Application Type	Original Application
STN	125613/0
CBER Received Date	August 29, 2016
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Division / Office	DCEPT /OTAT
Priority Review	No
Reviewer Name(s)	Winson Tang, MD FACP
Review Completion Date / Stamped Date	APPROVED
Supervisory Concurrence	APPROVED
Applicant	Kamada Ltd.
Established Name	Rabies Immune Globulin (Human)
(Proposed) Trade Name	KEDRAB
Pharmacologic Class	Immune Globulin (Human)
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 with rabies vaccine. There is no age limit since rabies is a fatal disease.
Orphan Designated (Yes/No)	No

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GLOSSARY

Ab	antibody
ACIP	Advisory Committee on Immunization Practices
ADR	Adverse Drug Reaction
Ag	antigen
AE	adverse event
ANOVA	analysis of variance
AUC_I	area under the curve to infinity
AUC_T	area under the curve to time
BLA	biologics license application
BUN	blood urea nitrogen
BW	body weight
C_{max}	maximal concentration
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
G	glycoprotein
GA	Georgia
GCP	Good Clinical Practice
GMT	geometric mean titers
HAV	hepatitis A virus
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HRIG	human rabies immunoglobulin
ICH	International Council for Harmonisation
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IND	investigational new drug
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
IU	international units
KamRAB	Name of Kamada's anti rabies immunoglobulin Investigational Product
KEDRAB	Proprietary name for KamRAB
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
PEP	post-exposure prophylaxis
PREA	Pediatric Research Equity Act
PrEP	pre-exposure prophylaxis
PSP	Pediatric Study Plan
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)
$t_{1/2}$	half-life
TACV	Test Article or Comparator with Vaccine
TASMC	Tel Aviv Sourasky Medical Center
T_{max}	time to maximal concentration
TEAE	treatment emergent adverse event
US	United States
WHO	World Health Organization

1. Executive Summary

Rabies is a zoonotic disease due to infection by RNA viruses of the Genus *Lyssavirus*. 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 is estimated to be between 26,400 to 61,000 in 2010 with the majority of deaths in Asia and Africa. Death due to rabies is rare in the United States and other developed countries. In 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. The estimated annual worldwide cost of rabies is US $6 billion (95% CI, $4.6–7.3 billion), with almost US $2 billion due to lost productivity after premature deaths and a further US $1.6 billion spent directly on post-exposure prophylaxis.

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 generally 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. The encephalitis may be dominated by a hyperactive or furious form (80% of cases) or a paralytic form (20% of cases). The major clinical signs are probably due to different site-specific responses. 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. Treatment is generally supportive. Therefore, current therapy is directed towards prophylaxis, either pre-exposure or post-exposure. The first vaccine was developed by Louis Pasteur in 1885 and was derived from desiccated nerve tissue. However, these inactivated nerve tissue vaccines (NTVs) have been supplanted by cell culture and embryonated egg-based vaccines (CCEEV) because they are safer and more immunogenic. The currently available vaccine strains were raised against rabies species of phylogroup I and will cross react with others viruses in phylogroup I. However, they are ineffective against infection by phylogroup II lyssaviruses. Pre-exposure immunization is recommended only for individuals at high risk for infection such as veterinarians and other animal health care providers. The World Health Organization (WHO) recommends a schedule of three vaccinations given on days 0, 7, 21 (or day 28 if it is more convenient).

Post-exposure prophylaxis (PEP) consists of a combination of active plus passive immunization with local infiltration of rabies immunoglobulin (RIG) into and around the wound followed immediately by immunization with rabies vaccine. Infiltration of RIG around the wound provides immediate passive protection while awaiting the patient's immune response to take effect. Rabies neutralizing antibodies in plasma are usually detected within 24 hours following intramuscular human RIG (HRIG) administration with peak levels achieved at 3 to 7 days. The elimination half-life of HRIG is approximately 21 days. By comparison, rabies vaccine administered on Days 0, 3, 7, 14 and 28 induces production of host neutralizing antibodies in approximately 7-10 days with rabies virus neutralizing activity (RVNA) peaking at around 14 to 28 days. A major concern is RIG binding with antigens within the vaccine thereby decreasing rabies antibody production in response to vaccination.

