralizing antibody (RVNA) were assessed by measuring rabies antibody neutralization activity using the Rapid Focus Fluorescence Inhibition Test (RFFIT). Pharmacokinetic parameters were calculated using non-compartmental analysis.

Results:

Plasma RVNA was detected earlier in KEDRAB group (Day 3) compared to placebo group (Day 14). None of the subjects in either group developed a RVNA ≥ 0.5 IU/mL until Day 14.

Table 4 Descriptive Statistics of Rabies Virus Neutralizing Antibody (RVNA) Titers (IU) Following IM Injection of HRIG with an Active Rabies Vaccine [Arithmetic Mean (SD)], Study RD 154/24061 PK Population

DAY	KEDRAB 20 IU/kg + Rabies Vaccine					Placebo+ Rabies Vaccine				
	N	Mean	SD	95% CL		N	Mean	SD	95% CL	
0	7	0	0	0.00	0.00	8	0	0	0.00	0.00
3	7	0.11	0.06	0.07	0.15	8	0	0	0.00	0.00
7	7	0.10	0.08	0.04	0.16	8	0	0	0.00	0.00
14	7	1.39	2.48	-0.44	3.23	8	5.05	4.51	1.93	8.18
28	7	0.93	1.20	0.04	1.81	8	2.19	2.19	0.67	3.71
35	7	3.22	1.76	1.91	4.52	8	16.49	15.15	5.99	26.98
42	7	9.36	10.72	1.42	17.30	8	23.98	21.11	7.79	36.75

Abbreviations: CL: confidence limit; IU: international units; KEDRAB: Kamada-HRIG; kg: kilogram; PK: pharmacokinetic; SD: standard deviation

From day 14 to day 42 post IM injection, the levels of RVNA titer of the KEDRAB group were lower than RVNA levels of the placebo group. The AUC_T for KEDRAB 20 IU/kg treatment (85.17 ± 92.16 day*IU/mL) was also lower than AUC_T for the placebo treatment (276.30 ± 204.70 day*IU/mL).

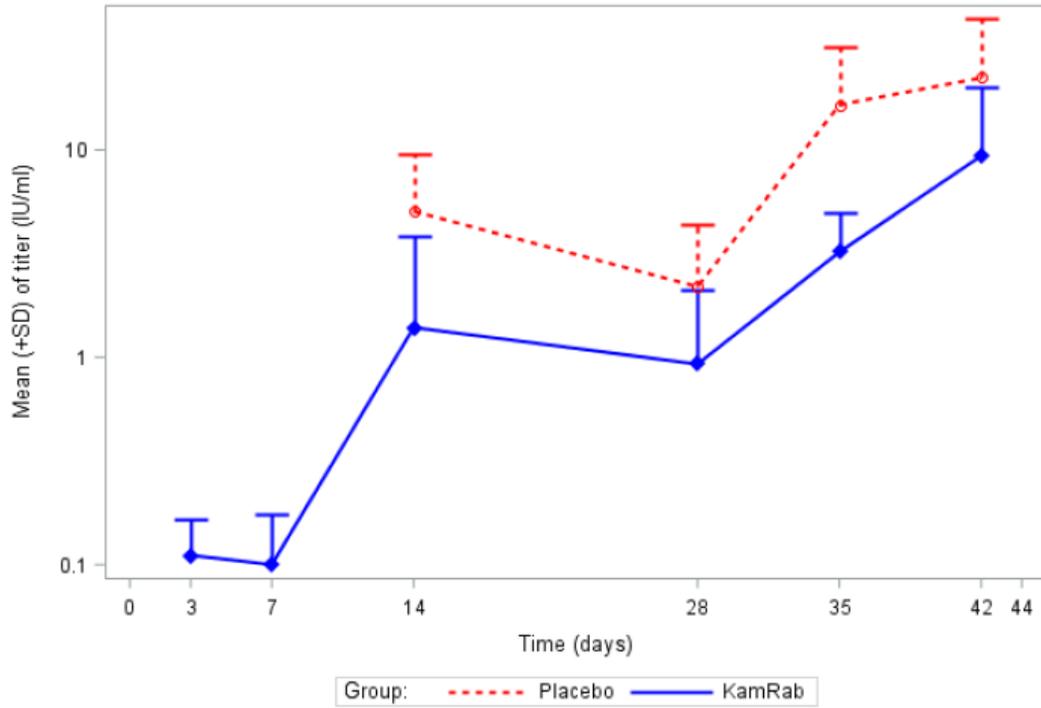
The results indicate that KEDRAB interferes with the active immunity induced by active rabies vaccine.

