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1.1.1.1.1.1 BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125613/76
CBER Received Date	Jul 17, 2020
PDUFA Goal Date	May 17, 2021
Division / Office	CBER/OTAT/DCEPT/GMB1
Priority Review (Yes/No)	No
Reviewer Name(s)	Agnes Lim, M.D.
Review Completion Date / Stamped Date	
Team Leader Concurrence	Melanie Blank, M.D.
Branch Chief Concurrence	Elizabeth Hart, M.D.
DCEPT Concurrence	Ilan Irony, M.D.
Applicant	Kamada Ltd.
Established Name	Rabies Immune Globulin (Human)
(Proposed) Trade Name	Name of Finished Product: KEDRAB in the US
Pharmacologic Class	Immune sera and immune globulins
Formulation(s), including Adjuvants, etc.	Sterile, non-pyrogenic liquid preparation enriched with anti-rabies immunoglobulins (not less than 95% protein as IgG)
Dosage Form(s) and Route(s) of Administration	2 mL and 10 mL fills at 150 IU/mL Local infiltration into wound/exposure site
Dosing Regimen	20 IU/kg body weight
Indication(s) and Intended Population(s)	Passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination concurrently with a full course of rabies vaccine in children ages 0 month to <17 years
Orphan Designated (Yes/No)	No

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APPENDIX 1

GLOSSARY

Ab	antibody
ACIP	Advisory Committee on Immunization Practices
ADR	Adverse Drug Reaction
Ag	antigen
AE	adverse event
ANOVA	analysis of variance
AR	Adverse Reaction
BLA	biologics license application
BUN	blood urea nitrogen
BW	body weight
CBC	complete blood count
CCEEV	cell culture and embryonated egg-based vaccines
CDC	Center for Disease Control and Prevention
CI	confidence interval
CNS	central nervous system
CRC	clinical research center
ERIG	equine rabies immunoglobulin
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	geometric mean titers
HIV	human immunodeficiency virus
HRIG	human anti-rabies immunoglobulin
ICH	International Council for Harmonization
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IND	investigational new drug
IU	international units
KAMRAB	Proprietary name of KEDRAB, Kamada's anti-rabies immunoglobulin, used outside U.S.
KEDRAB	Proprietary name for KEDRAB, Kamada's anti-rabies immunoglobulin, in the U.S.
Kg	kilogram
L	liter
LDH	lactate dehydrogenase
LS	least square
M	matrix
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
nm	nanometer
N	nucleoprotein
NAT	nucleic acid testing
NMDA	N-methyl-D-aspartate
NTV	nerve tissue vaccines
P	phosphoprotein
PAS	Prior approval supplement
PEP	post-exposure prophylaxis
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act

PrEP	pre-exposure prophylaxis
PSP	Pediatric Study Plan
RWE	Real World Evidence
RFFIT	Rapid Fluorescent Focus Inhibition Test
RIG	rabies immunoglobulin
RVNA	rabies virus neutralizing antibody
SAE	serious adverse event
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class (MedDRA)
t1/2	half-life
TEAE	treatment emergent adverse event
US	United States
WHO	World Health Organization

1. **Executive Summary**

This efficacy supplement, submitted July 17, 2020, contains the Final Study Report for the completed Post Marketing Requirement (PMR) pediatric study (KAMRAB-004) that was conducted in accordance with the Pediatric Research Equity Act (PREA) as a condition for the approval of BLA 125613/0. The initial Pediatric Study Plan (iPSP) for the current study (KAMRAB-004) was agreed to by the FDA on May 20, 2016 following interactive review. The primary objective of the pediatric study was to confirm the safety of KEDRAB in children ages 0 months to <17 years when administered as part of post-exposure prophylaxis (PEP) and was intended to support the use of KEDRAB in the pediatric population. The pediatric study Final Study Report was submitted to FDA on July 16, 2020, meeting the January 15, 2021 PMR milestone date. The applicant is claiming that the data from Study KAMRAB-004 provides support for a claim of efficacy and safety for KEDRAB in the pediatric population.

KEDRAB is the accepted proprietary name for the product under review in this BLA supplement and this name will be used through this document to refer to Applicant's anti-rabies immunoglobulin. "HRIG" will be used when referring to human rabies immunoglobulin in general.

KEDRAB is a sterile liquid preparation enriched with human anti-rabies immunoglobulins (HRIG) for injection around the infected wound site and for intramuscular (IM) administration. It is manufactured from (b) (4) plasma of healthy human donors immunized with rabies vaccine. KEDRAB, approved in 2017 in the U.S., is indicated for passive, transient post-exposure prophylaxis of rabies infection when given immediately after contact with a rabid or possibly rabid animal in combination with rabies vaccine. KEDRAB has been used to treat rabies worldwide since 2008.

To best understand the issues raised in this application, it is important to appreciate that rabies is a lethal zoonotic disease that results from an infection by RNA viruses of the Genus *Lyssavirus* that first manifests as an acute meningoencephalitis. The current standard of care for a patient who has not been vaccinated and is suspected or known to have been exposed to rabies is infiltration of HRIG into and around the wound followed immediately by immunization with rabies vaccine. The World Health Organization (WHO) recommends a schedule of 4 vaccinations given on days 0, 3, 7 and 14. To augment the protective effects of vaccine, rabies immunoglobulin (RIG), originally derived from rabbit serum, is used to augment the survival benefit. RIG has been in use since 1955 after Baltazard et al.[1] showed a marked survival benefit with its use compared to the rabies vaccine alone. The combination of RIG and vaccine when administered as labeled is nearly always effective. In fact, there has never been a single reported case of PEP failure in the US since the introduction of HRIG and modern cell culture vaccines in the 1980s. The few who have died despite PEP involved deviations from the WHO-recommended prophylaxis protocol or severe facial wounds.

The ability of a vaccine to elicit RVNA is generally viewed as a reasonable surrogate of protection. Although a definitive "protective" titer cannot be described for all hosts under all exposure scenarios, two working definitions of adequate RVNA reference values have been developed to define an appropriate, intact adaptive host response to vaccination. There are 2 accepted indicators of an adequate adaptive immune response: "a target of ≥0.5 IU/mL by the rapid fluorescent focus inhibition test (RFFIT)" [(favored by World Health Organization (WHO) and used in this study] and "achievement of complete virus neutralization at a 1:5 serum dilution

[1] Baltazard et al. Practical test of anti-rabies serum in bites by rabid wolves. Bull WHO 1955; 13:747-72.

by the RFFIT" [favored by Advisory Committee on Immunization Practices (ACIP) and Center for Disease Control (CDC)]. The WHO parameter limit of 0.5 IU/mL for RVNA is the most widely held convention because it is the minimum antibody level determined after evaluation of peak responses in early human clinical trial studies. There are no data to support the efficacy of a level lower than this close-to-peak vaccine response. For a fatal disease such as rabies, where vaccination and passive immunity (use of HRIG) are absolutely required for protection upon exposure, verification of the RVNA assay level is the most expedient way to ensure vivo protection against the virus. Because placebo-controlled trials are unethical in rabies, RVNA produced in the recipient of HRIG and vaccine (usually measured at day 14) is accepted as a surrogate to measure efficacy of the overall treatment regimen.

The study that provided support for this efficacy supplement in the pediatric population, KAMRAB-004, was conducted at 2 sites in the U.S. and enrolled 30 subjects between the ages 6 months and 14.9 years who were likely to have had exposure to rabies through possible contact with a suspected or known rabid animal. Thirteen subjects had confirmed animal bites (including one confirmed from a rabid animal), and 2 subjects had known exposure to an animal who tested positive for rabies, and the other 5 subjects had exposure to a potentially rabid animal. Based on the standard WHO benchmark of RVNA ≥ 0.5 IU/mL, 93.3% of all pediatric subjects had a documented adequate immune response at day 14. The 2 subjects who had RVNA titers < 0.5 IU/mL at day-14 were a 4.2- year old male, whose RVNA titer was 0.23 IU/mL and an 11.8 year old female, whose RVNA titer was 0.44 IU/mL. Neither of these subjects had an immunodeficiency and all procedures for immunization and administration of KEDRAB appeared to have been followed properly (e.g. full dose administered IM in both cases at a site anatomically remote from vaccine site of administration). At day 84, no subjects had developed clinical rabies, although 2 subjects were lost to follow-up. There were no Serious Adverse Events (SAEs) and the adverse reactions were similar to what was seen in adults.

The suboptimal immune response at day-14 in 2 of the pediatric subjects raised potential concerns that KEDRAB may have interfered with the host immune response to the rabies vaccine. However, as reported in Briggs et al, subjects who do not mount an adequate response at 14-days may mount an adequate response by day 30.[2] This may have also occurred for the 2 subjects with suboptimal immune responses at day-14 in KAMRAB-004, but is unknown as day 30 RVNA titers were not assessed.

Although this study was inadequate to determine efficacy of KEDRAB in children, as there was no 30-day RVNA titer, long-term clinical follow-up or pediatric PK data, Real World Evidence (RWE) provides data to support the efficacy of KEDRAB in children.
The applicant provided data on the use of KAMRAB, an identical formulation as that approved in the U.S., that has been used in Israel for 13 years. Based on an Israeli public health data base, during this time, 2,754 patients received PEP with KAMRAB, and there were no death or active cases of rabies. Within the U.S., according to the Applicant's review of the claims database, 172 children (≤17 years) have been treated with KEDRAB between 2018-2020. As Rabies is a reportable condition, the Center for Disease Control and Prevention (CDC) knows of all U.S. cases of rabies, and there were no cases of rabies between 2018-April 2021 amongst people who received PEP with any product.

[2] Briggs et al, Bulletin of the World Health Organization, 2000, 78 (5), 693-8.