The efficacy of the RIG/vaccine combination has never been rigorously tested under controlled conditions since deliberately exposing subjects to rabies is not practical. The current recommendations are based upon refinement of a field study from Iran when a rabid wolf bit 29 persons in an Iranian village over several hours in 1954. The mortality rate among those receiving only the nerve tissue vaccine was 60% (3 of 5 subjects) and was reduced to 8% (1 of 12 subjects) with the addition of RIG to the vaccine. These encouraging findings were corroborated by a report from Russia in 1959 where none of the 36 patients who were bitten by rabid wolves and received RIG and vaccine developed rabies while two children who received only the vaccine developed clinical rabies. Since then, the efficacy of the RIG/rabies vaccine combination for PEP has been repeatedly demonstrated with a variety of different RIGs and rabies vaccines.

Kamada Ltd. submitted a BLA for a human rabies immunoglobulin, KamRAB (tradename: KEDRAB) given in combination with a rabies vaccine for passive, transient post-exposure prophylaxis of rabies infection. KamRAB is the name given to the Investigational Product (IP) administered in the clinical studies and will be the name used in this review document. It is manufactured from (b) (4) plasma of healthy human donors immunized with Rabies vaccine. KamRAB is a sterile, nonpyrogenic liquid preparation enriched with anti-rabies immunoglobulins (>95% protein as IgG) with a labeled potency of 150 IU/mL. The proposed dose is 20 IU/kg body weight (BW) that will be infiltrated locally into the wound/exposure site as per the current WHO and Center for Disease Control and Prevention (CDC) guidelines. KamRAB has been administered to more than 250,000 patients outside of the US over the last ten years.

The current application consists of three clinical studies: two Phase 1 studies and a single Phase 2/3 study. A pediatric study plan has been agreed upon and the study will begin in 2017. The two Phase 1 studies were conducted at a single site in Israel (Simbec-Tel Aviv Sourasky Medical Center) while the Phase 2/3 study was conducted at a single site in the US (Prism Research, St Paul, MN). The studies were conducted according to the International Council for Harmonisation (ICH) – Good Clinical Practice (GCP) guidelines. The submission was well organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

The three clinical trials individually addressed a different question but in aggregate, complemented each other. The PK objective of the first Phase 1 study (23630) was to demonstrate that KamRAB was bioequivalent to BayRAB® (a HRIG marketed in Israel).

However, the two HRIGs were not bioequivalent as the lower bound of the 90% CI for the point estimate of the ratio of C_{max}, AUC_T, and AUC_I of KamRAB relative to BayRAB were all below 80% (75.3%, 77.4%, and 79.5%, respectively).

The second Phase 1 study (24061) assessed the interference of active anti-rabies antibody production when KamRAB was administered simultaneously with a rabies vaccine (Rabipur®). This inhibition is well described and has been reported for all other HRIGs. Nonetheless, despite this inhibition, a therapeutic anti-rabies IgG antibody titer ≥0.5 IU/mL was achieved by day 14. The arithmetic mean titers were 1.39 IU/mL in the KamRAB + Rabipur® group and 5.05 IU/mL in the Placebo + Rabipur® group confirming inhibition of anti-rabies antibody production in response to Rabipur®.

