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<b>Applicant</b>	Kamada Ltd.
<b>Established Name</b>	Rabies Immune Globulin (Human)
<b>(Proposed) Trade Name</b>	Kamada-HRIG
<b>Pharmacologic Class</b>	
<b>Formulation(s), including Adjuvants, etc</b>	
<b>Dosage Form(s) and Route(s) of Administration</b>	Single use vials containing 2 mL or 10 mL ready to use solution with a potency of 150 IU/mL via intramuscular injection.
<b>Dosing Regimen</b>	A single dose of Kamada-HRIG per 20 IU/kg body weight and a full course of rabies vaccine.
<b>Indication(s) and Intended Population(s)</b>	For 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.

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## GLOSSARY

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AE	adverse event
ACIP	Advisory Committee on Immunization Practices
BLA	biologics license application
BMI	body mass index
BW	body weight
CDC	Centers for Disease Control and Prevention
CI	confidence interval
EDR	Electronic Document Room
FDA	Food and Drug Administration
HRIG	human rabies immune globulin
IM	intramuscular
IP	investigational product
PEP	post-exposure prophylaxis
PI	principal investigator
PK	pharmacokinetic
RIG	rabies immune globulin
RNA	ribonucleic acid
SAE	serious adverse event
US	United States
WHO	World Health Organization

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## 1. EXECUTIVE SUMMARY

This biologics license application (BLA) is for approval of the human rabies immune globulin (HRIG) Kamada-HRIG, indicated for 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.

The primary evidence to support the safety and effectiveness of the product is based on the final analysis results of the pivotal study KamRAB-003: a single-center, prospective, randomized, double-blind study designed to compare the safety and efficacy of Kamada-HRIG with an HRIG Comparator (HyperRAB) in healthy volunteers. For the primary endpoint of an anti-rabies IgG concentration  $\geq 0.5$  IU/mL on Day 14, 98.2% (56/57) of the subjects in the Kamada-HRIG group and 100% (59/59) of subjects in the HRIG Comparator group achieved this concentration. The HRIG in both treatment groups was co-administered with an active rabies vaccine (RabAvert). The difference between the proportions of subjects with an anti-rabies IgG antibody titer  $\geq 0.5$  IU/mL on Day 14 in the Kamada-HRIG and HRIG Comparator groups was -1.8% and the 90% confidence interval (CI) was -8.1% to 3.0%. The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of -10%.

No major statistical issues were found during the review of this application. However, the pivotal study was a single-center trial and therefore the evidence may be limited in generalizability. In addition, the study was in healthy volunteers rather than in a genuine post-exposure prophylaxis setting, and is thus unable to directly evaluate clinical outcomes in individuals exposed to rabies.

No safety concerns were noted. I verified the primary efficacy results for the pivotal study KamRAB-003. The statistical evidence supports the proposed indication for Kamada-HRIG.

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

Rabies is a zoonotic disease caused by Ribonucleic acid (RNA) viruses in the Family *Rhabdoviridae*, Genus *Lyssavirus*. Unique among infectious diseases, rabies infection is almost universally fatal once symptoms appear. The disease presents as an acute, progressive encephalomyelitis. Human infection occurs when the infected animal transmits the virus to man through saliva via a bite, scratch, contact with mucous membranes, such as the eyes, nose or mouth, or licking of a wound. Rabies can also be transmitted by transplantation between humans. Once the virus enters the body there is a variable latency period. This may last only a few days, or up to several years. Typically, the average incubation period is 1 to 3 months. Rabies can progress through 5 stages: incubation period (5 days to more than 2 years: United States (US) median: approximately 35 days), prodrome state (0 to 10 days), acute neurologic period (2 to 7 days), coma (5 to 14 days), and death. Wild animals are the most important potential source of infection for both humans and domestic animals in the US. In recent years, the majority of human cases in the US have resulted from bites by or other exposure to infected bats; raccoons, skunks, and foxes are other vectors (Centers for Disease Control and Prevention [CDC] 2016).