Table 5 Pharmacokinetic Parameters for Rabies Virus Neutralizing Antibody (RVNA) Study 24061 PK Population

Treatment	C _{max} (IU/ml)	T _{max} * (Day)	AUC _T (Day*IU/mL)
IM Inj. KamRAB 20 IU/kg	9.36 (SD 10.72)	42 (42-42)	85.17 (SD 92.16)
IM Inj. NaCl 0.9% 0.133ml/kg (Placebo)	23.98 (SD 21.11)	42 (14-42)	276.3 (SD 204.7)

* Median and (range) from nominal sampling times

Figure 2. Arithmetic Mean Plasma Rabies Virus Neutralizing Antibody (RVNA) Titer vs Time Profile (Semi-log Plot), Study 24061 PK Population



Abbreviations: IU: international units; KamRab: Kamada-HRIG; mL: milliliter; PK: pharmacokinetic; RVNA: rabies virus neutralizing antibody; SD: standard deviation

Study # 3

Study Title: A Phase 2/3 prospective, randomized, double-blind, non-inferiority study of the safety and effectiveness of simulated post-exposure prophylaxis with Kamada human rabies immune globulin (KEDRAB[®], KamRAB) with co-administration of active rabies vaccine in healthy subjects. (Study No. KamRAB-003).

Objectives:

1. To evaluate the safety and tolerability of KEDRAB (KamRAB) in comparison with the human rabies immune globulin (HRIG) comparator product.
2. To assess whether KEDRAB (KamRAB) interferes with the development of self-active antibodies when given simultaneously with active rabies vaccine, as compared to the HRIG comparator product, also given in conjunction with the active rabies vaccine.

Study Design:

This was a prospective, randomized, double-blind, single-period, non-inferiority and safety study. Subjects were randomized to receive single dose (20 IU/kg by weight) of KEDRAB or HRIG Comparator (HyperRAB) on Day 0. All subjects were to receive active rabies vaccine (RabAvert; 1 mL of ≥ 2.5 IU/mL) on Days 0, 3, 7, 14, and 28. Follow-up visits occurred on Day 49 and Day 185.

Group A: KEDRAB (20 IU/kg by weight [bw]) intramuscular (IM), rabies vaccine (1.0 mL; ≥ 2.5 IU/mL) IM

Group B: HRIG Comparator product, HyperRAB by Grifols¹ (20 IU/kg bw) IM, rabies vaccine (1.0 mL; ≥ 2.5 IU/mL) IM

KEDRAB/HyperRAB was to be administered as follows: the first 5 mL of the dose was to be administered to the left leg lateral muscle; the remainder (up to 5 mL) was to be administered to the right leg lateral muscle. Additional amounts up to 2.5 mL (for a subject >75 kg but ≤ 93.75 kg) were to be administered to the left arm deltoid muscle. The right arm deltoid muscle was to be utilized for the administration of the rabies vaccine. KEDRAB/HyperRAB was never to be administered into the same anatomical site as vaccine, because it could partially suppress active production of antibody.

RabAvert[®] by Novartis Vaccines and Diagnostics GmbH (Marburg, Germany) was to be used as the rabies vaccine (approved and marketed in the US). A 1.0 mL dose of rabies vaccine (≥ 2.5 IU/mL) was to be administered via IM injection in the deltoid muscle of the upper right arm on 5 occasions: Days 0, 3, 7, 14, and 28 (according to post-exposure prophylactic schedule).

¹ Notes: BayRAB and HyperRAB are the same product in same BLA101144.

One hundred and eighteen (118) subjects were enrolled and dosed and 113 subjects completed the study. There was a similar percentage of females (Group A: 62.7%; Group B: 65.5%) as well as a similar mean age (Group A: 43.3 years; Group B: 46.5 years) and body weight (Group A: 75.3 kg; Group B: 76.6 kg) between the treatment groups.