The Phase 2/3 study (KamRAB-003) demonstrated that KamRAB is not inferior to HyperRAB (a HRIG marketed in the United States) when administered in combination with a rabies vaccine (RabAvert®) for post-exposure prophylaxis. The primary endpoint of this study was the difference in the geometric mean anti-rabies antibody titers (GMT) between KamRAB and HyperRAB in the proportions of subjects with a GMT ≥ 0.5 IU/mL at Day 14. The null hypothesis was that the difference in the GMT would be ≤ -0.1 (-10%). Fifty five of the 56 subjects in the KamRAB group (98.2%; 95% CI: 90.4, 100) and all 58 subjects (95% CI: 93.8, 100) in the HyperRAB group had an anti-rabies IgG antibody titer ≥0.5 IU/mL on Day 14. The difference between the proportion of subjects with an anti-rabies IgG antibody titer ≥0.5 IU/mL on Day 14 in the KamRAB and HyperRAB groups was -1.8% (90% CI: -8.2, 3.1). Thus, KamRAB met the predefined and agreed upon endpoint and was deemed not inferior to HyperRAB. However, the geometric mean anti-rabies immunoglobulin concentration on Day 3 (a timepoint when the virtually all serum rabies virus neutralizing antibody (RVNA) is originated from the HRIG and not from the active immunization) was significantly lower in the KamRAB group when compared to HyperRAB (0.176 vs 0.216 IU/mL, $p<0.0003$).

The safety data from the 91 subjects who were enrolled and treated with KamRAB in the three clinical trials indicate that KamRAB is safe and well-tolerated. There were no deaths or pregnancies during the conduct of the three studies. A single Serious Adverse Event (intraductal proliferative breast lesion that was probably not related to study treatment) occurred in a female subject who received KamRAB and rabies vaccine in Study KAMRAB-003. The Adverse Event (AE) profile of KamRAB was similar to that of the two Comparator HRIGs (BayRAB and HyperRAB). The most common AE in these studies was injection-site pain, occurring in approximately one-third of the study population. However, other injection-site related AEs such as hematoma, hemorrhage, discomfort, paresthesia, pruritus were uncommon (≤1%).

In general, the three clinical studies comprising this BLA were well executed. There are a number of minor issues such as the paucity of study centers as the three studies were all single-center studies with two studies conducted at the same site. The patient population that was studied was limited primarily to young Caucasians. As with other marketed HRIGs, there is a paucity of information regarding the use of KamRAB in the multi-ethnic, pediatric, geriatric, immunocompromised, pregnant and lactating populations. However, KamRAB has been administered to more than 250,000 patients around the world over the last 10 years. The Applicant believes that these diverse populations have been exposed to KamRAB with no major safety concerns reported to date. In addition,

Kamada has committed to a Phase 4 pediatric study (required under the Pediatric Research Equity Act (PREA)) that will assess PEP failure in addition to pharmacokinetics in subjects between the ages of 0 to 17 years.

The major concern regarding this application is the Day 14 time-point for the assessment of the primary endpoint in the Phase 2/3 trial, which is consistent with the current recommendation of the WHO and CDC. It is not obvious why the 14-day time-point was selected, perhaps because the incubation period for rabies is long (20-90 days). Alternatively, HRIGs are administered in conjunction with a rabies vaccine and D14 is the T_{max} for the combination therapy. Historically, HRIG approvals have been based upon achieving a serum RVNA of 0.5 IU/mL on Day 14. However, the C_{max} and T_{max} of serum RVNA following IM administration of HRIGs occur between Days 3 and 5. Given that the half-life of HRIGs (administered intravenously) is ~21 days, serum RVNA from KamRAB has already decreased to ~60-65% of peak levels by Day 14. Since HRIG is administered with rabies vaccine, host antibody production begins on Days 7-10. Therefore, one is no longer assessing the activity of HRIGs on Day 14 but a combination of the passive and active anti-rabies antibody response. Theoretically, one can tease out the two by fractioning RVNA for IgG and IgM.

The pharmacokinetic profile of KamRAB is inferior to that of two other marketed HRIGs. The lower bound of the 90% CI for $C_{max,}$ $AUC_{T,}$ and AUC_I of KamRAB relative to BayRAB were all below 80%; they were 75.34%, 77.39%, and 79.45%, respectively. However, these differences are minute and unlikely to be clinically meaningful. Furthermore, the selection of 90% CI (or -10%) is arbitrary and is based on plasma bioequivalence margins that are known to be important for small molecules and protein replacement therapies. By comparison, the clinical significance of plasma RVNA is uncertain since it represents a surrogate of a surrogate biomarker as the action of HRIGs is localized to the interstitial tissues surrounding the wound/exposure site. Nonetheless, it is likely that serum RVNA correlates with interstitial levels and the former is likely a surrogate for the latter. However, the dilemma one is left with is that the optimal tissue RVNA is unknown and a serum RVNA $\geq$0.5 IU/mL has been generally accepted as protective.