### 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

For patients with suspected exposure to rabies virus, the Advisory Committee on Immunization Practices (ACIP) of the US Public Health Service has provided treatment guidelines for post-exposure prophylaxis (PEP) against rabies infection. For patients who have not been previously vaccinated for rabies and are thus unprotected, the ACIP recommendations for PEP include a single administration of rabies immune globulin (RIG), in conjunction with rabies vaccine (CDC 2008; CDC 2010). RIG is administered as an intramuscular (IM) injection and is infiltrated around the wound, providing immediate passive immunity via antibodies for a short period of time until the subject can mount an active immune response and produce rabies antibodies in response to rabies vaccine. This active immune response requires approximately 7 to 10 days to begin to develop and protection usually persists for 2 years or more. The ACIP recommends the

administration of RIG on the day of exposure to rabies or, if that is not possible, up to a week after exposure.

The World Health Organization (WHO) guideline for PEP against rabies infection is similar to the ACIP guideline, and includes administration of RIG in conjunction with rabies vaccine (WHO 2016).

## **2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission**

The product was developed under IND 13333. A Type B, pre-BLA meeting was held on March 17, 2016 (CRMTS #10129) with meeting minutes issued to the applicant by the Food and Drug Administration (FDA) on April 15, 2016. There was no statistical questions in the meeting package or the response from the FDA.

## **2.6 Other Relevant Background Information**

In the pivotal study, another HRIG, HyperRAB was chosen as the comparator because it is FDA-approved and commercially available in the US. In addition, HyperRAB is available in the same concentration as Kamada-HRIG (i.e., 150 IU/mL) and can be administered in the same manner and at the same dose as Kamada-HRIG.

## **3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

The submission is adequately organized for conducting a complete statistical review of the primary efficacy endpoint without unreasonable difficulty.

## **5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW**

### **5.1 Review Strategy**

Two clinical studies submitted in this BLA contain efficacy information: KamRAB-003 (a phase 2/3 study) and RD 154/24061 (a phase 1 study). Since KamRAB-003 is the pivotal study for this submission, only KamRAB-003 is reviewed in this memo and RD 154/24061 will not be reviewed.

### **5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review**

The following documents and datasets for the BLA were reviewed. All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

BLA	105612/0	
	Module 1.14	Labeling
	Module 2.5	Clinical Overview
	Module 2.7	Clinical Summary
	Module 5.2	Tabular Listing of all Clinical Studies
	Module 5.3.5.1	Study Reports
		KamRAB-003: study report body, protocol, statistical analysis plan.
	Module 5.3.5.1	Data Files
		KamRAB-003: adsl.xpt, addv.xpt
	105612/0/20	
	Module 5.3.5.1	Study Reports
		Post Hoc PK and Safety Analyses

### 5.3 Table of Studies/Clinical Trials

The following clinical studies, summarized in Table 1, are included in the submission.

Table 1 Summary of clinical studies in the BLA

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of \Follow up	Study Status;
<b>Pivotal Study</b>								
Phase 2/3	KAMRAB-003	Safety and efficacy of simulated post-exposure prophylaxis with Kamada- HRIG vs. comparator HRIG (HyperRAB®) co- administered with active rabies vaccine (RabAvert®; 1.0 mL IM on Days 0, 3, 7, 14 and 28)	Prospective, randomized, double- blind, single period non- inferiority, standard-of- care- controlled, parallel- group study	Kamada-HRIG HyperRAB®  Single dose (20 IU/kg) on Day 0  IM injection	118	Healthy subjects	Subjects were followed for 185 days (6 months) after Day 0	Completed
<b>Supportive Study</b>								
Phase 1	RD 154/23630 (Study 23630)	Safety of a single dose of Kamada- HRIG  Pharmacokinetic profile of Kamada- HRIG compared to positive control (BayRab®)	Randomized, double- blind, single- dose, two- period crossover study	Kamada-HRIG BayRab®  Single dose (20 IU/kg) on Day 1 and Day 21  Each subject received a single dose of each study product, with a 21 day washout period	26 (of these, 23 subjects received both products )	Healthy subjects	Subjects were observed for 21 days after each study treatment, for a total of 42 days of follow-up	Completed

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of \Follow up	Study Status;
				between doses. IM injection				
Phase 1	RD 154/24061 (Study 24061)	Safety and efficacy of Kamada- HRIG co- administered with active rabies vaccine (Rabipur®; 1.0 mL IM on Days 0, 7, 28)	Balanced, randomized, double-blind, single-dose, one period, placebo-controlled, parallel study	Kamada-HRIG Placebo (saline)  Single dose (20 IU/kg) on Day 0  IM injection	16	Healthy subjects	Subjects were followed for 42 days after Day 0	Completed  Study 24061 Clinical Study Report