Blood samples for PK assessment were collected at baseline (Day 0), and Days 3, 7, 14, 28, 49, and 185. Rabies virus neutralizing antibody (RVNA) titers were measured using the Rapid Focus Fluorescence Inhibition Test (RFFIT). Pharmacokinetic parameters were calculated using non-compartmental analysis.

Administration of active rabies vaccine increases anti-rabies antibody titer. To compare pharmacokinetic profiles of KEDRAB 20 IU/kg and the comparator, HyperRab 20 IU/kg, pharmacokinetic and statistical analysis was conducted in subjects who had the single IM injection of human rabies immune globulin and all 5 doses of active rabies vaccine. One hundred thirteen (113) subjects completed the study with single IM injection of HRIG and all 5 doses of active rabies vaccine. However, one of the 113 subjects had higher than expected baseline plasma RVNA concentration and was determined that the subject had been previously exposed to rabies antigen based on additional examination. This subject was excluded from pharmacokinetic analysis. Therefore, 112 subjects were included in pharmacokinetic and statistical analysis.

Results:

The plasma human rabies immune globulin (HRIG) concentration-time profiles following intramuscular injection of KEDRAB or control HRIG, HyperRab appeared to be similar. At Day 14, plasma anti-rabies antibody titers of both KEDRAB and HyperRAB treatment groups reached peak levels: 71.88 ± 97.89 IU/mL (KEDRAB) and 53.94 ± 54.58 IU/mL (HyperRab). Plasma HRIG concentrations appeared to decline in a biphasic manner after the absorption phase was complete in both treatment groups.

Table 6 Arithmetic Mean Plasma Anti-Rabies Antibody Concentration (IU/mL) – Study KamRAB-003

Time (day)	KEDRAB (n=55)				Comparator HRIG (n=57)			
	Mean (IU/mL)	%CV	Min (IU/mL)	Max (IU/mL)	Mean (IU/mL)	%CV	Min (IU/mL)	Max (IU/mL)
0	0.003	741.62	0.000	0.185	0.00	-	0.000	0.000
3	0.186	27.41	0.115	0.455	0.225	24.93	0.000	0.370
7	0.304	123.75	0.110	2.225	0.359	121.46	0.095	3.190
14	70.957	138.63	0.180	655.055	51.920	106.87	1.090	328.320
28	25.275	74.27	0.820	73.720	24.448	85.00	0.655	77.020
49	12.845	75.75	0.875	38.620	13.566	84.52	0.950	53.510
185	3.498	131.97	0.155	19.145	3.321	116.21	0.340	18.210

Bioequivalence assessment was conducted comparing the test product, Kamada’s KEDRAB IM Injection, 20 IU/kg to the comparator HRIG, Grifol’s HyperRAB IM Injection, 20 IU/kg. KEDRAB IM was not bioequivalent to the comparator HRIG when co-administered with a five-dose rabies vaccine regimen: the 90% confidence interval (CI) of C_{max}, AUC_T, and AUC_I were out of the bioequivalence limit of 80-125% (90.62 – 171.28%, 79.03 – 134.98%, and 80.48 – 141.54% for C_{max}, AUC_T, and AUC_I respectively). The mean RVNA titer on Day 3 was lower in the KEDRAB with rabies vaccine group than that in the comparator HRIG with vaccine group (0.188±0.051 vs 0.229±0.054, P=0.0005). However, these pharmacokinetic differences are not expected to affect clinical outcomes. Please refer to the review by Dr. Winson Tang for details.

Table 7 Arithmetic Mean Pharmacokinetic Parameters of Rabies Virus Neutralizing Antibody (RVNA) Titers (IU), Study KamRAB003 PK Population