Although the prospective primary endpoint was achieved in the phase 2/3 study, the appropriateness of the time-point for determining efficacy may be questioned. From a practical viewpoint, approving KamRAB based on RVNA on Day 14 implies the FDA's decision to approve is based on the lack of KamRAB's interference with the vaccinee's antibody response to rabies vaccine. Therefore, Dr Brett Petersen of the CDC was consulted. Dr Petersen confirms that the selection of Day 14 for the evaluation of a HRIG and vaccine regimen is a precedent that has been established based upon the WHO and CDC recommendations. The importance of a RVNA $\geq$0.5 IU/mL at early time-points (initial 1-7 days) is difficult to ascertain as there are no clinical data. Nonetheless, there have been almost no documented failures when the current PEP regimen is administered appropriately. Finally, the small differences in the pharmacokinetic profile of KamRAB relative to the Comparator HRIGs are not likely to be clinically meaningful.

In support of this application, the "real world" experience with KamRAB has been encouraging. KamRAB has been administered to over 250,000 patients around the world within the past decade. There have been no reports of PEP failure or excessive toxicity. A

more thorough analysis of the clinical experience with KamRAB was provided by data from the Israeli Ministry of Health (IMoH). From 2010 to 2015, 84,287 people in Israel received PEP due to suspected exposure to rabies. All subjects with suspected rabies are followed at one of the 16 regional IMoH public health offices. Of these, 1,863 individuals were confirmed to have been exposed to a rabid animal and received treatment in accordance with the WHO guidance. All patients in Israel were administered KamRAB as part of their post-exposure prophylaxis. None of these 1,863 individuals developed clinical rabies and there were no deaths attributed to rabies during this reporting period. Therefore, based upon a favorable benefit-risk profile, this Reviewer recommends the approval of KamRAB to be used in conjunction with rabies vaccine for the post-exposure prophylaxis of rabies.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The three clinical studies submitted under this BLA were conducted in Israel and Minnesota. The study population was homogenous consisting of primarily young, healthy Caucasian volunteer subjects (Table 1). There were insufficient numbers of subjects within many of the demographic subgroups to assess their impact on the efficacy or safety of KamRAB. However, it is unlikely that gender and ethnicity would have an effect although age may affect absorption.

Table 1: Demographics of the Pooled Study Population
(Reviewer's Table)

	KamRAB (N=91)	**Comparator HRIG (N=84)**	**Placebo + Vaccine (N=8)**
Age (years)	37.6±15.3	40.7±15.1	26.9±3.4
Sex			
Male	46 (50.6%)	42 (50%)	5 (62.5%)
Female	45 (49.5%)	42 (50%)	3 (37.5%)
Race			
White	89 (97.8%)	78 (92.9)	8 (100%)
Asian	1 (1.1%)	0	0
Black	0	4 (4.8%)	0
Other	1 (1.1%)	2 (2.4%)	0

2. Clinical and Regulatory Background

Kamada Ltd. is seeking licensure in the United States for a HRIG 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. Kamada-HRIG 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. Kamada-HRIG has been used outside of the US for 10 years. It is estimated that over 250,000 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.

2.1 Rabies

Rabies ("rage" or "madness" in Latin) is an acute meningoencephalitis due to infection by RNA viruses of the Order *Mononegavirales*, Family *Rhabdoviridae* and Genus *Lyssavirus*. The name of the genus derives from the Greek goddess of rage, fury, raging madness and frenzy, Lyssa. Lyssaviruses have a 12-kb non-segmented RNA genome of negative polarity that encodes five viral proteins (3´ to 5´) in the following order: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and an RNA-dependent RNA polymerase (or large protein, L). The matrix protein forms the inner side of the bilayer lipid envelope. The lipid envelope of the virus is derived from the host cytoplasmic membrane during budding. Knobbed glycoprotein spikes (5–10 nm in length and ~3 nm in diameter) consisting of three glycosylated ectodomains (which carry the main antigenic sites) protrude through the viral membrane and bind the virion to host cell receptors.