HRIG: human rabies immune globulin; IM: intramuscular; IU: international units; kg: kilogram; mL: milliliter; PK: pharmacokinetics  
Source: Original BLA 125613.0; Module 5.2, Tabular Listing of all Clinical Studies.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1 KamRAB-003

#### 6.1.1 Objectives (Primary, Secondary, etc)

1. To evaluate the safety and tolerability of Kamada-HRIG in comparison with the HRIG comparator product.
2. To assess whether Kamada-HRIG 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.

#### 6.1.2 Design Overview

This was a single-center, prospective, randomized, double-blind, parallel-group study to evaluate the safety and effectiveness of Kamada-HRIG compared with an HRIG commercially available in the US (HyperRAB® by Grifols Therapeutics Inc.; hereafter referred to as HRIG Comparator) when co-administered with an active rabies vaccine (RabAvert® rabies vaccine produced by Novartis Vaccines and Diagnostics GmbH; hereafter referred to as rabies vaccine) in healthy male and female volunteers. Subjects were randomized into one of the following treatment groups in a 1:1 ratio.

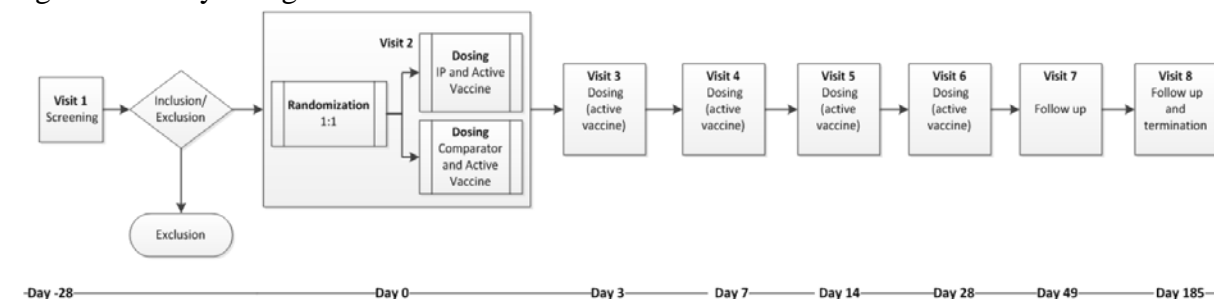
**Group A:** Kamada-HRIG (20 IU/kg by weight [bw]) intramuscular (IM), rabies vaccine (1.0 mL;  $\geq 2.5$  IU/mL) IM

**Group B:** HRIG Comparator product (20 IU/kg bw) IM, rabies vaccine (1.0 mL;  $\geq 2.5$  IU/mL) IM

There were seven additional visits to the study site after the screening visit, Visit 1. Visits 2 to 6 were treatment visits (Days 0, 3, 7, 14, and 28, respectively) and Visits 7 (Day 49) and 8 (Day 185) were follow-up visits. A single dose of Kamada-HRIG or HRIG

Comparator was administered on Visit 2 (Day 0). Subjects received five 1.0 mL doses of rabies vaccine on Visits 2 to 6 (on Days 0, 3, 7, 14, and 28, respectively, in conjunction with HRIG on Day 0). The serum sample for the efficacy endpoint, Rabies IgG titer testing, was taken prior to any drug administration at Visit 2 to Visit 6. Figure 1 presents the flow chart of the study design.

Figure 1 Study Design



Source: Original BLA 125613.0; Module 5.3.5.1, Clinical Study Report, Figure 1.

### 6.1.3 Population

Subjects who met all of the following criteria were eligible for the study:

1. Healthy male or female subjects of 18-75 years of age, inclusive, who had not previously been immunized against rabies.
2. No previous exposure to rabies epidemic, rabies vaccine, and/or rabies immune globulin.
3. No significant abnormalities in serum hematology, serum chemistry, and serum immunogenic markers (C3, C4, and CH50), according to the Principal Investigator's (PI) judgment.
4. No significant abnormalities in urinalysis according to the PI's judgment.
5. No significant abnormalities in ECG per the PI's judgment.
6. Male subjects were using at least one effective contraceptive method before study start and throughout the entire duration of the study.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

**Kamada-HRIG:** the Investigational product (IP) was administered as a single dose of 20 IU/kg body weight via IM injection on Day 0.