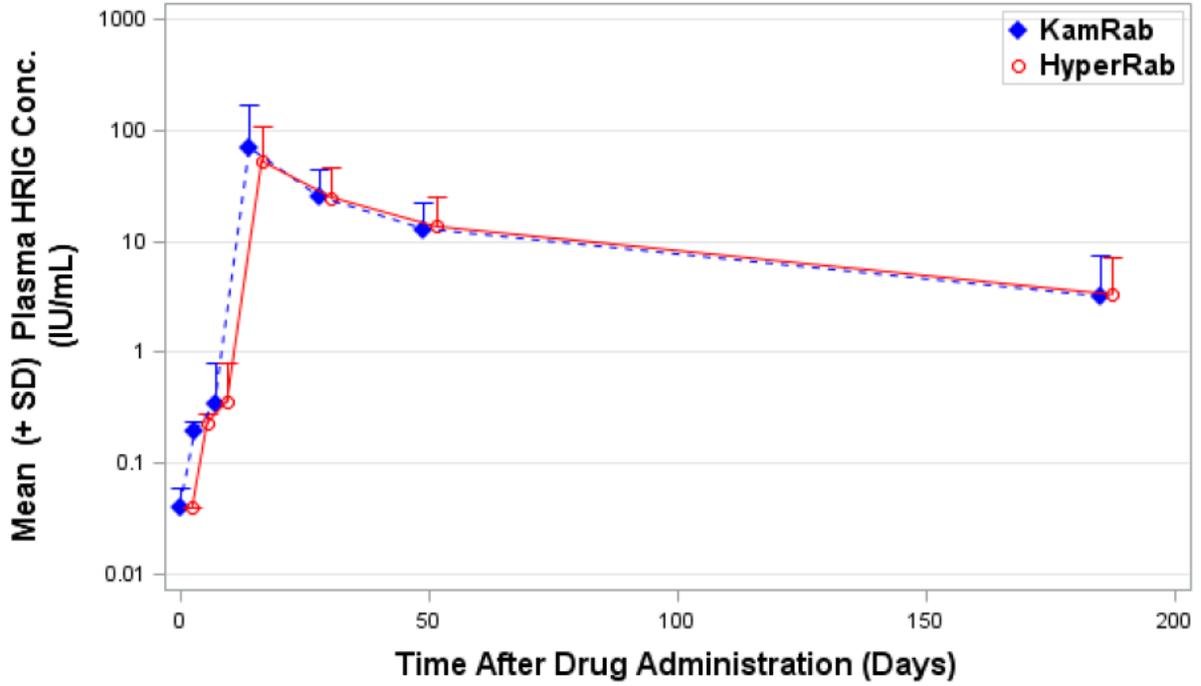
Parameter (units)	KEDRAB				Comparator HRIG				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _T (day*IU/ml)	2411.68	78.74	105.04	9115.38	2249.88	77.23	129.96	7496.19	1.07
AUC _I (day*IU/ml)	2876.41	85.85	171.27	10993.82	2536.56	78.49	417.12	8822.56	1.15
C _{max} (IU/ml)	71.84	136.26	0.84	655.02	53.90	101.26	1.05	328.28	1.33
T _{max} * (day)	14	--	14	49	14	--	14	49	1.00
K _{el} (day ⁻¹)	0.015	39.28	0.003	0.029	0.014	27.56	0.005	0.022	1.10
T _{1/2} (day)	57.70	63.69	24.32	245.38	53.92	35.58	31.14	139.04	0.99

* T_{max} values are presented as median, range

Table 8 Summary of Bioequivalence Assessment, Study KEDRAB-003, Study KamRAB003 PK Population

Human Rabies Immune Globulin for Intramuscular Injection					
Dose: 20 IU/kg BW					
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	KEDRAB	Comparator HRIG	Ratio (%)	90% C.I.	
C _{max} (IU/mL)	44.87	36.02	124.59	90.62	171.28
AUC _T (IU*day/mL)	1741.40	1686.03	103.28	79.03	134.98
AUC _I (IU*day/mL)	2045.87	1916.90	106.73	80.48	141.54

Figure 3. Arithmetic Mean Plasma RVNA Titer vs Time Profile (Semi-log Plot) Study KamRAB-003 PK Population



Recommendations

The clinical pharmacology reviewer recommends approval for this biological license application.

Labeling Comments

12 Clinical Pharmacology

12.1 Mechanism of Action

Rabies is a zoonotic disease caused by RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus*. Virus is typically present in the saliva of clinically ill rabid mammals and is transmitted primarily through a bite. ~~Rabies virus migrates from the site of entry into the body toward the central nervous system, and then to the brain, where the virus causes an acute, progressive encephalomyelitis that is almost always fatal. The incubation period in humans is usually several weeks to months, but ranges from days to years.~~

HRIG/KEDRAB is infiltrated into the inoculation site administered once (i.e., at the beginning of anti-rabies prophylaxis PEP) to previously unvaccinated persons, to provide immediate passive rabies virus neutralizing antibody protection until the patient's immune system responds to vaccination by actively producing antibodies.

