Application Type	BLA Supplement
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Division / Office	DB/OBE
Committee Chair	Agnes Lim, M.D.
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Project Manager	Rommel Maglalang
Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Kamada Ltd.
Established Name	Rabies Immune Globulin (Human)
(Proposed) Trade Name	KamRAB
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Single use vials containing 2 mL or 10 mL ready to use solution with a potency of 150 IU/mL via intramuscular injection.
Dosing Regimen	A single dose of KamRAB per 20 IU/kg body weight and a full course of rabies vaccine.
Indication(s) and Intended Population(s)	Current: 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. New: To include pediatric subject results.

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
BW	Body Weight
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
HRIG	Human Rabies Immune Globulin
IM	Intramuscular
IP	Investigational product
PEP	Post-exposure Prophylaxis
PMR	Post-Marketing Requirement
RFFIT	Rapid Fluorescent Focus Inhibition Test
RVNA	Rabies Virus Neutralizing Antibody
SAE	Serious Adverse Event
sBLA	Supplemental Biologics License Application
SD	Standard Deviation
US	United States
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Kamada-HRIG is a human rabies immune globulin (HRIG) FDA-licensed product (2017), 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.

This supplemental Biologics License Application (sBLA) provides the final study report for study, KamRAB-004, the Required Pediatric Assessment as agreed to for the Post-Marketing Requirement (PMR) in the BLA approval letter (STN BL 125613/0). It also proposes label updates to include the pediatric results from KamRAB-004.

KamRAB-004 was an open-label post-marketing study of KamRAB administered as a single dose with active rabies vaccine in children exposed to rabies. The primary endpoints were frequency and severity of local and systematic adverse events (AEs) occurring within 14 days of KamRAB treatment and of serious adverse events (SAEs) occurring within 84 days of treatment. The efficacy evidence is from the secondary endpoint: the number of subjects with rabies virus neutralizing antibody (RVNA) titer levels ≥ 0.5 IU/mL on Day 14. Of the 30 enrolled subjects, 28 (93.3%) met the criteria. The RVNA titer levels for the 30 subjects had a geometric mean (standard deviation, SD) of 18.89 (31.61),

median 8.81 and a range of 0.21 – 153.62. No subject had a rabies infection by Day 84.

No major statistical issues were found during the review of this application. No safety concerns were noted. I verified the efficacy results for the post-marketing study KamRAB-004. The statistical evidence supports the inclusion of pediatric results in the label.

2. CLINICAL AND REGULATORY BACKGROUND

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

This submission is a Prior Approval Supplement with the submission of a final study report for the Required Pediatric Assessment as agreed to in PMR #1 in Kamada's August 23, 2017 BLA approval letter (STN BL 125613/0).

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 sBLA contain efficacy information: KamRAB-003 (a phase 2/3 study) and KamRAB-004 (a phase 4 study). Since KamRAB-003 has been reviewed in the original BLA, only KamRAB-004 is reviewed in this memo.

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 FDA/CBER Connect.

BLA	125613/76	
	Module 1.14	Labeling
	Module 5.2	Tabular Listing of all Clinical Studies
	Module 5.3.5.1	Study Reports
		KamRAB-004: study report body, protocol.
	Module 5.3.5.1	Data Files
		KamRAB-003: demog.xpt, exam.xpt

5.3 Table of Studies/Clinical Trials

The following clinical study, 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**
Phase 2/3	KAMRAB-003	To evaluate the safety and tolerability of KamRAB in comparison with the human rabies immune globulin (HRIG) comparator product. To assess whether 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.	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
Phase 4	KAMRAB-004	Primary Objective: • To confirm the safety of KamRAB in children ages 0 months to <17 years, when administered as part of post-exposure prophylaxis (PEP). Secondary Objectives: • To obtain data on anti-rabies antibody levels after treatment with KamRAB and rabies vaccine according to US Center for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations for PEP. • To evaluate the efficacy of KamRAB, when administered	Open-label, non-controlled study of KamRAB 20 IU/kg IM administered in conjunction with rabies vaccine.	Kamada-HRIG RabAvert® Single dose (20 IU/kg) on Day 0 IM injection	30	Healthy pediatric subjects	From dosing to follow-up, subjects participated in study for 85 days.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 KamRAB-004

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective is:

- To confirm the safety of KamRAB in children ages 0 months to <17 years, when administered as part of post-exposure prophylaxis (PEP).