**HRIG Comparator product:** HyperRAB® by Grifols Therapeutics Inc. is approved and marketed in the US and available in the same concentration as Kamada-HRIG (i.e., 150 IU/mL). It was administered via IM injection once on Day 0 in the same manner and at the same dose as Kamada-HRIG.

**Rabies vaccine:** RabAvert® from Novartis Vaccines and Diagnostics GmbH (Marburg, Germany) is approved and marketed in the US. A 1.0 mL dose of RabAvert® ( $\geq 2.5$  IU/mL) was administered via IM injection in the deltoid muscle of the upper right arm on five occasions: Days 0, 3, 7, 14, and 28.



#### 6.1.6 Sites and Centers

This is a single center study conducted in the US.

#### *Reviewer Comment:*

*Evidence from a single-center clinical trial may not be generalizable.*

#### 6.1.8 Endpoints and Criteria for Study Success

##### Primary Endpoint

The primary endpoint was binary, where a success was defined as reaching an anti-rabies IgG concentration  $\geq 0.5$  IU/mL on Day 14. The primary hypothesis was that the proportion of successful Kamada-HRIG subjects would not be less than the corresponding proportion of successful HRIG Comparator subjects by as much as 0.1. That is, the study success criterion was pre-specified that the lower bound of a 90% CI for the difference in proportions be greater than -0.1.

##### Secondary Endpoint(s)

The secondary endpoints include:

- Local and systemic reactions (classified according to timing after injection and relation to treatment)
- Hematology, serum chemistry, serology, and urinalysis variables
- Unsolicited adverse events (AEs)

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

##### Determination of Sample Size

The applicant assumed a reference group proportion of 0.95 successes and computed power for the case that the true proportion of successes for the treatment group is also 0.95. A sample size of 53 subjects in each group achieves 80% power to conclude non-inferiority using a margin (tolerable difference between group proportions) of -0.10, with a one-sided Type I error rate of 0.05. Allowing for 10% loss, the sample size is increased to 59 in each group.

##### Analysis Populations

###### *Safety Population:*

The safety population included all randomized subjects who received at least one dose of study medication. Subjects in this population were to be analyzed based on actual medication received, regardless of the medication assigned. All safety summaries were to be performed using this population.

###### *As-Treated Population:*

The As-Treated population was to include all randomized subjects who received at least three vaccine doses (before the Day 14 serum sample was taken at the beginning of the visit) and one dose of the HRIG. The analysis of the primary efficacy endpoint was to be performed on the As-Treated population.

##### Primary Efficacy Endpoint Analysis

The following hypotheses were tested at a (pre-specified) 5% one-sided level:

Null hypothesis  $H_0: C_p \leq -0.1$   
Alternative hypothesis  $H_A: C_p > -0.1$

$C_p$  = the difference in the proportion of successes between Kamada-HRIG and the HRIG Comparator.

The 90% binomial CI was planned to be calculated from the Farrington-Manning score statistic.

#### Missing data

There is no imputation plan for missing data.

#### Interim Analysis

No interim analyses were planned.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

Of the 118 subjects in the Safety population, 116 subjects (98.3%) were included in the As-Treated population (57 in the Kamada-HRIG group and 59 in the HRIG Comparator group). Two subjects (1.7%) were excluded from the As-Treated population because they did not meet the definition of receiving at least three vaccine doses (until Day 14 before the serum sample was taken) and one dose of HRIG. These subjects are discussed in Section 6.1.10.1.3.

##### 6.1.10.1.1 Demographics

Subjects were predominately female (63.6%), White (93.2%), were not of Hispanic or Latino ethnicity (97.5%), and had a median age of 47.5 years. The other baseline characteristics and demographics of the safety population are shown in Table 2 and Table 3, respectively.