The rabies virus was considered to be a single pathogen until the 1950s when serologically distinct viruses were first identified. Currently, the International Committee on the Taxonomy of Viruses recognizes 12 *Lyssavirus* genotypes divided into two phylogroups based upon their serologic cross-reactivity and genetic sequence. There are two other genotypes that cannot be included in either of these phylogroups and may constitute a third phylogroup. Lyssaviruses show broad antigenic cross-reactivity at the level of the nucleocapsid due to sequence conservation of the nucleoprotein. Thus, similar reagents can be used for diagnosis by immunofluorescence. By comparison, the ectodomain of the G protein is more variable between phylogroups (<62% amino acid identity in the ectodomain) then among lyssaviruses of the same phylogroup (>74% amino acid identity in the ectodomain,). Therefore, all the available human and veterinary vaccine strains which were raised against rabies species in phylogroup I cross react with other viruses in phylogroup I but are ineffective against infection by phylogroup II lyssaviruses.

Rabies virus is the only known lyssavirus species in the Americas and accounts for the vast majority of human rabies cases in the world. It belongs to phylogroup I and is maintained as an enzootic agent in several mammalian species within the orders Carnivora (terrestrial mammals) and Chiroptera (bats). Rabies perpetuated and transmitted by Carnivora has a global circulation and is phylogenetically distinct from those transmitted by Chiroptera, which are restricted to the Americas. However, the reservoir host species differs among geographic regions. In the United States, there are 5 distinct antigenic rabies virus variants associated with 8 terrestrial reservoir species and >13 rabies virus variants associated with bats. Six of the eight terrestrial variants are closely related to the canine variant despite the elimination of canine rabies in the US.

The major cause of rabies transmission in the world is canines although the United States, Western Europe, Australia, Canada, Japan, Malaysia, and some Latin American countries have been declared free of canine rabies. More than 99% of rabies cases in countries where rabid dogs exist are due to dog bites. In the US, bats are the most common cause of transmission followed by raccoons, skunks, and foxes. Rabies transmitted by bat species is broadly distributed across the United States while rabies associated with mesocarnivore species (i.e., raccoons, skunks, and foxes) are distributed in distinct geographic regions.

For example, raccoon transmission is found on the Eastern seaboard from Florida to Maine while skunks are the culprit in California.

Although death due to rabies is rare in the US and other developed countries, the annual number of human rabies deaths globally is estimated to have been between 26,400 to 61,000 in 2010 with the majority of the deaths in Asia and Africa. In regions free of canine rabies, human deaths from canine rabies are restricted to people exposed while living or travelling in areas endemic for canine rabies. About two deaths per year due to imported human rabies have been reported in Europe, North America and Japan. Between 1990 and 2010, ~33% of the imported cases originated in South and Southeast Asia (predominantly India and the Philippines), another third in Africa, almost 20% in Latin America and the Caribbean and over 10% from Eastern Europe and Central Asia. The estimated annual worldwide cost of rabies is US$6 billion (95% CI, $4.6–7.3 billion), with almost US$2 billion due to lost productivity after premature deaths and a further US$ 1.6 billion spent directly on post-exposure prophylaxis.

In the United States, 37 people were diagnosed with rabies between 2003 and Oct 2015 with 34 deaths. Twenty six of the individuals (70%) acquired the disease in the US or Puerto Rico. Bats were the primary source of infection and were implicated as the source in 17 of the 26 individuals (65%) with organ or tissue transplantation identified in another five subjects (19%). The remaining 4 cases consisted of two patients who were infected with a raccoon rabies virus variant, a mongoose variant from Puerto Rico, and an unknown variant. In the 11 rabies cases acquired outside of the US, phylogenetic analysis or epidemiologic links indicated infection occurred in 8 different countries. These included a dog in 7 cases, fox in 1 case, vampire bat in 1 case, and an unknown exposure involving a canine rabies virus variant in 2 cases.