Based on this data, the clinical review team has determined that efficacy and safety of KEDRAB for PEP in the pediatric population has been demonstrated and recommends that the indication specify that the product is indicated for persons of all ages, whereas previously there was no age specification. Also, the clinical review team recommends including details of the pediatric study and RWE in the label.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For both the safety population and the as-treated population, the majority of subjects were white (21 subjects [70.0%]). Seven subjects (23.3%) were Black/ African American and 2 subjects (6.7%) were Asian. The mean (SD) age was 7.45 (4.3%) years (Age range: 0.5 - 14.9 years). There were 14 (46.7%) female subjects and 16 (53.3%) male subjects.

Table 1 below illustrates the baseline demographic characteristics of the population and includes data on baseline age, race, sex, comorbidities, concomitant medications, history of transfusion in prior 180 days and indication.

Table 1 Demographic Characteristics (Safety and As-Treated Population)

Demographic	**KEDRAB + Vaccine (N=30)**
Age, n	30
Age, Mean (SD)	7.5
Age, Median	7.1
Age Range (Min, Max)	0.5, 14.9
Female, n (%)	14 (46.7)
Male, n (%)	16 (53.3)
Asian, n (%)	2 (6.7)
Black or African American, n (%)	7 (23.3)
White, n (%)	2 (70.0
Hispanic or Latino, n (%)	3 (10.0)
Not Hispanic or Latino, n(%)	27 (90.0)
Height, n	30
Height (cm), mean (SD)	122.68 (31.0)
Height, median	122.0
Height range, (Min, Max)	62.0, 171.2
Weight, n	30
Weight, Mean (SD)	32.61 (21.8)
Weight, Median	22.25
Weight Range, (Min, Max)	6.6, 85.7
BMI, n	30
BMI (kg/m^2), Mean (SD)	19.9 (4.5)
BMI (kg/m2), Median	17.7
BMI Range (Min, Max)	13.7, 30.2

Source: Table 11-1, Clinical Study Report (KAMRAB-004), page 43 of 63.
Abbreviation: Standard Deviation (SD)
Percentages are based on the number of subjects in the safety population.

2. **Clinical and Regulatory Background**

Kamada is seeking a labeling change to include use in pediatric patients in the United States for KEDRAB for passive, transient post-exposure prophylaxis (PEP) against rabies infection when given immediately after contact with a rabid or possibly rabid animal in combination with a rabies vaccine. KEDRAB is a stable, sterile, non-pyrogenic liquid preparation of IgG (>95%) manufactured from the (b) (4) plasma of healthy human donors immunized with rabies vaccine. KEDRAB (Kamada-HRIG), approved in the U.S. in 2017 and comprising ~20% of the US market per the applicant, has been used outside of the US for 10 years. It is estimated that between 250,000 and 500,000 individuals worldwide have been treated with Kamada-HRIG. Kamada has not received any adverse reaction reports associated with the clinical use of Kamada-HRIG. The proposed proprietary name for the product is KEDRAB.

The initial Pediatric Study Plan (iPSP) for the current study (KAMRAB-004) was agreed to by the FDA on May 20, 2016 and the final protocol was submitted on December 14, 2016 following

interactive review. The primary objective of the pediatric study was to confirm the safety of KEDRAB in children ages 0 months to <17 years when administered as part of post-exposure prophylaxis (PEP) and was intended to support the use of KEDRAB in the pediatric population. The secondary objectives of the study were to obtain data on day-14 RVNA levels after treatment with KEDRAB and rabies vaccine according to ACIP recommendations for PEP and to evaluate efficacy of KEDRAB, when administered with rabies vaccine according to ACIP recommendations for PEP, in the prevention of rabies disease.

2.1 Rabies

Rabies is an acute meningoencephalitis due to infection by RNA viruses of the Order Mononegavirales, Family Rhabdoviridae and Genus Lyssavirus. The infection is universally fatal once clinical symptoms have developed. The major source of rabies transmission in the world is canine; more than 99% of rabies cases in countries where rabid dogs exist are due to dog bites. Bats are the most common cause of transmission in the United States. The annual global mortality of human rabies was estimated to be between 26,400 and 61,000 in 2010, with the majority of deaths in Asia and Africa. In the US and other developed countries, human deaths from rabies are generally restricted to people exposed while living in or travelling to areas endemic for canine rabies. About two deaths per year due to human rabies imported from endemic regions have been reported in Europe, North America and Japan. Death due to rabies is rare in the US; only 31 cases were confirmed in the decade 2003-2013, of which eight were in children under the age of 18 (Dyer et al. 2013). The number of individuals treated for suspected exposure to rabies virus is estimated by the Centers for Disease Control and Prevention (CDC) to be on the order of 40,000-50,000 per year. It is not known how many of these treatments are given to children. Children are at higher risk of dog bites and globally account for a large proportion of rabies deaths.

The latency period of rabies varies depending upon the amount of virus in the inoculum, the density of motor endplates at the wound site, and the proximity of the viral entry site to the central nervous system (CNS). Virus cannot be detected in the plasma as there is no viremic dissemination. Instead, the virus is amplified in skeletal myocytes near the site of inoculation. It then enters the nervous system through unmyelinated sensory and motor terminals. The latent period may vary from a few days to several years but is most often between 20 to 90 days. During this time, the virus migrates to the central nervous system (CNS). Rabies manifests clinically as an acute meningoencephalitis with survival rare after the onset of clinical symptoms. The first specific clinical symptom is neuropathic pain caused by viral replication in the dorsal root ganglia and inflammation induced by cellular immunity at the site of the bite. Muscle weakness in paralytic rabies is likely due to peripheral nerve axonopathy or myelinopathy. Functional neuronal impairment likely accounts for the coma. Death is usually caused by respiratory arrest and occurs two to ten days after appearance of the first symptoms. Rabies encephalitis is associated with the highest case fatality rate of any infectious disease.

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

Table 2 Clinical and Regulatory History

Date	Pre- and Post-submission Regulatory Activity Related to the Submission
February 2004 - April 2004	Clinical development of Kamada-HRIG began in February 2004, with the initiation of Phase 1 Study RD 154/23630 at a single site in Israel. The study was completed in April 2004.
November 2004 - December 2004	A second Phase 1 study RD 154/24061 was initiated at a single site in Israel in November 2004. This study was completed in December 2004.
March 2007	An Investigational New Drug (IND) application was submitted by Kamada submitted IND 13333/0 in March 2007 to conduct a Phase 2/3 study (KAMRAB-003) in the US. This IND was based on a previous IND (13193) application that was withdrawn at the recommendation of the FDA. The study was approved to proceed in May 2007.
January 2010	In response to a Type C meeting request, FDA agreed to a request to eliminate the planned PK comparison between Kamada-HRIG and a licensed comparator product under IND 13333. This decision was made since an earlier Phase 1 PK Study 24061 had already been conducted.
April 2012 – March 2014	There were four amendments to Study 003 were submitted to and approved by the FDA. The most clinically relevant amendments were: Changed rabies vaccine due to market shortage (v. 2, 11/26/12) and hemolysis workup added to safety evaluation (v.4, 8/29/13).
April 2013 - August 2014	The Phase 2/3 Study 003 was initiated at a single site in the US under IND 13333 in April 2013 and completed in August 2014.
December 2015 – December 2016	A Pediatric Study Plan (PSP) submitted to FDA in December 2015. Kamada received comments on February 19, 2016 and resubmitted a revised PSP on April 21, 2016 incorporating all of the FDA recommendations. The initial PSP was agreed to by the FDA on May 20, 2016. After additional exchange of information dated June 20 and Sept 8, 2016, 2016, Kamada submitted a protocol for study KAMRAB-004 on Dec 14, 2016. The study plans to confirm the safety of KEDRAB in children ages 0 months to <17 years when administered as part of PEP. The data from this study will be submitted to the FDA to support the use of KEDRAB in children.
March 2016	Kamada had a face-to-face Type B pre-Biologics License Application (BLA) meeting with FDA in March 2016.
July 12, 2017	The pediatric study protocol was approved by PeRC during a meeting on July 12, 2017. A deferral of the pediatric study was granted.
August 29, 2016	CBER receipt date, BLA 125613/0
August 2017	Approval of KEDRAB BLA 125613/0; deferred PMR pediatric study (KAMRAB-004) as a condition of the approval. • Final Protocol Submission: December 14, 2016 • Study Initiation Date: March 31, 2017 • Study Completion Date: June 15, 2020 • Final Report Submission: January 15, 2021
July 17, 2020	Received Post Approval Supplement (PAS) #76 containing the PMR pediatric Final Study Report and associated labeling changes to include the pediatric study results and to include use in children. • Labeling due 4/17/21 • PeRC 3/30/21 • PAS due 5/17/21

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

The treatment of rabies includes HRIG and Rabies Vaccine. HRIG supplies antibodies to help neutralize virus in the first few days after exposure until the adaptive immune reaction to the vaccine is mounted, unless the dose of the HRIG is optimized, vaccine interference may occur.[3] To mitigate this possibility, the dose has been optimized to 20 IU/kg. As shown in figure 1, by day 14, the vaccine's effect is peaking and the HRIG levels are very low (below 0.1 IU/mL). Favorable PK comparisons at day 3 when the HRIG levels peak increase confidence that the HRIG is effective (see Figure 1). Most of the day-14 RVNA effect is attributable to vaccine, not HRIG.