Table 2 Baseline Characteristics, Safety Population (N=118)

Statistic		Kamada-HRIG + Vaccine (N=59)	HRIG Comparator + Vaccine (N=59)	Overall (N=118)
<b>Age (years)</b>	N	59	59	118
	Mean (SD)	43.3 (16.15)	46.3 (14.50)	44.8 (15.35)
	Median	43.0	49.0	47.5
	Min, Max	18, 69	20, 72	18, 72
<b>BMI (kg/m<sup>2</sup>)</b>	N	59	59	118
	Mean (SD)	26.37 (3.712)	26.32 (3.798)	26.35 (3.740)
	Median	26.10	26.80	26.32
	Min, Max	19.8, 35.5	18.7, 33.0	18.7, 35.5

	Statistic	Kamada-HRIG + Vaccine (N=59)	HRIG Comparator + Vaccine (N=59)	Overall (N=118)
<b>Weight (kg)</b>	N	59	59	118
	Mean (SD)	75.31 (10.096)	76.56 (11.458)	75.93 (10.770)
	Median	75.00	78.20	77.05
	Min, Max	54.5, 93.6	52.9, 93.6	52.9, 93.6
<b>Height (cm)</b>	N	59	59	118
	Mean (SD)	169.02 (8.343)	170.53 (8.417)	169.77 (8.379)
	Median	168.30	170.30	168.95
	Min, Max	153.6, 198.8	148.5, 187.5	148.5, 198.8

Source: Original BLA 125613.0; Module 5.3.5.1, Clinical Study Report, Table 8.

Table 3 Demographics, Safety Population (N=118)

	Kamada-HRIG + Vaccine (N=59)	HRIG Comparator + Vaccine (N=59)	Overall (N=118)
	n (%)	n (%)	n (%)
<b>Sex</b>			
Female	37 (62.7)	38 (64.4)	75 (63.6)
Male	22 (37.3)	21 (35.6)	43 (36.4)
<b>Race</b>			
Asian	1 (1.7)	0	1 (0.8)
White	57 (96.6)	53 (89.8)	110 (93.2)
Black or African American	0	4 (6.8)	4 (3.4)
Other	1 (1.7)	2 (3.4)	3 (2.5)
<b>Ethnicity</b>			
Hispanic or Latino	2 (3.4)	1 (1.7)	3 (2.5)
Not Hispanic or Latino	57 (96.6)	58 (98.3)	115 (97.5)

Source: Original BLA 125613.0; Module 5.3.5.1, Clinical Study Report, Table 8.

#### 6.1.10.1.3 Subject Disposition

A total of 236 subjects were screened, and 118 of these subjects were randomized and received one of the treatments during the study. Overall, 113 of the 118 subjects (95.8%) completed the study. A total of seven subjects either discontinued treatment (Kamada-HRIG: n=3; HRIG Comparator: n=2) and/or did not receive all five doses of vaccine during the study (Kamada-HRIG: n=3; HRIG Comparator: n=1); two of these subjects were excluded from the As-Treated population. A summary of discontinuation and missing data for these subjects are presented in Table 4.

Table 4 Summary of Subjects with Discontinuation or Missing Vaccine Treatment

Subject ID	Treatment	Missed Vaccine Dose					Discontinued (Last Day)	As-Treated Population	IgG Titer (IU/mL)	
		D0	D3	D7	D14	D28			D0	D14
0021	Kamada-HRIG			X			N	N	0.04	0.32
0054	Kamada-HRIG						Y (Day 28)	Y	0.04	24.5
0076	Kamada-HRIG			X	X	X	Y (Day 24)	N	0.04	-
0114	Kamada-HRIG				X	X	Y (Day 46)	Y	0.04	25.57
0062	Comparator						Y (Day 161)	Y	1.74	724.11
0087	Comparator						Y (Day 144)	Y	0.04	65.4
0108	Comparator					X	N	Y	0.04	61.13

Source: Original BLA 125613.0; Module 5.3.5.1, Clinical Study Report, Table 10.

The two subjects who were not included in the As-Treated Population are as follows:

- Subject 0021 did not arrive for the Day 7 visit and missed this dose of vaccine, therefore, this subject did not meet the definition for the As-Treated population and was excluded. Of note, the subject did receive vaccine at baseline and Days 3, 14, and 28.
- Subject 0076 received only two doses of vaccine (baseline and Day 3) and therefore did not meet the definition for the As-Treated Population and was excluded. This subject discontinued treatment at the discretion of the Principal Investigator, due to prohibited medication use.