12.2 Pharmacodynamics

~~A placebo-controlled Phase 1 study of a single 20 IU/kg intramuscular dose of KEDRAB or saline placebo, together with three doses of an active rabies vaccine on Days 0, 7, and 28, was conducted in 16 healthy volunteer subjects at risk for occupational exposure to rabies. Rabies virus neutralizing antibody titers were evaluated by rapid fluorescent focus inhibition test (RFFIT). The main findings are shown in Table 3. Rabies virus neutralizing antibody levels were lower following administration of Kamada HRIG and rabies vaccine, compared with saline placebo and rabies vaccine. Given the known interference of HRIG, lowering the response to active immunization with rabies vaccine, this finding is expected.~~

A protective threshold for rabies virus neutralizing activity (RVNA) has never been established. However, the WHO has generally accepted a RVNA of at least 0.5 IU/mL measured 14 days after initiation of PEP as protective. By comparison, the ACIP recommends complete neutralization of rabies virus at a 1:5 serum dilution by a rapid fluorescent focus inhibition test (RFFIT) from 1 to 2 weeks after prophylaxis; this corresponds to RVNA ~0.11-0.20 IU/mL. In support of these recommendations, there has been almost no documented clinical disease when the current rabies PEP regimen is administered appropriately (ACIP).¹

KEDRAB has the potential to attenuate the vaccinee's immune response to rabies vaccine. This was evaluated in a double-blind, randomized study where 16 healthy subjects were administered either KEDRAB (20IU/kg IM) or saline placebo followed by three doses of a rabies vaccine on Days 0, 7 and 28 (Table 3). The lower RVNA in the KEDRAB + vaccine group compared to the

placebo + vaccine group at all time-points beginning on Day 14 confirmed that KEDRAB interferes with the host immune response to rabies vaccine.

Table 3 — Pharmacokinetic Parameters for Rabies Virus Neutralizing Antibody, Phase 1 Placebo-Controlled Study of Kamada HRIG with Rabies Vaccine

Treatment Group	C_{max}	T_{max}	AUC_{0-last}
	(IU/mL) (Mean [SD])	(Days) (Median [Range])	(Day*IU/mL) (Mean [SD])
Kamada HRIG with rabies vaccine (N=7)	9.36 ± 10.72	42 (42—42)	85.17 ± 92.16
Saline placebo with rabies vaccine (N=8)	23.98 ± 21.11	42 (14—42)	276.3 ± 204.7

Abbreviations: AUC: area under the concentration-time curve; C_{max} : maximum concentration; HRIG: human rabies immune globulin; IU: international units; mL: milliliter; SD: standard deviation; T_{max} : time to maximum concentration

Table 4: Descriptive Statistics using Arithmetic Mean (SD), Study 24061 PK Population

DAY	N	KamRab 20 IU/kg				Placebo				
		Mean	SD	95% CL		N	Mean	SD	95% CL	
0	7	0	0	0.00	0.00	8	0	0	0.00	0.00
3	7	0.11	0.06	0.07	0.15	8	0	0	0.00	0.00
7	7	0.10	0.08	0.04	0.16	8	0	0	0.00	0.00
14	7	1.39	2.48	-0.44	3.23	8	5.05	4.51	1.93	8.18
28	7	0.93	1.20	0.04	1.81	8	2.19	2.19	0.67	3.71
35	7	3.22	1.76	1.91	4.52	8	16.49	15.15	5.99	26.98
42	7	9.36	10.72	1.42	17.30	8	22.27	20.89	7.79	36.75

Abbreviations: CL: confidence limit; IU: international units; KamRAB: Kamada-HRIG; kg: kilogram; PK: pharmacokinetic; SD: standard deviation

12.3 Pharmacokinetics

A randomized, single-dose, two-period, two-treatment, two-sequence, double-blind, crossover study assessed the pharmacokinetics of KEDRAB. Twenty-six healthy volunteer subjects were randomized to receive a single IM injection of 20 IU/kg HRIG on two separate occasions (KEDRAB or Comparator HRIG). Subjects received the second treatment (A or B) following the 42-day test period and a 21-day washout period. Single dose IM injection of KEDRAB resulted

in maximum plasma RVNA levels of 0.25 IU/mL. The median Tmax was 7 days (range: 3 – 14 days). The elimination half-life was approximately 17.9 days. A statistical analysis of the pharmacokinetic parameters showed that KEDRAB was not bioequivalent to the Comparator HRIG (Table 3).