Figure 1: From Helmick, et al: RVNA by day

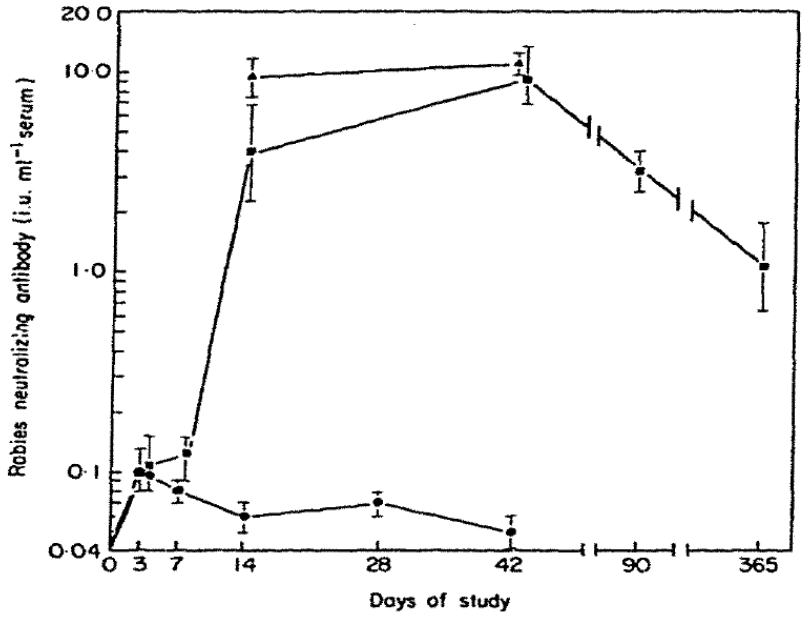


Fig. 1. Rabies antibody titres following administration of biologicals. Coded as: ●, Group A, 20 i.u. kg^{-1} M-HRIG on day 0; ▲, Group B, 1 dose of M-HDCV on days 0, 3, 7, 14, 28; ■, Group C, 20 i.u. kg^{-1} M-HRIG on day 0 and 1 dose of M-HDCV on days 0, 3, 7, 14, 28. Vertical bars indicate GMTs with 95% confidence limits

Rabies vaccines: IMOVAX Rabies (HDCV) and RabAvert (PCEC)

2.3 Safety and Efficacy of Pharmacologically Related Products

There are two human rabies immunoglobulins (HRIGs) that have been approved for marketing in the United States: HyperRAB™ S/D and Imogam® Rabies-HT, marketed by Grifols Therapeutics Inc and Sanofi Pasteur, respectively. The products are standardized against the U.S. Standard Rabies Immune Globulin to contain an average potency value of 150 IU/mL. To

3 Helmick CG et al, A Clinical Study of Human Merieux Rabies Immune Globulin, Jl of Biological Standardization, 1982, 10, 357-367.

date there have been no efficacy or safety risks identified for either of these two HRIG products for the approved indication.

The BLA files for HyperRAB and Imogam were not available since they were approved in 1974 and 1984, respectively. The Package Insert for HyperRAB does not discuss the basis for its clinical approval. The Package Insert for Imogam reports RVNA at Day 3 and Day 14. By day three, 60% of each group had detectable antibody titers of ≥0.05 IU/mL. By day 14, the geometric mean titers (with 95% confidence interval) were 19 IU/mL (11-38) in the IMOGAM® Rabies Pasteurized + vaccine group and 31 IU/mL (20-48) in the IMOGAM® RABIES (non-heat treated) + vaccine group.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

KEDRAB has been used in children and adults in the U.S. since 2017, and it has been used outside of the U.S. for 10 years. It is estimated that approximately 450,000-500,000 individuals worldwide have been treated with Kamada-HRIG since the product launce in 2003. Kamada has not received any adverse reaction reports associated with the clinical use of Kamada-HRIG. There have been no reports of PEP failure or excessive toxicity. (Please see RWE efficacy section for additional details).

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

2.6 Other Relevant Background Information

N/A

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. The provided material was supplemented with review of the Center for Disease Control and Prevention data on Rabies cases in the United States.

3.2 Compliance with Good Clinical Practices And Submission Integrity

The study was conducted in compliance with GCP.

3.3 Financial Disclosures

The Applicant has certified that they have not entered into any financial arrangement with the listed clinical investigators (Ambika Eranki MD, Nicholas W Hobart-Porter, DO, Carmen J Martinez-Martinez MD, and James Linakis MD) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). They also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests and further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4. **SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES**

4.1 Chemistry, Manufacturing, and Controls

Please refer to the original BLA CMC review memo for more details on KEDRAB.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the original BLA Pharmacology/Toxicology review memo for more details on KEDRAB.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The rabies RNA virus is typically present in the saliva of rabid mammals and is transmitted primarily through a bite. KEDRAB is infiltrated into the inoculation site(s) in 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.

The intramuscular (IM) administration and infiltration of RIG around the wound is intended to provide immediate passive protection for a short period of time until the patient can produce active antibodies in response to the rabies vaccine. RVNA in plasma is usually detected within 24 hours with peak levels within 2 to 7 days of IM administration. The elimination half-life of human RIG is approximately 21 days. Rabies vaccine induces an active immune response that includes the production of neutralizing antibodies but requires approximately 7-10 days to develop.

4.4.2 Human Pharmacodynamics (PD)

N/A

4.4.3 Human Pharmacokinetics (PK)

As per protocol, the PK of KEDRAB was not tested in Study KAMRAB-004.

4.5 Statistical

Please see FDA Biostatistical Review Memo.

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

5.1 Review Strategy

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The documents considered for this review were the following:

From BLA 125613/76 submission:

- Study Protocol
- Final Study Report
- Summary of Clinical Safety

- Clinical Overview

From other EDR documents

- Review Memo of BLA 125613/0, August 2017
- Review of BLA 125613/0 SBRA, August 23, 2017

5.3 Studies/Clinical Trials

The Applicant conducted three clinical trials in support of the BLA 125613/0 licensing application; all of them were in normal healthy volunteers. These studies were not reviewed as part of this efficacy supplement.

1. Study 23630: A single site Phase 1 study Israel in healthy male and female volunteers who were administered KEDRAB.

2. Study 24061: A single site Phase 1 study to evaluate the safety and efficacy of KEDRAB co-administered with active vaccine in healthy male and female volunteers.

3. KAMRAB-003: "A Prospective, Randomized, Double-Blind, Non-inferiority, Phase II/III Study of the Safety and Effectiveness of Simulated Post-Exposure Prophylaxis with Kamada Human Rabies Immune Globulin (KamRAB) with Co-administration of Active Rabies Vaccine in Healthy Subjects"

To support the efficacy supplement, the sponsor conducted a clinical trial in children. This study is the focus of the review for the efficacy supplement.

The deferred PMR pediatric study: KAMRAB-004: **"**Open-label Post-marketing Study of KEDRAB Administered as a Single Dose with Active Rabies Vaccine in Children Exposed to Rabies"

5.4 Consultations

5.4.1 Advisory Committee Meeting

N/A

5.4.2 External Consults/Collaborations

N/A

5.5 Literature Reviewed

The literature reviewed was the following:

- Aoki FY, Rubin ME, Friesen AD, Bowman JM, Suanders JR. 1989. Intravenous human rabies immunoglobulin for post-exposure prophylaxis: serum rabies neutralizing antibody concentrations and side-effects. J Biol Stand. 17(1):91-104
- Aoki FY, Rubin ME, Fast MV. 1992. Rabies neutralizing antibody in serum of children compared to adults following post exposure prophylaxis. Biologicals. 20:283-287.
- Baltazard et al. Practical test of antirabies serum in bites by rabid wolves. Bull WHO 1955; 13:747-72.
- Briggs et al, Bulletin of the World Health Organization, 2000, 78 (5), 693-8.

- Helmick CG et al, A Clinical Study of Human Merieux Rabies Immune Globulin, Jl of Biological Standardization, 1982, 10, 357-367.A clinical study of rabies immune globulin*, Journal of Biological Standardization (1982) 10, 357--367
- Rupprecht CE, Briggs D, Brown CM, Franka R, Katz SL, Kerr HD, Lett SM, Levis R, Meltzer MI, Schaffner W, Cieslak PR. 2010. Use of a reduced (4-dose) vaccine schedule for post exposure prophylaxis to prevent human rabies: recommendation of the advisory committee of immunization practices. MMWR. 59(RR02):1-9.
- Susan M. Moore, Kansas State University Rabies Laboratory, Manhattan, Kansas, USA; Rabies vaccination and level of protection.
- World Health Organization. 2013. Expert Consultation on Rabies. Second Report. Geneva: WHO Press. Technical Report Series (No. 982).
- United States Centers for Disease Control and Prevention. 2011. Rabies: Diagnosis in animals and humans.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 KAMRAB-004

The title of the Post Marketing Requirement pediatric study is, “Open-label Post-marketing Study of KEDRAB Administered as a Single Dose with Active Rabies Vaccine in Children Exposed to Rabies.” The study is an open-label, non-controlled study in the U.S. to confirm the safety of KEDRAB in children ages 0 months to <17 years, when administered with active rabies vaccine as a part of PEP.

6.1.1 Objectives

Primary Study Objective:

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

Secondary Study Objectives:

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

6.1.2 Design Overview

This was an open-label, single-arm study of 20 international unit (IU)/kg intramuscular (IM) of KEDRAB administered in conjunction with rabies vaccine. The primary objective of the study was to confirm the safety of KEDRAB in children ages 0 months to <17 years, when administered with active rabies vaccine as part of PEP. The secondary objectives of the study were to obtain data on rabies virus neutralizing antibody (RVNA) levels after treatment with KEDRAB and rabies vaccine according to ACIP recommendations for PEP and to evaluate efficacy of KEDRAB, when administered with rabies vaccine according to ACIP recommendations for PEP, in the prevention of rabies disease. The study was conducted in pediatric subjects with exposure or possible exposure to rabies virus in whom PEP against rabies infection was indicated. Subjects aged 0 months to <17 years who met the study entry criteria and exclusion criteria received a single dose of 20 IU/kg KEDRAB on Day 0 and a 1 mL dose of licensed rabies vaccine (RabAvert®; Novartis Vaccines and Diagnostics) on Days 0, 3,

7 and 14, according to ACIP recommendations. Subjects were contacted via telephone on Days 28, 56 and 84. Subjects were followed for a total of 3 months (84 days) after treatment.

Safety data collected included local and systemic adverse event (AEs) data and physical examination findings collected for 14 days following administration of KEDRAB, and serious adverse event (SAE) data collected at every study contact (including telephone follow-up) up to Day 84. Efficacy data collected included rabies virus neutralizing antibody (RVNA) titer evaluated using a validated rapid fluorescent focus inhibition test (RFFIT) at Day 14, and number of cases of active rabies infection in subjects treated with KEDRAB and rabies Vaccine up to Day 84.