*Reviewer Comment:*

*Another subject, 0062 (Comparator group), was originally excluded from the As-Treated population by the applicant because he had a higher than expected level of plasma HRIG at baseline (Day 0; 1.74 IU/mL), Day 3 (1.89 IU/mL), Day 7 (63.87 IU/mL), and Day 14 (724.11 IU/mL) and was suspected of being previously exposed to rabies antigen. However, since this subject met the definition of the As-Treated population in Section 6.1.9, the applicant agreed to include the subject in the primary efficacy endpoint analysis (Amendment 20).*

Therefore, there are 116 subjects in the As-Treated population.

Of the five subjects who received treatment but discontinued early, three are in the Kamada-HRIG group and two are in the HRIG Comparator group. Of these three subjects in the Kamada-HRIG group, two subjects (0054, 0114) terminated early because of AEs and another subject (0076) was because of Investigator's discretion. Subject 0054 discontinued study treatment after four doses of rabies vaccine and subject 0114 discontinued study treatment after three doses of rabies vaccine.

Subject, 0114, who was included in the As-Treated population for the primary efficacy endpoint analysis, discontinued the study due to an AE on Day 7 and thus did not have data

for the Day 14 visit. However, because the subject's Early Discontinuation Visit was (coincidentally) conducted on Day 14, an IgG titer value at Day 14 was available (this value is presented in Table 4). A sensitivity analysis in Section 6.1.11.1 was performed which excluded the subject's Early Discontinuation value in the evaluation of the primary endpoint, instead of treating it as an eligible value.

## 6.1.11 Efficacy Analyses

### 6.1.11.1 Analyses of Primary Endpoint(s)

The proportion of successful subjects in the Kamada-HRIG group was 98.2% (56/57) compared to 100% (59/59) subjects in the HRIG Comparator group. The IgG antibody titer on Day 14 for the subject who did not meet the criterion was 0. The difference between the proportion of successes in the Kamada-HRIG and HRIG Comparator groups was -1.8% and the 90% CI was -8.1% to 3.0%. The lower limit of the CI was greater than the pre-specified non-inferiority margin of -10%, thus Kamada-HRIG was non-inferior to the HRIG Comparator for the primary endpoint. Table 5 presents the analysis results.

Table 5 Analysis results of the Primary Endpoint- As-Treated Population

	<b>Kamada-HRIG + Vaccine (N=57)</b>	<b>HRIG Comparator + Vaccine (N=59)</b>
Number of subjects who had IgG antibody titer values, n	57	59
IgG antibody titer $\geq 0.5$ IU/mL, n (%)	56 (98.2%)	59 (100%)
Exact 95% CI for proportion <sup>1</sup>	(90.6%, 100%)	(93.9%, 100%)
Difference ( $P^a - P^b$ ) <sup>2</sup> (%)	-1.8%	
Exact 90% CI for difference <sup>1</sup>	(-8.1%, 3.0%)	

1. Based on Farrington-Manning score statistic [Chan, 1999].

2.  $P^a$  and  $P^b$  are the proportion of participants with IgG antibody titer  $\geq 0.5$  IU/mL on Day 14 in KamRAB and HRIG Comparator groups, respectively.

Source: Original BLA 125613.0.20; Module 5.3.5.1 Clinical Study Report, Table 14.2.1.1.

A sensitivity analysis was conducted to evaluate the primary efficacy results by excluding subjects 0114 and 0062 (see Section 6.1.10.1.3) from the As-treated population. Results were consistent with the primary efficacy results, and showed that Kamada-HRIG was non-inferior to HRIG Comparator based on the difference in the proportion of successful subjects (-1.8% [90% CI: -8.1, 3.0]). Table 6 presents the analysis results.