A prospective Phase 1 crossover study of single 20 IU/kg intramuscular doses of KEDRAB and comparator HRIG 21 days apart was conducted in 26 healthy volunteer subjects who were not previously immunized against rabies. Rabies virus neutralizing antibodies were evaluated by RFFIT, and pharmacokinetic parameters were assessed. The main pharmacokinetic findings are shown in Table 4.

Table 43 Statistical Analysis of Pharmacokinetic Parameters for Rabies Virus Neutralizing Antibody Pharmacokinetic Parameters [Mean (SD)], Phase 1 Crossover Study of KEDRAB

<u>Parameter</u>	<u>Units</u>	<u>Geometric LS Mean</u>		<u>Test/Reference</u> (%)	<u>90% Confidence Interval</u> (%)
		<u>KEDRAB</u>	<u>Comparator HRIG</u>		
<u>C_{max}</u>	<u>IU/mL</u>	<u>0.24</u>	<u>0.30</u>	<u>81.71</u>	<u>75.34-88.62</u>
<u>AUC_{0-last}</u>	<u>Day*IU/m</u>	<u>5.08</u>	<u>6.17</u>	<u>82.35</u>	<u>77.39-87.63</u>
<u>AUC_{0-inf}</u>	<u>Day*IU/m</u>	<u>6.64</u>	<u>7.86</u>	<u>84.44</u>	<u>78.63-90.68</u>

Data are presented as geometric mean

Abbreviations: AUC: area under the concentration-time curve; C_{max}: maximum concentration; IU: international units; mL: milliliter; PK: Pharmacokinetic; RVNA: rabies virus neutralizing antibody

<u>Treatment</u>	<u>C_{max}⁺</u> (<u>IU/mL</u>)	<u>T_{max}⁺</u> (<u>Day</u>)	<u>AUC_T</u> (<u>Day*IU/mL</u>)	<u>AUC_I</u> (<u>Day*IU/mL</u>)	<u>t_{1/2}</u> (<u>Days</u>)
<u>KEDRAB</u>	<u>0.249</u> (<u>SD 0.063</u>)	<u>7</u> (<u>range 3—14</u>)	<u>5.222</u> (<u>SD 1.297</u>)	<u>6.734</u> (<u>SD 1.274</u>)	<u>17.87</u> (<u>SD 6.370</u>)

⁺Median (range)