6.1.3 Population

The population included healthy pediatric subjects aged 0 months to <17 years with exposure or possible exposure to rabies virus in whom PEP against rabies infection was indicated and met the study entry criteria and exclusion criteria. The main inclusion criterion was the following: Subjects were healthy children (male and female) ages 0 months to <17 years with exposure or possible exposure to rabies, for whom PEP against rabies infection is indicated. Subjects had documented informed consent and, for subjects old enough to provide assent (per institutional regulations) documentation of the child's assent to participate in the study.

Inclusion Criteria

1. Healthy children (male and female) ages 0 months to <17 years;
2. Exposed or possibly exposed to rabies;
3. Indicated to receive post-exposure prophylaxis (PEP) against rabies infection; and
4. Informed consent from the child's parent(s) or legal guardian(s) and assent from the child if appropriate.

Exclusion Criteria

1. History of previous administration of rabies vaccine or human rabies immune globulin (HRIG);
2. Rabies exposure or possible rabies exposure more than seven days prior to initiation of PEP, or timing of exposure unknown;
3. History of live virus vaccine administration, e.g., measles vaccine, within the last three months or;
4. History of hypersensitivity reaction to any components of the licensed rabies vaccine;
5. History of allergy to blood or blood products;
6. History of bleeding disorders;
7. Fever (oral temperature >101ºF/38.3ºC) at screening;
8. Clinically significant intercurrent illnesses including cardiac, hepatic, renal, endocrine, neurological, hematological, neoplastic, immunological, skeletal or other that in the opinion of the Investigator, that could interfered with the safety, compliance or other aspects of this study;
9. Psychiatric disorder, other mental disorder or any other medical disorder that could impair the subject's ability to give informed consent or to comply with the requirements of

the study protocol, or which could have limited the ability of caregiver or study personnel to adequately monitor AEs;
10. Participation in another clinical trial within 30 days prior to the baseline visit;
11. Pregnancy; or
12. Currently breastfeeding or any other factor that, in the opinion of the Investigator, could have prevented the subject from complying with the requirement of the protocol or which could have increased the risk of participation.

6.1.4 Study Treatments or Agents Mandated by the Protocol

On Day 0, screening, baseline evaluations were performed, and subjects were administered study treatment.

All enrolled subjects received a single dose of 20 IU/kg KEDRAB by IM injection on Day 0 and 1 mL doses of active rabies vaccine by IM injection on Days 0,3, 7, and 14.

6.1.5 Directions for Use

The treatment dose is 20 IU/kg body weight (BW) that will be infiltrated locally into the wound/exposure site and/or into the distal extremity in combination with rabies vaccine. If a bite site was detectable, as much of the dose was infiltrated as possible around the wound(s). Any KEDRAB that remained after infiltration of the wound site, was administered as an IM injection in the lateral (vastus lateralis) muscle of the left leg. When the bite site was unknown, or if the bite site did not enable infiltration (e.g., lips, fingers, knee, etc.) the full dose was administered by the IM route. The gluteal region was not be used as an injection site (absorbance is unpredictable and might damage the sciatic nerve).

KEDRAB was to be injected at site(s) different and distant from the site of the rabies vaccine and not in the buttocks.

6.1.6 Sites and Centers

Four centers across the US were planned in this multi-center study; however, only 2 centers had enrollment (Arkansas Children’s Hospital and Rhode Island Hospital):

Arkansas Children’s Hospital
1 Childrens Way,
Little Rock, AR, US 72202

Rhode Island Hospital
593 Eddy Street,
Providence RI USA 02903

SUNY Upstate Medical University (No enrolment)
505 Irving Avenue,
Syracuse, NY, USA, 13210

Advent Health Orlando (No enrolment)
601 East Rollins Street
Orlando, Florida USA 32803

6.1.7 Surveillance/Monitoring

Table 3 Schedule of Assessments

Study day	Day 0 Screening Baseline	Day 0 Treatment	Day 1 Telephone Follow-up	Day 3 Treatment	Day 7 Treatment	Day 14 Treatment	Day 28 Telephone Follow-up[1]	Day 56 Telephone Follow-up[1]	Day 84 Telephone Follow-up	Unscheduled Visit
Window (Days)	NA	NA	24-34 hours post KamRAB	NA	NA	NA	±2	±4	+4	NA
Informed consent	X									
Assent (if applicable)	X									
Inclusion/exclusion criteria	X									
Demographic data	X									
Medical history	X									
Rabies Exposure evaluations[2]	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Subject diary issuance/instructions [3]		X								
Subject Diary reviews[3]			X	X	X	X				
Physical Exam, Vital Signs[4]	X	X		X	X	X				X
Record of Injection Reactions [4,5]		X		X	X	X				
Height, Weight	X									

Study day	Day 0 Baseline	Day 0	Day 1 Telephone Follow-up	Day 3	Day 7	Day 14	Day 28 Telephone Follow-up[1]	Day 56 Telephone Follow-up[1]	Day 84 Telephone Follow-up	Unscheduled Visit
Window (Days)	NA	NA	24-32 hours post KamRAB	NA	NA	NA	±2	±4	+4	NA
Complete Blood Count	X					X				
Serum Chemistries[6]	X					X				
Urinalysis (with microscopic analysis of sediment)	X					X				
Pregnancy Test[7]	X									
Assign Subject #	X									
KamRAB 20 IU/kg		X								
Rabies Vaccine		X		X	X	X				
Serum sample for RVNA Titer (RFFIT)						X				
Rabies Disease Evaluation	X			X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X				X[8]
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X

Source: Clinical Study Report (KAMRAB-004), Table 9-3, p27/63

[1] The Phone call was made within a pre-scheduled time frame and if possible, notifications was sent to subject/guardian prior to the phone call using an available communication path i.e. text message, email, phone etc. If subject/guardian was not reached on the pre-scheduled phone call, at least five attempts to contact the subject/guardian were made at different times, using different communication paths (i.e. text, email, phone),

[2] Rabies exposure evaluation included date, time of exposure, and nature of exposure, animal, confirmation of rabies in animal (when possible) (Note: A diagnosis of rabies in the animal was considered confirmed upon autopsy of the animal. If the animal was not caught and/or autopsied upon death/sacrifice, a rabies diagnosis could not be confirmed)

[3]The subject's parent/guardian was provided a diary and instructed to record information on any adverse reactions experienced by the child. They were asked to bring the diary with them on the Day 3, Day 7 and Day 14 visits to discuss with the Investigator.

[4]Performed >20 minutes following KEDRAB administration.

[5]Injection site reactions (i.e. swelling, pain, redness) were recorded following administration of KEDRAB and RabAvert

[6]Electrolytes, Glucose, Aspartate aminotransferase (AST), ALT, serum creatinine, blood urea nitrogen, lactate dehydrogenase (LDH), total bilirubin

[7]Female subjects of childbearing potential required a negative urine pregnancy test before study treatment with KEDRAB.

[8]AEs were collected only if the unscheduled visit occurred within 14 days of Day 0 treatment

IU: international units; kg: kilogram; NA: Not applicable; RFFIT: rapid fluorescent focus inhibition test; RVNA: rabies virus neutralizing antibodies, AST; ALT; LDH

6.1.8 Endpoints and Criteria for Efficacy

RVNA levels ≥ 0.5 on Day 14 IU/mL are considered a traditional threshold for the required plasma level, per World Health Organization (WHO).

Reviewer Comments:

1. *The antibody level recommended by WHO as an adequate response to rabies vaccination is 0.5 IU/mL. Assays advocated by WHO are the Rapid Fluorescent Focus Inhibition Test (RFFIT) and ELISA--if the RFFIT is not available. The RFFIT measures rabies virus neutralizing antibody (RVNA) levels in serum. The active antibody response develops in approximately 7-10 days, and detectable RVNA generally persist for several days. The 0.5 IU/mL value is not a level of protection but rather the minimum antibody level determined after evaluation of peak responses in early human clinical trial studies. Using the RVNA level to assess the vaccine response is supported by studies establishing RVNAs as the most significant immune component in preventing rabies after exposure. Animal rabies challenge models show 0.5 IU/mL to be a robust level of protection, though not absolute—as some animals survive experimental challenge with RVNA levels below 0.5 IU/mL, implying that other immune effectors are involved in protection. Other factors in real life exposures, such as the location and severity of bite, the virus variant and the amount of virus received can also influence the strength of immune response required to prevent rabies.*

2. *In the BLA 125613/0 clinical review memorandum, the reviewer states,*

    a. *The primary endpoint selected for the Phase 2/3 study (KEDRAB-003) was the proportion of subjects with anti-rabies IgG titer ≥ 0.5 IU/mL antibody measured on Day 14. "The rationale for the selection of Day 14 as the time-point for the readout of efficacy (>0.5 IU/mL) is unclear. As stated in Section 2.2.2, the goal of post-exposure prophylaxis is to achieve a serum rabies neutralizing activity of >0.5 IU/mL. This target neutralizing activity was derived based upon animal studies. Nonetheless, this is the current CDC and WHO recommendation. There were no discussions regarding the appropriateness of this endpoint in the minutes of the original IND teleconference (Apr 25, 2007) or during the pre-BLA meeting (Mar 17, 2016)."*

    b. *The BLA files for HyperRAB and Imogam were not available since they were approved in 1974 and 1984, respectively. The Package Insert for HyperRAB does not discuss the basis for its clinical approval. In contrast, the Package Insert for Imogam reports RVNA for both Day 3 and Day 14 although the levels were >0.5 IU/mL only on Day 14.*

    c. *As per protocol, the PK of KEDRAB was not tested in Study KAMRAB-004. Because it cannot be assumed that pediatric PK is identical to adult PK, conclusions regarding the efficacy of KEDRAB in children cannot be made from this study (i.e., conclusions regarding its ability to provide temporary prophylaxis while the vaccine is "kicking in" and conclusions regarding a lack of interference with vaccine effect). Although no children had clinical rabies infection at day 84, because rabies onset can be delayed up to 1-2 years, it could not be confirmed from this study that the regimen was 100% effective at preventing the development of clinical rabies which is the expectation of*

rabies PEP. Please refer to the section on Real World Evidence to support the pediatric efficacy of KEDRAB.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see Biostatistics review memo.