Table 6 Sensitivity Analysis results of the Primary Endpoint- As-Treated Population (excluding subjects 0114 and 0062)

	<b>Kamada-HRIG + Vaccine (N=56)</b>	<b>HRIG Comparator + Vaccine (N=58)</b>
Number of subjects who had IgG antibody titer values, n	56	58
IgG antibody titer $\geq 0.5$ IU/mL, n (%)	55 (98.2%)	58 (100%)
Exact 95% CI for proportion <sup>1</sup>	(91.8%, 100%)	(95.0%, 100%)
Difference ( $P^a - P^b$ ) <sup>2</sup> (%)	-1.8%	
Exact 90% CI for difference <sup>1</sup>	(-8.2%, 3.1%)	

1. Based on Farrington-Manning score statistic [Chan, 1999].

2.  $P^a$  and  $P^b$  are the proportion of participants with IgG antibody titer  $\geq 0.5$  IU/mL on Day 14 in KamRAB and HRIG Comparator groups, respectively.

*Reviewer Comment:*

*As the primary endpoint analysis is a non-inferiority test, a per-protocol analysis would provide a supportive evaluation. But for this submission, the per-protocol population was not defined in the protocol and after checking the data, the two subjects (0021, 0076) in the Kamada-HRIG group who had protocol deviations during the study are already excluded from the As-Treated population. Therefore, it is not necessary to do a sensitivity analysis on per-protocol population for this application.*

6.1.11.2 Analyses of Secondary Endpoints

N/A

6.1.11.3 Subpopulation Analyses

The primary endpoint was analyzed by demographic subgroups, including age (categorized by the median age), sex, and race. Because of the number of non-white subjects is very small (n=3, all in the HRIG comparator group), the analysis for race was not performed. The results are presented in Table 7.

Table 7 Subgroup Analyses of the Primary Endpoint by demographic subgroups –  
As-Treated Population

Subgroup Parameter		Kamada-HRIG + Vaccine (N=57)	HRIG Comparator + Vaccine (N=59)
Age ≤47.5	Number of subjects who had IgG antibody titer values, n	31	28
	IgG antibody titer ≥0.5 IU/mL, n (%)	31 (100%)	28 (100%)
	Exact 95% CI for proportion <sup>1</sup>	(88.8%, 100%)	(87.7%, 100%)
	Difference (P <sup>a</sup> -P <sup>b</sup> ) (%) <sup>2</sup>	0.0%	
	Exact 90% CI for difference <sup>1</sup>	Not Applicable	
Age > 47.5	Number of subjects who had IgG antibody titer values, n	26	31
	IgG antibody titer ≥0.5 IU/mL, n (%)	25 (96.2%)	31 (100%)
	Exact 95% CI for proportion <sup>1</sup>	(80.4%, 99.9%)	(88.8%, 100%)
	Difference (P <sup>a</sup> -P <sup>b</sup> ) (%) <sup>2</sup>	-3.8%	
	Exact 90% CI for difference <sup>1</sup>	(-17.0%, 5.2%)	
Sex=Male	Number of subjects who had IgG antibody titer values, n	22	21
	IgG antibody titer ≥0.5 IU/mL, n (%)	22 (100%)	21 (100%)
	Exact 95% CI for proportion <sup>1</sup>	(84.6%, 100%)	(83.9%, 100%)
	Difference (P <sup>a</sup> -P <sup>b</sup> ) (%) <sup>2</sup>	0.0%	
	Exact 90% CI for difference <sup>1</sup>	Not Applicable	
Sex=Female	Number of subjects who had IgG antibody titer values, n	35	38
	IgG antibody titer ≥0.5 IU/mL, n (%)	34 (97.1%)	38 (100%)
	Exact 95% CI for proportion <sup>1</sup>	(85.1%, 99.9%)	(90.7%, 100%)
	Difference (P <sup>a</sup> -P <sup>b</sup> ) (%) <sup>2</sup>	-2.9%	
	Exact 90% CI for difference <sup>1</sup>	(-12.8%, 4.4%)	

1. Based on Farrington-Manning score statistic [Chan, 1999].

2. 'P<sup>a</sup>' and 'P<sup>b</sup>' are the proportion of participants with IgG antibody titer ≥0.5 IU/mL on Day 14 in KamRAB and HRIG Comparator groups, respectively.

Source: Original BLA 125613.0.20; Module 5.3.5.1 Clinical Study Report, Table 14.2.1.1.