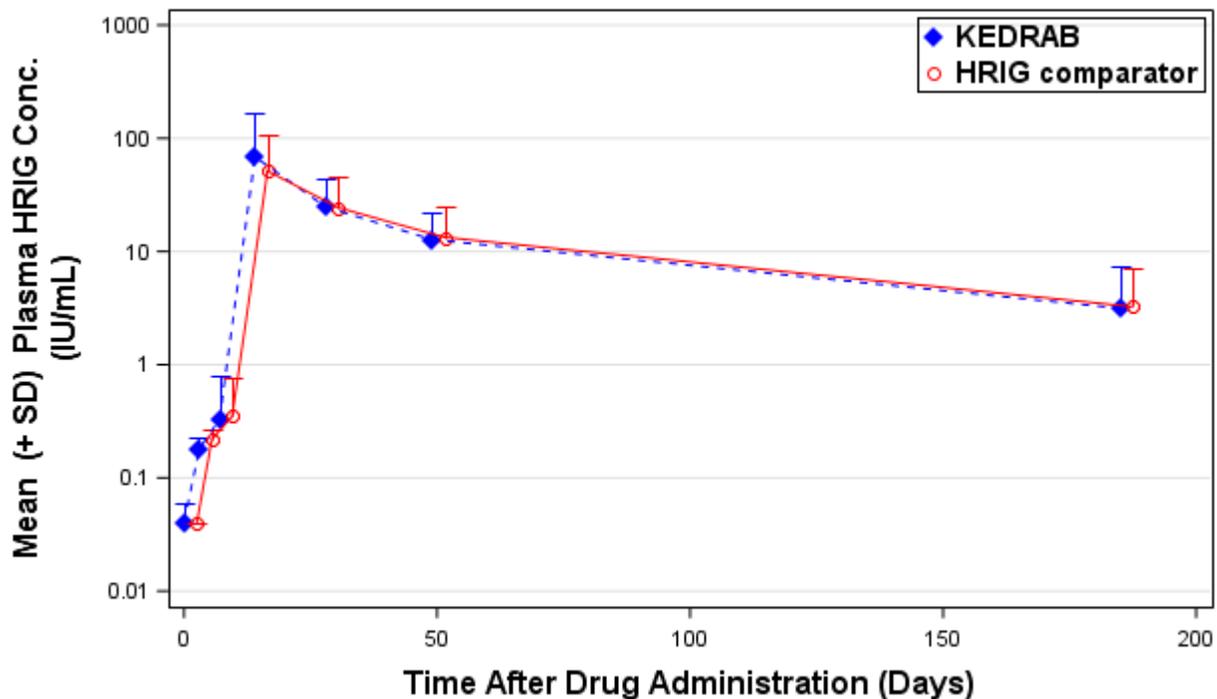
Abbreviations: AUC: area under the concentration time curve; C_{max}: maximum concentration; HRIG: human rabies immune globulin; IU: international units; mL: milliliter; SD: standard deviation; t_{1/2}: terminal elimination half life; T_{max}: time to maximum concentration

In the placebo controlled Phase 1 study of KEDRAB or saline placebo administered concurrently with three doses of rabies vaccine on Days 0, 7, and 28 [see Pharmacodynamics (12.2)], on Day 14, average

rabies virus neutralizing antibody titers in the KEDRAB group were ≥ 0.5 IU/mL and 3 of 7 subjects in this group had titers ≥ 0.5 IU/mL. On Day 28, 4 of 7 subjects in the KEDRAB group had titers ≥ 0.5 IU/mL, and on Day 35, after three doses of rabies vaccine, all 7 subjects had titers ≥ 0.5 IU/mL. In this study, subjects did not receive a dose of rabies vaccine on Day 3, which resulted in lower antibody levels at Day 14, compared with subjects receiving HRIG and rabies vaccine according to the standard post-exposure prophylaxis schedule.

Plasma rabies virus neutralizing antibody titer concentration-time (Figure 1) and demonstrated that, in both treatment groups, plasma rabies virus neutralizing antibody concentrations declined in a biphasic manner after the absorption phase was complete.

Figure 2: Plasma HRIG Concentrations [Mean (\pm SD)] at Scheduled PK Sampling Days (Semi-log Scale), Phase 2/3 Study, Pharmacokinetic Analysis



Additionally, in a prospective, randomized, double-blind, non-inferiority, controlled-Phase 2/3 study/clinical trial, evaluated the pharmacokinetics, safety and effectiveness of simulated post-exposure prophylaxis with KEDRAB with co-administration of active rabies vaccine in 118 healthy subjects. Subjects were randomized into two treatment groups (59 per treatment group) to receive intramuscular KEDRAB or comparator HRIG at a dose of 20 IU/kg on Day 0, and profile of rabies virus neutralizing antibodies following a single 20 IU/kg intramuscular dose of KEDRAB or comparator HRIG, each administered on Day 0 with 5 doses of rabies vaccine on Days 0, 3, 7, 14 and 28, was assessed (Table 5). The peak plasma RVNA was 71.9 IU/mL and 53.9 IU/mL for KEDRAB and comparator HRIG respectively. For both treatment groups, the median Tmax was 14 days (range: 14 – 49 days). The half-lives were 48.6 hours and 52.7 hours

for **KEDRAB** and comparator **HRIG** respectively. Rabies virus neutralizing antibody concentrations were assessed using RFFIT.