All statistical analyses were performed by using SAS® Version 9.3 or higher. Summary tables of data are provided as appropriate, showing the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum for continuous variables, and counts and percentage for categorical variables. Appendix listings were also provided. Due to the small sample size and the descriptive nature of this study calculations 90% CI for the mean of continuous variables and categorical variables were omitted from the analysis.

Efficacy Analysis

Subjects' rabies virus neutralizing antibody (RVNA) titer levels on Day 14 after administration of KEDRAB based on RFFIT assay were measured. This parameter was reported as an efficacy parameter using As-Treated population where efficacy was determined by the number of subjects with no active rabies infection.

The **As-treated Population** was defined as all subjects who received at least 3 vaccine doses (until day 14) and one dose of KEDRAB. This included all 30 subjects.

Safety Data Analysis

With specific regard to the primary endpoint (adverse events), in a sample of 30 subjects, the likelihood was 80% that an adverse event for which the true incidence rate of 5.3% or higher would be observed; and was 90% for an adverse event for which the true incidence rate was 7.4% or higher. Subjects who discontinued prior to completion of study procedures were not replaced.

The safety analyses used the safety population and focused on the following endpoints:

- Local and systemic AE (classified according to timing after injection and relation to treatment)
- Serious Adverse Events (SAEs)

These endpoints were analyzed by descriptive statistics.

6.1.10 Study Population and Disposition

This is a multicenter study conducted between August 2016 and November 2019. This study was intended to be executed in four centers across the US. The subjects were enrolled in the study at only two sites (Arkansas Children's Hospital and Rhode Island Hospital). Thirty-three

subjects were screened, of which 30 subjects were enrolled in this study. Three subjects failed screening and were not enrolled in this study.

Subject Disposition

All 30 (100%) enrolled subjects were treated and were in the study on Day 14; of these, 28 (93.3%) subjects completed the study (Day 84). Out of 30 subjects that were enrolled in the study, 2 (6.7%) did not complete all study visits.

Protocol Deviation

A total of 28 (93.3%) subjects had at least one minor protocol deviation. Two subjects ((b) (6)) had a major deviation in the study as follows; for Subject (b) (6) , the subjects' biological mother signed the initial consent forms instead of the subject's legal guardian and for Subject (b) (6) , a pregnancy test was ordered per protocol, however, study procedures began before the test results were available; (they test was negative).

6.1.10.1 Populations Enrolled/Analyzed

The study population was pediatric subjects, aged 6 months to <14.9 years, with exposure or possible exposure to rabies virus in whom post-exposure prophylaxis (PEP) against rabies infection with KEDRAB administered as part of PEP was indicated.

A total of 30 subjects (100%) were included in the as-treated population. Of the 30 safety subjects, 28 subjects completed the study at day 84.

6.1.10.1.1 Demographics

For both the safety population and the as-treated population, the majority of subjects were white (21 subjects [70.0%]). Seven subjects (23.3%) were Black or African American and 2 subjects (6.7%) were Asian. The mean (SD) age was 7.45 (4.3%) years (Age range: 0.5 - 14.9 years). There were 14 (46.7%) female subjects and 16 (53.3%) male subjects.

The mean (SD) weight for the subjects was 32.61 kgs (21.83), and mean (SD) height was 122.68 (31.03) cm. The mean (SD) BMI was 19.19 (4.48) kg/m^2.
The safety and as-treated population have identical results. The demographic table is presented again below for convenience (Table 4).

Table 4. Demographic Characteristics (Safety and As-Treated Population)

Demographic	**KEDRAB + Vaccine (N=30)**
Age, n	30
Age, Mean (SD)	7.5
Age, Median	7.1
Age Range (Min, Max)	0.5, 14.9
Female, n (%)	14 (46.7)
Male, n (%)	16 (53.3)
Asian, n (%)	2 (6.7)
Black or African American, n (%)	7 (23.3)
White, n (%)	2 (70.0
Hispanic or Latino, n (%)	3 (10.0)
Not Hispanic or Latino, n(%)	27 (90.0)
Height, n	30
Height (cm), mean (SD)	122.68 (31.0)
Height, median	122.0
Height range, (Min, Max)	62.0, 171.2
Weight, n	30
Weight, Mean (SD)	32.61 (21.8)
Weight, Median	22.25
Weight Range, (Min, Max)	6.6, 85.7
BMI, n	30
BMI (kg/m^2), Mean (SD)	19.9 (4.5)
BMI (kg/m2), Median	17.7
BMI Range (Min, Max)	13.7, 30.2

Source: Table 11-1, Clinical Study Report (KAMRAB-004), page 43 of 63.
Abbreviation: Standard Deviation (SD)
Percentages are based on the number of subjects in the safety population.

6.1.11 Efficacy Analyses

Study Design:
The prospective pediatric study enrolled 30 children (0 months to <17 years), and all subjects were administered KEDRAB at a dose of 20 IU/kg IM at the wound site and/or distally at the same time rabies vaccine was initiated. Evaluation of efficacy of KEDRAB, when administered with rabies vaccine is according to ACIP recommendations for PEP, in the prevention of rabies disease. This was a secondary objective of the study.

Reviewer Comment:

1. *RVNA titers were measured only at Day 14 (as mandated in the agreed PSP). However, this does not allow for the detection of delayed rise in RVNA titers by 30-days, in the event that there are RVNA titers below the threshold of 0.4 IU/ml at 14 days.*

2. *HRIG provides passive immunization and protection from day 0-7. PK data during this time is needed to evaluate whether the pharmacokinetics for KEDRAB are the same in children as adults. The lack of this data is a limitation of the study design.*

Extent of Rabies Exposure:
Of the 30 enrolled subjects, 3 (10.0%) subjects had contact with animals who had confirmation of rabies.

Five animals with potential rabies who were the source of exposure for 5 subjects ((b) (6)) were tested for rabies; of these, 3 animals ((b) (6)) tested positive for rabies and 2 animals ((b) (6)) tested negative for rabies. There is no data on the animals that came into contact with the other subjects. At Site 002-Arkansas Children's Hospital, none of the animals were tested (or confirmed) for rabies.

Potential rabies exposure included a confirmed animal bite in 13 subjects ((b) (6)). One of the subjects bitten was bitten by an animal confirmed to have rabies.

EFFICACY RESULTS:
All enrolled subjects received study drug. Efficacy was assessed via evaluation of Day 14 anti-rabies virus neutralizing antibody (RVNA) titer data generated using a validated rapid fluorescent focus inhibition (RFFIT), and number of cases of active rabies infection in subjects treated in the study. On Day 14, a blood sample was collected for assessment of the RVNA level by RFFIT. Subjects' rabies virus neutralizing antibody (RVNA) titer levels on Day 14 after administration of KEDRAB based on RFFIT assay were measured. This parameter was reported as an efficacy parameter using as-treated population where efficacy was determined by the number of subjects with no active rabies infection.

Efficacy was assessed via evaluation of Day 14 RVNA titer data generated using a validated RFFIT, and number of cases of active rabies infection in subjects treated in the study. Per WHO, RVNA levels ≥ 0.5 IU/mL are considered adequate response. Subjects' RVNA titer levels on Day 14 after administration of KEDRAB based on RFFIT were measured and active rabies infection was evaluated by the investigator. Rabies disease infection was also evaluated and documented on Days 0, 3, 7, 14, 28, 56, and 84, and at any unscheduled visits.

According to investigator assessment on Day 14 and through the day 84 follow-up, none of the 30 subjects had active rabies infection. On day 14, 28 (93.3%) subjects had RVNA titer levels ≥ 0.5 IU/mL, and according to the World Health Organization (WHO), RVNA levels ≥ 0.5 IU/mL are considered a traditional threshold for the required plasma level. On Day 14, RVNA titer levels for 30 subjects had a mean (SD) of 18.89 (31.61), median 8.81 and a range of 0.21 – 153.62.

Reviewer Comment:

1. 2 subjects ((b) (6)) were lost to follow-up and did not complete the day 84 visit. However, since these subjects had RVNA titers at Day 14 ≥ 0.5 IU/mL and no

cases of rabies were reported to the CDC (see RWE section), this missing data is less concerning.

2. Since HRIG is administered IM and acts locally, serum levels of antibody are only approximations of the level of antibody at the site of activity. The IM administration and infiltration of RIG around the wound provides immediate passive protection for a short period of time until the patient can produce active antibodies from the rabies vaccine. Rabies neutralizing antibodies in plasma are usually detected within 24 hours with peak levels within 2 to 7 days of IM administration. The elimination half-life of human RIG is approximately 21 days. Rabies vaccine induces an active immune response that includes the production of neutralizing antibodies but requires approximately 7-10 days to develop. A major concern is RIG binding with antigens within the vaccine thereby decreasing the rabies antibody produced in response to vaccination. Clinical rabies typically develops within 1 year in children, and therefore 84 days is too short to determine clinically if there is interference. (Please see RWE section for long-term clinical efficacy data).

RVNA Titers

At day 14, 28 (93.3%) subjects had RVNA antibody titer levels ≥ 0.5 IU/mL. Two subjects did not reach
RVNA titer levels of ≥ 0.5 IU/mL at the time point; their RVNA titters
were 0.4 IU/mL and 0.21 IU/mL, respectively.

- Subject (b) (6) is a 4.2 year-old, non-Hispanic, white male. He had potential exposure to rabies from a wild racoon in July 2019. The animal was confirmed to have rabies, but the child did not have confirmed contact. His 14-day RVNA titer was 0.21 IU/mL. During the study follow-up he did not have clinical Rabies.

- Subject (b) (6) is a 11.8 year-old, non-Hispanic, white female. She had a potential exposure to rabies from a wild woodchuck in June 2019. The animal was not able to be tested for rabies. There was confirmed contact, a superficial, 1cm x 1cm bite on the child's hand between the 3rd and 5th fingers. Her 14-day RVNA titer was .44 IU/ml. During the study follow-up she did not have clinical rabies. F W from Site 15. (value = 0.44 IU/mL)

(Please see Appendix 2 for complete narratives on these subjects.)