The secondary objective is:

- To obtain data on anti-rabies antibody levels after treatment with KamRAB and rabies vaccine according to US Center for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations for PEP.
- To evaluate the efficacy of KamRAB, when administered with rabies vaccine according to ACIP recommendations for PEP, in the prevention of rabies disease.

6.1.2 Design Overview

This was an open-label, non-controlled study of KamRAB administered as a single dose of 20 IU/kg in conjunction with rabies vaccine. The study was conducted in pediatric subjects with exposure or possible exposure to rabies virus in whom PEP against rabies infection was indicated. From dosing to follow-up, subjects participated in the study for 85 days. Subjects were screened/dosed on Day 0, follow-up visits were performed on Days 3, 7, and 14; telephone follow-ups were performed on days 1, 28, 56, and 84.

6.1.3 Population

Subjects who qualified for entry into this study:

1. were healthy children (male and female) ages 0 months to <17 years,
2. had been exposed or possibly exposed to rabies,
3. were indicated to receive PEP against rabies infection,
4. had documented informed consent from the child's parent(s) or legal guardian(s) and assent from the child if appropriate.

6.1.4 Study Treatments or Agents Mandated by the Protocol

KamRAB: Investigational product (IP) was administered as a single dose of 20 IU/kg body weight via intramuscular (IM) injection on Day 0.

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* (≥2.5 IU/mL) was administered via IM injection in the deltoid muscle of the upper right arm on four occasions: Days 0, 3, 7, and 14.

6.1.6 Sites and Centers

A total of four centers were initiated in the Unites States (US); however, only two centers enrolled subjects.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint(s)
The primary endpoint were frequency and severity of local and systematic AEs occurring within 14 days of KamRAB treatment and of SAEs occurring within 84 days of treatment.

Secondary Endpoint(s)

- Key secondary endpoint: number of subjects who had RVNA titer levels ≥ 0.5 IU/mL on Day 14.
- Occurrence of rabies disease within 3 months (84 days) of study treatment.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size
No sample size calculations were performed for this descriptive study. The sample size of 30 was based on the feasibility of enrolling pediatric subjects with a possible rabies exposure at sites with experience in administering rabies PEP to children; with allowance for loss to follow-up, and for obtaining complete data.

Analysis Populations
Safety Population:
The safety population included all subjects who received any amount of KamRAB (20 IU/kg). This population was used for the safety data summaries and baseline characteristic summaries.

As-Treated Population:
The As-Treated population included those subjects in the safety population who received at least three vaccine doses (until day 14) and one dose of KamRAB (20 IU/kg). The efficacy analysis was based on this population.

Primary Safety Endpoint Analysis
Descriptive statistics were planned. No formal testing was performed.

Key Secondary Efficacy Endpoint Analysis
Descriptive statistics were planned. No formal testing was performed.

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

All 30 enrolled subjects were included in both the Safety population and As-treated population.