Rabies is a zoonotic disease that in most cases develops when an infected animal transmits the virus to man through saliva via a bite, scratch, contact with mucous membranes, or licking of a wound. Contact with blood, urine, feces, or the handling of a rabid animal does not constitute exposure. However, rabies has been transmitted by infected organs and vascular graft following transplantation from an unrecognized infected donor in 2004. All four of the transplant recipients developed clinical symptoms and died. The virus enters the body through wounds or by direct contact with mucosal surfaces since it cannot cross intact skin. Rabies virus replicates in the muscle and gains access to motor endplates and motor axons to invade the central nervous system (CNS). Virions are carried in transport vesicles by fast retrograde transport along motor axons, with no uptake by sensory or sympathetic endings. Viruses can also enter motor axons in peripheral nerves directly during a penetrating injury and in some bat variants, viral propagation may also occur via sensory nerves due to skin tropism.

Once the virus enters the body there is a variable latency period, 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 CNS. Virus cannot be detected in the plasma as there is no viremic spread. Instead, the virus replicates in skeletal muscle cells 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 generally between 20 to 90 days. During this time, the virus migrates to the CNS. The estimated speed of viral migration depends on whether it moves by centripetal retrograde

axonal transport or centrifugal spread. It is rapid in the former with speeds of 50–100 mm/day because neuron populations of the same synaptic order are infected simultaneously. In contrast, centrifugal spread is slow as it is probably mediated by passive diffusion rather than active transport. The rapid centripetal phase leads to widespread neuronal migration within the central nervous system and to infection of dorsal root ganglia via their central connections with the initially infected motor neurons and spinal interneurons. The virus then spreads centrifugally from the CNS via slow anterograde axoplasmic flow in motor axons to the ventral roots and nerves and in peripheral sensory axons of the infected dorsal root ganglia, leading to infection of muscle spindles, skin, hair follicles and other non-nervous tissues, such as salivary glands, heart muscle, lung and abdominal visceral organs via their sensory neurons. By the onset of clinical symptoms, the virus is widely disseminated throughout the CNS and probably to other organs.

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. Human rabies manifests as encephalitis that may be dominated by a hyperactive or furious form (80% of cases) or a paralytic form (20% of cases) that does not correlate with a specific CNS anatomical localization of infection. The major clinical signs are probably due to different site-specific responses. The weakness in paralytic rabies is likely due to peripheral nerve axonopathy or myelinopathy. In furious rabies, preferential entry via the motor route explains why subclinical anterior horn cell dysfunction localized to body segments corresponding to the site of the bite precedes sensory loss before progressively spreading to other locations. It is likely that less virus is present in the brain of individuals with paralytic rabies and preserved consciousness than in those with furious rabies. Functional neuronal impairment may also account for the coma. Death is usually caused by respiratory arrest and occurs two to ten days after appearance of the first symptoms and survival is rare after the development of symptoms.

A diagnosis of rabies is difficult since it can be diagnosed only after the onset of symptoms. The diagnosis is readily made in a patient presenting with classical symptoms such as hydro- or aerophobia and documented exposure to a laboratory confirmed rabid animal. In the absence of pathognomonic symptoms or a history of exposure, a diagnosis is unreliable as atypical or non-classical rabies is increasingly being recognized.

2.2 Currently Available Treatment(s)/Intervention(s)

2.2.1 Pre-Exposure Immunization

Rabies was a universally fatal disease until a vaccine developed by Louis Pasteur was famously used to save the life of a 9-year old Parisian boy in 1885. The original vaccine was an attenuated virus derived from the desiccated spinal tissues of infected rabbits. Inactivated nerve tissue vaccines (NTVs) have improved over time and are currently produced in the brains of sheep, goats, or suckling mice. NTVs were intended for post-exposure prophylaxis but require a prolonged and painful regimen of seven to ten immunizations since they are less immunogenic than cell-based vaccines. Furthermore, severe allergic encephalomyelitis and polyneuritis may develop in approximately 0.05% of vaccinated individuals due to an immune response to contaminating neuroproteins. The World Health Organization (WHO) has recommended discontinuation of nerve

tissue vaccines since 1984 although some countries in Asia and Latin America continue to use them because of financial reasons.