Reviewer Comment:

1. *It is unclear why these 2 subjects had 14-day RVNA titers less than 0.5 IU/ml as there were no administration errors and the subjects were immune-competent. As discussed above, it is possible that their 30-day titers could have been >0.5 IU/ml, which would have been reassuring, but this was not tested, so it remains unknown. Based on RWE and data on U.S. rabies cases from the CDC neither subject had rabies 19- and 21-months following exposure. Based on the lack of confirmed rabies in the animal and direct contact on the animal with the child, the risk for these children developing rabies with sub-optimal or no treatment is unclear.*

2. *Fewer subjects in the pediatric population (28/30) 93.3% achieved RVNA titers ≥0.5 IU/mL on Day 14 compared to the pivotal adult study for KEDRAB, 56/57 (98%) subjects and 59/59 (100%) of the HRIG comparator group. Despite these differences in percent of RVNA titers above the WHO threshold between children and adults, RWE supports that KEDRAB is efficacious and does not interfere with Rabies vaccine*

As shown in Table 5, the Day 14, RVNA titer levels for 30 subjects had a mean (SD) of 18.9 (31.6), median 8.8 and a range of 0.2 – 153.6. Figures 2 and 3 show the distribution of Day-14 RVNA levels. Figure 4 shows that there is no relationship between age and RVNA titers. Figure 5 shows that there is no relationship between the absolute dose (which equates to weight) and RVNA titers.

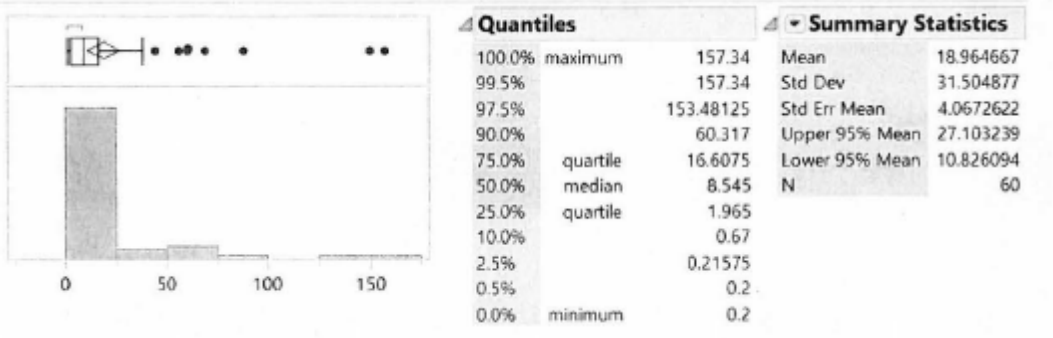
Table 5: Geometric mean and median (min/max) of RVNA Titer Levels on Day 14

	KEDRAB + Vaccine (N=30)
Day 14	
N	30
Geometric Mean (SD)	18.9 (31.6)
Median	8.8
Min, Max	0.2, 153.6

Source: BLA 125613/67, Table 11-3, Study Report Body

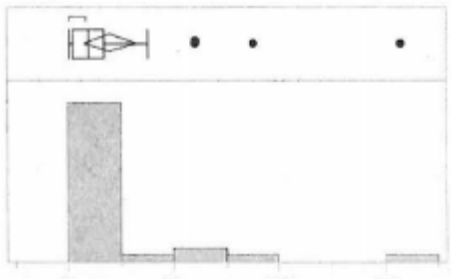
Note: Analysis of RVNA results was performed on the Geometric Mean of the results per subject per visit, as done in the KEDRAB-003 study. For analysis, the geometric mean was calculated. RVNA levels ≥ 0.5 IU/mL is considered a traditional threshold for the minimum required plasma level to confer protection)

Figure 2: Distribution of RVNA Titer Values at Day 14 using both values



Source: Figure by FDA Clinical Reviewer based on applicant's data.

Figure 3: Distribution of RVNA titer values at day 14 using only highest value (of 2) per subject



Quantiles

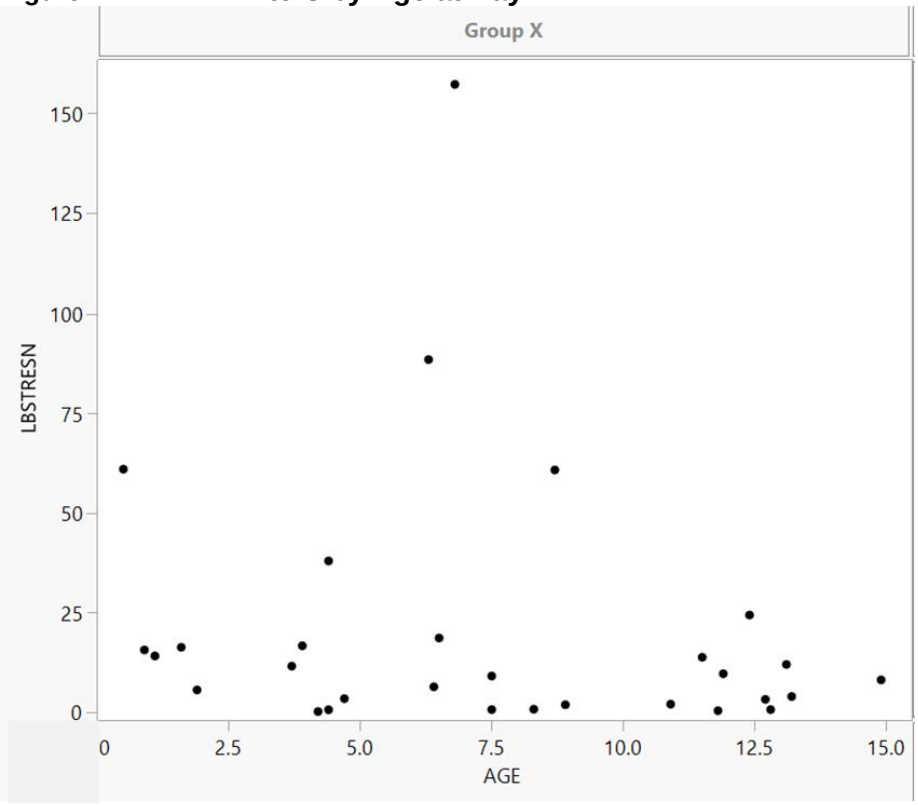
100.0%	maximum	157.34
99.5%		157.34
97.5%		157.34
90.0%		60.921
75.0%	quartile	17.1875
50.0%	median	9.415
25.0%	quartile	2.035
10.0%		0.674
2.5%		0.23
0.5%		0.23
0.0%	minimum	0.23

Summary Statistics

Mean	20.204
Std Dev	33.187557
Std Err Mean	6.0591912
Upper 95% Mean	32.596438
Lower 95% Mean	7.8115625
N	30

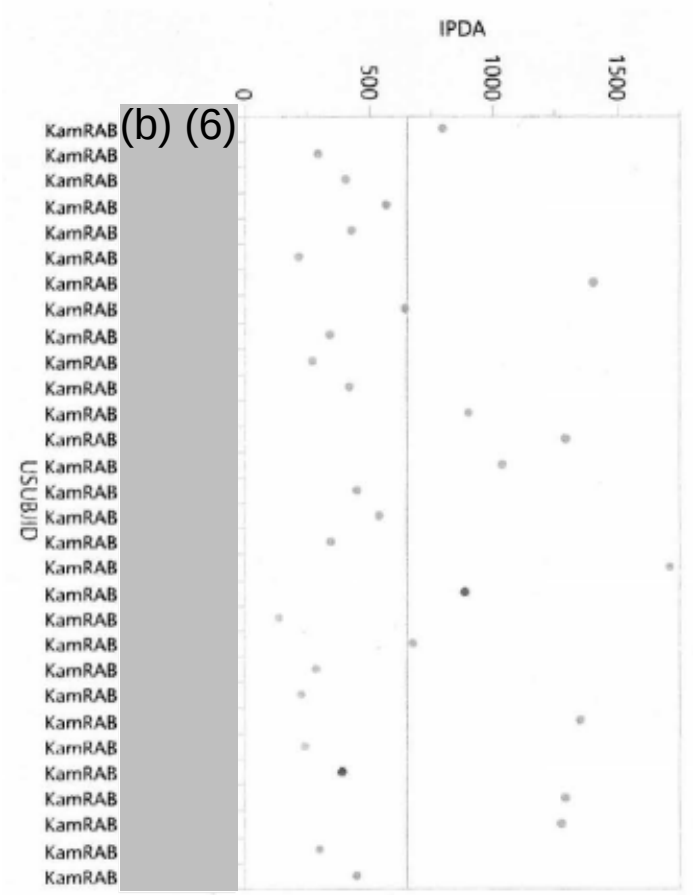
Source: Figure by FDA Clinical Reviewer based on applicant's data.

Figure 4: 2 RVNA Titers by Age at Day 14



Source: Figure by FDA Clinical Reviewer based on applicant's data.

Figure 5: Absolute Dose by Subject



Source: Figure by FDA Clinical Reviewer based on applicant's data.

Reviewer Comments:

1. *RVNA titers were not correlated with age or weight-based dose, which is reassuring for providing data for the entire pediatric age range.*

Rabies Disease

Rabies disease infection was evaluated with in-person assessments on Days 0, 3, 7 and 14 and also via telephone on days 28, 56, and 84, and at any unscheduled visits. Of the 30 treated subjects, 28 completed the 84-day study; 2 subjects terminated the study early. For all the time points there were no subjects with rabies disease.

Real World Evidence to Support Efficacy

RWE that supports the use of KEDRAB in children came from claims data that 172 U.S. children (≤17 years) were treated with KEDRAB between 2018-2020, and based on Center for Disease Control and Prevention data, no children in the U.S. treated with post-exposure prophylaxis

have been reported to have had rabies between 2018-April 2021.[4] During 2018-2019, in the U.S. there were a total of 3 cases of rabies, including 1 child, that all resulted in death; none of these patients received any post-exposure prophylaxis.