Bioequivalent assessment showed that **KEDRAB** was not bioequivalent to the comparator **HRIG** when co-administered with a five-dose rabies vaccine regimen (Table 4). Furthermore, the RVNA on Day 3 was lower in the **KEDRAB** with rabies vaccine group relative to the Comparator **HRIG** with vaccine group (0.188+0.051 vs 0.229+0.054, P=0.0005). However, these pharmacokinetic differences are not expected to affect clinical outcomes.

Table 4 Pharmacokinetic Comparison of Rabies Virus Neutralizing Antibody between KEDRAB and a Comparator HRIG Administered with Rabies Vaccine

<u>Parameter</u>	<u>Units</u>	<u>Geometric LS Mean Values</u>		<u>Test/Referenc</u> <u>e</u> <u>(%)</u>	<u>90% Confidence</u> <u>Interval</u> <u>(%)</u>
		<u>KEDRAB</u> <u>(Test)</u>	<u>Comparator</u> <u>HRIG</u> <u>(Reference)</u>		
<u>C_{max}</u>	<u>IU/mL</u>	<u>44.87</u>	<u>36.02</u>	<u>124.5</u>	<u>90.62-171.28</u>
<u>AUC_{0-last}</u>	<u>Day*IU/m</u>	<u>1741.40</u>	<u>1686.0</u>	<u>103.2</u>	<u>79.03-134.98</u>
<u>AUC_{0-inf}</u>	<u>Day*IU/m</u>	<u>2045.87</u>	<u>1916.9</u>	<u>106.7</u>	<u>80.48-141.54</u>

Abbreviations: AUC: area under the concentration-time curve; C_{max}: maximum concentration; IU: international units; mL: milliliter; PK: Pharmacokinetic; RVNA: rabies virus neutralizing antibody

Please see *Clinical Studies (14)* section for clinical efficacy.

Plasma rabies virus neutralizing antibody titer concentration-time profiles following IM injection of **KEDRAB** or **HRIG** comparator were similar and demonstrated that, in both treatment groups, plasma rabies virus neutralizing antibody concentrations declined in a biphasic manner after the absorption phase was complete.

Geometric mean (SD) rabies virus neutralizing antibody C_{max} values for the **KEDRAB** and comparator **HRIG** groups were similar.

Although plasma **HRIG** concentrations were still quantifiable on Day 185 in all subjects who completed the study, it was not possible to calculate a terminal phase t_{1/2} in all subjects. Geometric mean terminal phase t_{1/2} values were similar in the **KEDRAB** comparator **HRIG** groups.

No statistically significant differences in plasma rabies virus neutralizing antibody PK parameters (C_{max} , T_{max} , $AUC_{0-tlast}$, $AUC_{0-\infty}$, or $t_{1/2}$) or dose normalized plasma PK parameters ($C_{max}/Dose$, $AUC_{0-tlast}/Dose$, or $AUC_{0-\infty}/Dose$) were detected between the KEDRAB and comparator HRIG groups.

Table 5 — Geometric Mean (SD) of the Plasma HRIG Pharmacokinetic Parameters, by Treatment Group, Phase 2/3 Study, Pharmacokinetic Analysis Population

Parameter	Kamada HRIG with Rabies Vaccine (N = 59)	Comparator HRIG with Rabies Vaccine (N = 58)	P-value ^a
C_{max} (IU/mL)	39.9 (3.11)	36.2 (2.64)	0.6255
T_{max} (days)	15.6 (1.38)	16.5 (1.44)	0.4038
$AUC_{0-tlast}$ (IU•days/mL)	1313 (2.93)	1480 (2.24)	0.4976 ^b
$AUC_{0-\infty}$ (IU•days/mL)	1603 (2.27) ^e	1657 (2.17) ^d	0.8461
$t_{1/2}$ (days)	45.9 (1.39) ^e	50.9 (1.30) ^d	0.1106

^a P-value determined using Student's t test

^b Satterthwaite method used to account for unequal variances

^e N = 43

^d N = 44

Abbreviations: AUC: area under the concentration time curve; C_{max} : maximum concentration; HRIG: human rabies immune globulin; IU: international units; mL: milliliter; SD: standard deviation; $t_{1/2}$: terminal elimination half life; T_{max} : time to maximum concentration