6.1.10.1.1 Demographics

The mean (SD) age was 7.45 (4.3%) years and the age range was from 0.5 to 14.9 years. The majority of subjects were white (21 subjects [70.0%]). There were 14 (46.7%) female subjects and 16 (53.3%) male subjects. 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=30)

	Statistic	KamRAB + Vaccine
Age (years)	N	30
	Mean (SD)	7.45 (4.3)
	Median	7.15
	Min, Max	0.5, 14.9
BMI (kg/m^2)	N	30
	Mean (SD)	19.19 (4.476)
	Median	17.65
	Min, Max	13.7, 30.2
Weight (kg)	N	30
	Mean (SD)	32.61 (21.826)
	Median	22.25
	Min, Max	6.6, 85.7
Height (cm)	N	30
	Mean (SD)	122.68 (31.027)
	Median	122.0
	Min, Max	62.0, 171.2

Source: BLA 125613.76; Module 5.3.5.1, Clinical Study Report, Table 11-1.

Table 3 Demographics, Safety Population (N=30)

	KamRAB + Vaccine n (%)
Sex	
Female	14 (46.7)
Male	16 (53.3)
Race	
Asian	2 (6.7)
White	21 (70.0)
Black or African American	7 (23.3)
Ethnicity	
Hispanic or Latino	3 (10.0)
Not Hispanic or Latino	27 (90.0)

Source: BLA 125613.76; Module 5.3.5.1, Clinical Study Report, Table 11-1.

6.1.10.1.3 Subject Disposition

Thirty-three subjects were screened, of which 30 subjects were enrolled. All 30 (100%) subjects were in the study on Day 14.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoints are safety assessments and are discussed in 6.1.12.

6.1.11.2 Analyses of Secondary Endpoints

Of the 30 subjects, 28 (93.3%) had RVNA antibody titer levels ≥ 0.5 IU/mL on Day 14. The RVNA titer levels had a geometric mean (SD) of 18.89 (31.61) and a median (range) of 8.81 (0.21 – 153.62).

According to investigator assessment up to Day 84, all 30 (100%) subjects had no active rabies infection.

6.1.11.3 Subpopulation Analyses

No examination of subgroups was performed.

6.1.11.4 Dropouts and/or Discontinuations

All 30 subjects were in the study on Day 14 for the primary efficacy evaluation. Out of 30 subjects that were enrolled in the study, 2 (6.7%) of the subjects terminated early from the study (prior to Day 84). The primary reason for early termination was lost to follow-up for both subjects.

6.1.12 Safety Analyses

Twenty-one (70.0%) subjects experienced at least one AE within 14 days from KamRAB treatment period. All AEs were mild during the 14 days following KamRAB administration. The AEs occurring in at least 10% of subjects were injection site pain (7 subjects, 23.3%), headache (4 subjects, 13.3%), and arthropod bite and pain in extremity (each in 3 subjects, 10.0%).

6.1.12.3 Deaths

No deaths occurred during this study.

6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

There were no SAEs within 84 days of follow-up.

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 study KamRAB-004: an open-label post-marketing study of KamRAB administered as a single dose with active rabies vaccine in children exposed to rabies.

The primary endpoints were frequency and severity of local and systematic AEs occurring within 14 days of KamRAB treatment and SAEs occurring within 84 days of treatment. The efficacy evidence was from the key secondary endpoint, the proportion of subjects with RVNA titer levels ≥ 0.5 IU/mL on Day 14.

All 30 (100%) subjects had no active rabies infection; of these, 28 (93.3%) subjects had RVNA titer levels ≥ 0.5 IU/mL on Day 14. The RVNA titer levels for 30 subjects on Day 14 had a geometric mean (SD) of 18.89 (31.61) and a median (range) of 8.81 (0.21 – 153.62).

The safety evaluation revealed that there were no deaths, other SAEs, and other significant AEs during the study.

10.2 Conclusions and Recommendations

This sBLA submission is for the Required Pediatric Assessment as agreed to in PMR #1 in Kamada's August 23, 2017 BLA approval letter (STN BL 125613/0). The efficacy results indicated that 28 (93.3%) subjects had RVNA titer levels ≥ 0.5 IU/mL on Day 14. No safety concerns were noted. It is acceptable from a statistical perspective that the efficacy results or pediatric subjects exposed to rabies be included in the label.