According to the Applicant, KED-Rab, is an identical formulation of KEDRAB. as that approved in the U.S.) has been used outside of the US for over 13 years and is prescribed to children in India, Israel, Russia, and South Korea.

To date, it is estimated that over 450,000 individuals worldwide have been treated with Kamada-HRIG for post-exposure prophylaxis against rabies. The Israeli Ministry of Health data base confirms that over 13 years, between 2010-2019, there were no mortality or active rabies in 2,754 patients with exposure to a rabid animal who received post-exposure prophylaxis treatment with KEDRAB.

Efficacy Conclusions

- A total of 28 (93.3%) subjects had neutralizing rabies-virus antibody titer levels ≥ 0.5 IU/mL on Day 14. For the 30 subjects enrolled in the study, RVNA titer levels had a mean (SD) of 18.89 (31.61) IU/mL, median 8.81 IU/mL and a range of 0.21 – 153.62.

- Rabies disease infection was evaluated and documented on Days 0, 3, 7, 14, 28, 56, and 84, at any unscheduled visits. No subject had an active rabies infection on Day 14, or any time point up through day 84, (although 2 subjects were lost to follow-up between day 14-day 84).

- There is RWE, including U.S. data from the CDC to support that there were no cases of rabies amongst children treated with KEDRAB to support efficacy of KEDRAB.

Reviewer's Comment: KAMRAB-004 was designed as a safety study, and is difficult to interpret data about efficacy from this study based on its design. The primary study design limitations include the lack of PK data to allow comparisons between children and adults, RVNA levels being only checked at Day 14, and children being only followed for 84 days.

None the less, the RWE, primarily from CDC, is sufficient to support the claims of efficacy in children.

6.1.11.1 Analyses of Primary Endpoint(s)

6.1.12 Safety Analyses

Based on its pharmacovigilance database, Kamada considers that presently, no obvious differences between the safety profile of pediatrics and adults/elderly patients can be identified following Kamada-HRIG administration.

Safety was assessed via monitoring of local and systemic AEs and physical examination findings for 14 days following administration of KEDRAB and monitoring for SAEs during the

[4] Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data. Atlanta, GA. CDC Division of Health Informatics and Surveillance. Available at https://wwwn.cdc.gov/nndss/infectious-tables.html. Data from 2020-2021 are provisional.

entire study period (including telephone follow-up). Adverse events were assessed for relationship to KEDRAB and, separately, to active rabies vaccine.

The safety analyses used the Safety population and focused on the following endpoints:

- Local and systemic AE (classified according to timing after injection and relation to treatment)
- Serious Adverse Events (SAEs).

These endpoints were analyzed by descriptive statistics.

SAFETY RESULTS:

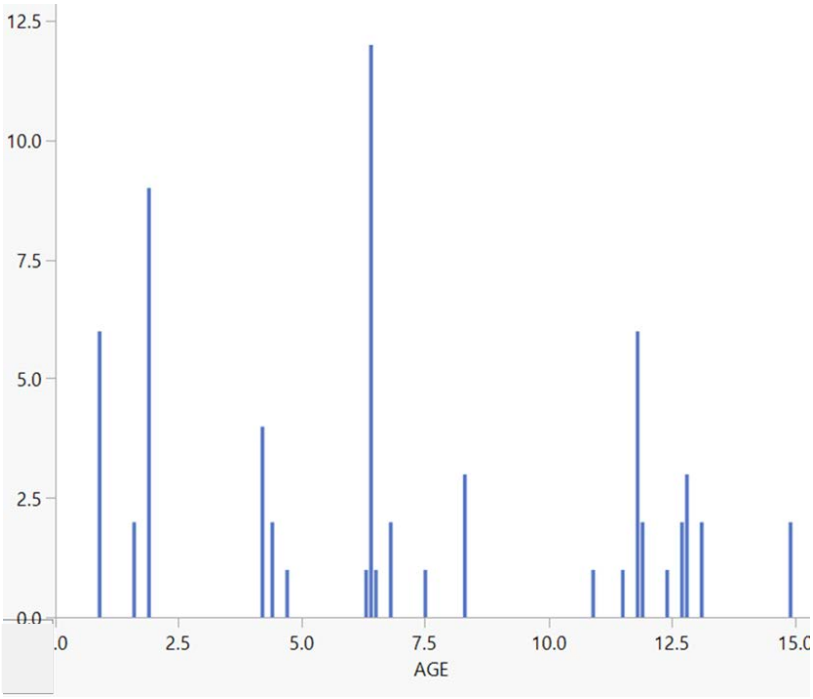
Twenty-one (70.0%) subjects experienced at least one AE within 14 days from KEDRAB treatment, administration. All AEs were mild during the 14 days following KEDRAB administration. The AEs occurring in at least 10% of subjects were injection site pain (8 subjects, 26.7%), headache (4 subjects, 13.3%), and arthropod bite and pain in extremity (each in 3 subjects, 10.0%). Adverse events were assessed for relationship to KEDRAB and, separately, to active rabies vaccine.

A total of 57 AEs was experienced within 14 days of KEDRAB administration. The majority of AEs experienced were general disorders and administration site conditions, (E = 16) experienced by 10 (33.3%) subjects. From SOC general disorders and administration site condition, injection site pain (E= 9) was experienced by 8 (26.7%) subjects.

Within 14 days of KEDRAB administration, other AEs observed were gastrointestinal disorder by 4 (13.3%) subjects, skin and subcutaneous tissue disorder by 5 (16.7%) subjects, nervous system disorders by 4 (13.3%) subjects, investigation (E = 5) by 4 (13.3%) subjects, musculoskeletal and connective tissue disorders by 4 (13.3%) subjects, psychiatric disorders by 2 (6.7%) subjects, metabolism and nutrition disorder by 1 (3.3%) subjects, ear and labyrinth disorders by 1 (3.3%) subject.

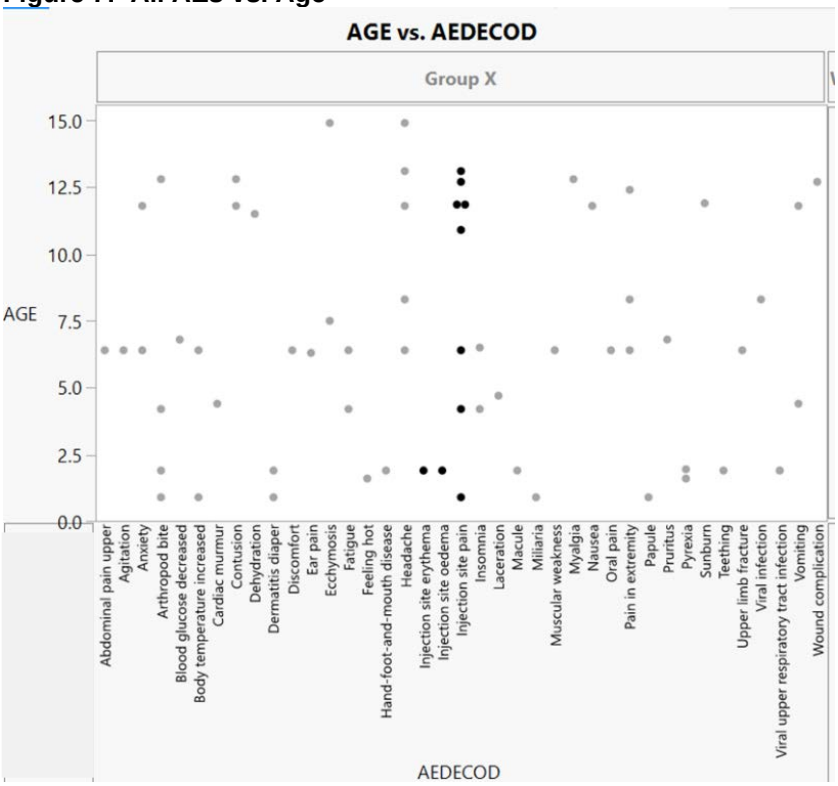
There were few AEs and no SAEs. Figures 6 and 7 shows that there was no relationship between AEs and age of subjects. All AEs except an elbow fracture were classified as mild.

Figure 6 Adverse Events: Relationship to Age



Source: Figure by FDA Clinical Reviewer based on applicant's data.

Figure 7: All AEs vs. Age



Source: Figure by FDA Clinical Reviewer based on applicant's data.

- Diaper rash concentrated among young subjects, as would be expected
- Contusion concentrated among older subjects

Overall, 22 (73.3%) subjects had any treatment-emergent AEs (TEAEs) during the study. (21 subjects had any TEAEs during 14 days of KEDRAB administration and one subject had a TEAE of limb fraction on day 24 from KEDRAB administration). Of these, 12 (40.0%) subjects had study drug related TEAEs. There were no subjects with serious TEAEs, with TEAEs leading to discontinuation of study treatment or with TEAEs leading to death (Table 6). The majority of these AEs were general disorders and administration site conditions experienced by 10 (33.3%) subjects. Out of 22 subjects that had TEAEs throughout the study, 7 (23.2%) were probably related, 5 (16.7%) were possibly related, 4 (13.3%) were unlikely related, and 6 (20.0%) were not related to the study drug. All of the TEAEs experienced were mild in severity with one (1) exception, which was moderate in severity (Table 7), a fracture that was deemed (reasonably) as unrelated.