#### 6.1.11.4 Dropouts and/or Discontinuations

Per the discussion in Section 6.1.10.1.3, subjects 0021 and 0076 were excluded from the As-Treated population because they did not meet the definition. A sensitivity analysis was conducted to evaluate the primary efficacy results by including the data on Day 14 for subject 0021 and imputing the data on Day 14 as ≤ 0.5 IU/mL (the worst-case scenario) for subject 0076. Results were slightly different from Table 5, and showed that Kamada-HRIG was inferior to HRIG Comparator based on the difference in the proportion of successful subjects (-5.1% [90% CI: -12.62, -0.32]). Table 8 presents the analysis results.

Table 8 Sensitivity Analysis of the Primary Endpoint- As-Treated Population  
(including 0021 and 0076)

	<b>Kamada-HRIG + Vaccine (N=59)</b>	<b>HRIG Comparator + Vaccine (N=59)</b>
Number of subjects who had IgG antibody titer values, n	59	59
IgG antibody titer $\geq 0.5$ IU/mL, n (%)	56 (94.9%)	59 (100%)
Exact 95% CI for proportion <sup>1</sup>	(87.4%, 99.6%)	(95.1%, 100%)
Difference ( $P^a - P^b$ ) <sup>2</sup> (%)	-5.1%	
Exact 90% CI for difference <sup>1</sup>	(-12.6%, -0.1%)	

1. Based on Farrington-Manning score statistic [Chan, 1999].

2.  $P^a$  and  $P^b$  are the proportion of participants with IgG antibody titer  $\geq 0.5$  IU/mL on Day 14 in KamRAB and HRIG Comparator groups, respectively.

## 6.1.12 Safety Analyses

### 6.1.12.3 Deaths

No deaths occurred during this study.

### 6.1.12.4 Nonfatal Serious Adverse Events

One subject (0054) in the Kamada-HRIG group had a SAE of intraductal proliferative breast lesion that was “moderate” in intensity, considered “not related” to study drug by the PI, and was ongoing at the end of the study. No other subjects had an SAE during this study, and no SAEs were considered related to study drug by the PI.

### 6.1.12.5 Adverse Events of Special Interest (AESI)

No subject reported inhibitory effects in this study.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

There is no major statistical issue in this BLA submission. The submission includes the final analysis of the pivotal study KamRAB-003: a single-center, prospective, randomized, double-blind study designed to compare the safety and efficacy of Kamada-HRIG with an HRIG Comparator (HyperRAB) in healthy volunteers. Because this study is a single-center trial, the results may not be generalizable. In addition, the study was in healthy volunteers rather than in a genuine post-exposure prophylaxis setting, and is thus unable to directly evaluate clinical outcomes in individuals exposed to rabies.

The primary endpoint was defined by reaching an anti-rabies IgG concentration  $\geq 0.5$  IU/mL on Day 14. The primary hypothesis was that the proportion of Kamada-HRIG + vaccine subjects with anti-rabies concentration  $\geq 0.5$  IU/mL on Day 14 would not be less than the corresponding proportion of the HRIG Comparator + vaccine subjects by as much as 0.1.

Fifty-six of 57 subjects (98.23%) in the Kamada-HRIG group and 59 of 59 (100%) subjects in the HRIG Comparator group had an anti-rabies IgG antibody titer  $\geq 0.5$  IU/mL on Day 14.



The difference between these two proportions was -1.8% and the 90% CI from Farrington-Manning score statistic was -8.1% to 3.0%. The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of -10%.

A sensitivity analysis was conducted by excluding subjects 0062 and 0114; similar results were obtained (-1.8%; 90% CI: -8.2% to 3.1%). The lower limit of the CI was still greater than the pre-specified non-inferiority margin of -10%.

The safety evaluation revealed that no subject reported inhibitory effects in this study.

## 10.2 Conclusions and Recommendations

In this BLA submission, the primary efficacy test for the pivotal study was the difference between proportions of subjects with an anti-rabies IgG antibody titer  $\geq 0.5$  IU/mL on Day 14 in the Kamada-HRIG vs the HRIG Comparator group. The results indicated that the lower bound of the 90% CI was greater than the pre-specified criterion. No safety concerns were noted. Therefore, the statistical evidence supports the proposed indication for 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.

\*\*\*\*\*  
**IMPORTANT - DO NOT CHANGE ANYTHING BELOW THIS SECTION!**  
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