Table 6 Summary of Treatment Emergent Adverse Events (Safety Population)

	KEDRAB + Vaccine (N=30) n (%)
Number of subjects with any Treatment-Emergent Adverse Events (TEAEs)	22 (73.3)
Number of subjects with study drug related TEAEs	12 (40.0)
Number of subjects with serious TEAEs	0
Number of subjects with TEARs leading to discontinuation of study treatment	0
Number of subjects with TEARs leading to Death	0

Source: BLA 125613/76, Study Report Body, Table 2

Table 7 Treatment-Emergent AEs by Severity (Safety Population) During the Entire Study

Severity of TEAEs	KEDRAB + Vaccine Number of Subjects and Percent n (%)
Mild	21 (70)
Moderate	1 (3.3)*
All	22 (73)

Source: BLA 125613/76, Study Report Body, Table 12-5; Table 14.3.1.7 (TEAEs by organ system)
*Occurred on Day 24 of KEDRAB administration

Thirteen (43.3%) subjects experienced an adverse reaction (AR) or suspected AR. Out of the 13 subjects who experienced an AR, there were 11 (36.7%) subjects experienced AR or suspected AR with onset occurring within 24 hours of KEDRAB administration and 2 (6.7%) subjects who had an immediate adverse reaction within the first 24-34 hours.

The adverse reactions (ARs) in the Final Study Report were also summarized according to immediate, local and systemic adverse reaction classifications (Table 8). Local adverse reactions are adverse reactions which were coded as 'Injection Site Reaction'. All other adverse reactions were systemic adverse reactions. Out of the 13 subjects who experienced an AR, 2

(6.7%) subjects had immediate Adverse Reactions (within the first subjects experienced local adverse reactions and 9 (30.0%) subjects experienced systemic adverse reactions.

Table 8 Immediate, Local and Systemic Adverse Reactions to KEDRAB (Safety Population)

	KEDRAB + Vaccine (N=30) n (%)
Number of subjects with Immediate Adverse Reactions (within the first 24-34 hours)	2 (6.7)
Number of subjects with Local Adverse Reactions*	7 (23.3)
Number of subjects with Systemic Adverse Reactions	9 (30.0)

Source: PAS 125613/76, Study Report Body, Table 12-2; Note: All the AEs were mild
*Local Adverse Reactions include adverse reactions coded as 'Injection Site Reaction".

Reviewer Comment: Based on the clinical review of the AEs, TEAEs, and ARs presented in the Final Study Report and the line data of subjects' AEs, clinical determined the following are Adverse Reactions >5% of pediatric subjects and recommends Table 9 be included in the labeling.

Table 9: Adverse Reactions Occurring in >5% of Pediatric Subjects within 14 Days of Post-exposure Prophylaxis with KEDRAB and Active Rabies Vaccine

	KEDRAB + Rabies Vaccine N = 30
Injection site pain	8 (27%)
Headache	4 (13%)
Fever (Pyrexia)	4 (13%)
Pain in extremity	3 (10%)
Bruising (hematoma)	2 (7%)
Fatigue	2 (7%)
Vomiting	2 (7%)

Source: Clinical reviewer independent analysis of Analysis Data set Data ADAE to day 14

The less common adverse reactions during the initial 14-days were erythema at injection site, edema at injection site, muscle pain, oral pain and wound complications. Insomnia occurred in <5% of pediatric subjects after 14-days of administration.

Reviewer's Comments: The Adverse Reactions to be listed in the label were determined after FDA adjudication.

Safety Conclusions

There were no deaths, other SAEs, or other significant AEs in the study. The most common adverse reaction are injection site pain. The adverse reactions in children are mild and similar to what was seen in adults.

6.1.13 Study Summary and Conclusions

KAMRAB-004 the open-label, single-arm study in 30 U.S. children demonstrated safety in pediatrics. There were no SAEs and the adverse reactions were mild and similar to what is seen with the product in adults. The RVNA titers were ≥ 0.5 IU/mL on day 14 in 28/30 (93% subjects). Efficacy based on this study was difficult to interpret due to 2 subjects not meeting the 14-day RVNA threshold as recommended by ACIP for PEP, the absence of 30-day RVNA titers in these subjects, lack of PK data during the first 7 days following KEDRAB administration, and clinical follow-up being limited to 84 days when clinical rabies sometimes takes over a year to manifest.

However, the applicant also provided RWE to support efficacy. The RWE was reliable as rabies is a reportable disease in the United States, so all cases are captured.

The data support the safety and efficacy of KEDRAB in children.

10. CONCLUSIONS

Rabies is an acute meningoencephalitis that is invariably fatal once patients develop symptoms. Therefore, PEP with HRIG and rabies vaccine are critical for treatment. The efficacy supplement contains sufficient information to support the safety and efficacy and a favorable benefit-risk of KEDRAB for children.

11. RECOMMENDATIONS

The short-term safety of KEDRAB in children was demonstrated in KAMRAB-004 where there were no significant safety signals in 30 exposed pediatric subjects who were monitored over an 84-day period. Efficacy was established from RWE. Most notably, the RWE included data that 172 children were treated with KEDRAB between 2018-2020 for potential rabies exposure in the United States and there were no cases of rabies according to the CDC between 2018-April 2021 treated with PEP.
KEDRAB's benefit-risk profile in the pediatric population is highly favorable.

11.3 Discussion of Regulatory Options

11.5 Labeling Review and Recommendations

Through interactive review the label was modified. The major revisions focused on details and description of clinical data in Section 8.4, details of the clinical study and results in section 14, and incorporation of FDA's adjudication of adverse reactions.

APPENDIX 1

Individual Case Description of the Two Subjects Who Did Not Reach RVNA titer levels of ≥ 0.5 IU/mL at Day 14

NARRATIVES FOR SUBJECTS WITH DAY 14 RVNA TITERS <0.5 IU/ML:

Subject (b) (6)
This 11.8-year-old white, non-Hispanic female had a potential rabies exposure through a wild reservoir animal (woodchuck) on 11-Jun-2019 at 18:30. Contact with the animal was confirmed, but confirmation of rabies in the animal could not be obtained since animal was not tested. The animal bite location was on the right hand between the 3rd and 5th fingers. The bite was about 1 cm in length and 1 cm in width and was superficial in depth. The subject had a medical history of oral herpes (intermittent), and attention deficit disorder.

On (b) (6) , the subject was enrolled in Study KAMRAB-004 after consent and assent were
obtained. A single dose of 20 IU/kg KEDRAB was administered on (b) (6) (Day 0) at 14:38, as 2.9 mL IM injections in the vastus lateralis muscle of both thighs. On (b) (6) (Day 0) at 14:38, (b) (6) (Day 3), (b) (6) (Day 7), (b) (6) (Day 14), 1 mL doses of an active rabies vaccine (RabAvert® 2.5 IU/mL) were administered to the subject as IM injections in the arm deltoid regions.

The subject was treated with Augmentin (anti-bacterial) from 11-Jun-2019 to 20-Jun-2019, acyclovir (antiviral) from 12-Jun-2019 that remained ongoing, and ibuprofen (anti-inflammatory) from 24-Jun-2019 to 26-Jun-2019 as concomitant medications during the study.

From 12-Jun-2019 to 12-Jun-2019, the subject experienced injection site pain (local pain at active vaccine injection site) that was assessed by the investigator as definitely related to the active vaccine. From 14-Jun-2019 to 14-Jun-2019, the subject experienced vomiting that was assessed as possibly related to study drug and/or active vaccine. From 19-Jun-2019 to 26-Jun-2019, the subject experienced contusion that was assessed as not related to the study drug and unlikely related to active vaccine. From 24-Jun-2019 to 26-Jun-2019, the subject experienced headache that was assessed as not related to study drug. From 26-Jun-2019 to 26-Jun-2019, the subject experienced nausea that was assessed as not related to study drug and unrelated to active vaccine. From 26-Jun-2019 to 26-Jul-2019 the subject experienced anxiety that was assessed as not related to study drug and unrelated to active. On 24-Jul-2019 to 24-Jul-2019, the subject experienced vomiting that was assessed as not related to study drug and possibly related to active vaccine. All of these events were mild in severity, and all resolved. The subject was not hospitalized for any of the adverse events experienced and completed the study.

The subject's RVNA titer on Day 14 after administration of KEDRAB based on RFFIT was measured and active rabies infection was evaluated by the investigator. On (b) (6) (Day 14), subject's RVNA titer was 0.4 IU/mL. No active rabies infection was reported through Day 84 (end of study).

Subject (b) (6)

This 4.2-year-old white, non- Hispanic male had a potential rabies exposure through a wild reservoir animal (raccoon) on 16-Jul-2019 at 18:30. Contact with the animal was not confirmed, but confirmation of rabies in the animal was obtained. The subject had a medical history of torticollis.

On (b) (6), the subject was enrolled in Study KAMRAB-004 after consent was obtained. A single dose of 20 IU/kg KEDRAB was administered on (b) (6) (Day 0) at 22:32, as 1.3 mL IM injections in the vastus lateralis muscle of both thighs. On (b) (6) (Day 0, injection administered in deltoid) at 22:32, and for days (b) (6) (Day 3), (b) (6) (Day 7), (b) (6) (Day 14), 1 mL doses of an active rabies vaccine (RabAvert ® 2.5 IU/mL) were administered to the subject as IM injections in the vastus lateralis muscle of both thighs
The subject was treated with Theragran (vitamins) from 29-Apr-2013 (ongoing), and children's Tylenol from 23-Jul-2019 to 23-Jul-2019 as concomitant medications during the study.
From 22-Jul-2019 to 05-Aug-2019, the subject experienced arthropod bite, that was assessed as not related to study drug and unrelated to active vaccine. From 23-Jul-2019 to 23-Jul-2019, the subject experienced fatigue that was assessed as possibly related to study drug and/or active vaccine. From 23-Jun-2019 to 23-Jun-2019, the subject experienced injection site pain (left leg RabAvert injection site) that was assessed as not related to the study drug and possibly related to active vaccine. From 02-Aug-2019 to 09-Aug-2019, the subject experienced insomnia that was assessed as probably related to study drug and possibly related to active vaccine. All of these events were mild in severity, and all resolved. The subject was not hospitalized for any of the adverse events experienced and completed the study.

The subject's RVNA titer on Day 14 after administration of KEDRAB based on RFFIT was measured and active rabies infection was evaluated by the investigator. On (b) (6) (Day 14), the subject's geometric mean RVNA titer was 0.2 IU/mL. No active rabies infection was reported through Day 84 (end of study).

Protocol violations: One day late for day 14 visit and late for day 84 follow-up phone call.