NTVs have been supplanted by cell culture and embryonated egg-based vaccines (CCEEV) because the latter are more immunogenic and safer. CCEEVs are made from virus that has been inactivated following propagation in cell substrates such as human diploid cells, fetal rhesus cells, primary Syrian hamster kidney cells, Vero cells (African green monkey kidney cells), or primary chick or duck embryo cells. Recently developed vaccines based on chick embryo and Vero cells are as safe and effective as human diploid cell vaccines but are less expensive. These vaccines are intended for both pre-exposure immunization and post-exposure prophylaxis.

Following natural infection, the immune response to rabies virus is delayed because the antigenic epitopes (G and N proteins) are largely unavailable to the immune system. By comparison, the CCEEVs induce an antibody response in more than 99% of vaccinees. Immunity is due to the formation of neutralizing antibodies to the G protein although cell-mediated immunity also plays an important role. Since a randomized controlled placebo-controlled human trial would be unethical, data on vaccine efficacy is derived from experience with post-exposure prophylaxis in humans exposed to rabid dogs.

Pre-exposure immunization is recommended only for people at high risk for infection such as veterinarians, animal handlers, wildlife officers, certain laboratory workers and travelers to regions with high risk of rabies. The WHO recommends a schedule of three vaccinations given on days 0, 7, 21 (or 28 if more convenient). The dose depends upon the specific vaccine product and the route of administration (intramuscular or intradermal). Periodic boosters are only recommended for individuals whose occupation places them at continuous or frequent risk of rabies exposure.

CCEEVs establish immunologic memory that presumably persists for the life of the individual even after titers of neutralizing antibodies decline. Individuals vaccinated respond to booster immunization, even if the initial course of pre- or post-exposure prophylaxis was administered years previously and regardless of the route of priming or booster immunization (intramuscular or intradermal) and the presence or absence of detectable titers of rabies virus-specific antibodies at the time of the booster. Periodic booster vaccination are not required after primary rabies vaccination, except as an additional precaution for people whose occupation puts them at continual or frequent risk of exposure. Nevertheless, all vaccinated individuals subsequently exposed to rabies, according to the WHO definition of exposure, should receive an abbreviated course of post-exposure prophylaxis.

In general, CCEEVs are safe and well tolerated. Adverse events may occur in 35–45% of those vaccinated manifesting as minor, transient erythema, pain or swelling at injection sites (particularly after intradermal administration of a booster). Mild systemic adverse effects including transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated people. Serious adverse events are rare but can include Guillain-Barré syndrome and allergic reactions.

2.2.2 Post-Exposure Prophylaxis

Rabies exposure is defined as contact with the saliva and/or brain/nervous system tissue of a rabid animal. Treatment for rabies is generally ineffective once symptoms manifest

and thus, the current goal is to provide post-exposure prophylaxis (PEP). Following exposure, prompt and thorough washing of the wound with soap and water will reduce the viral burden as will the use of povidone-iodine or alcohol. This is followed by a combination of active-passive immunization consisting of localized infiltration of rabies immunoglobulin (RIG) into and around the wound followed by immunization with rabies vaccine. The RIG should be administered as quickly as possible after exposure but no later than seven days after exposure. However, those who have been previously immunized should only receive a booster vaccination without RIG. The CDC estimates that ~23,000 individuals in the US receive PEP following exposure to a rabid animal. Unfortunately, precise data are not available because there is no national reporting system for rabies.

The intramuscular 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.

The WHO recommends either a 4-dose or 5-dose vaccination schedule for post-exposure prophylaxis. The 4-dose regimen consist of two doses administered on day 0 followed by single doses on days 7 and 21 or single doses given on days 0, 3, 7 and 14. The 5-dose regimen provides for single doses administered on days 0, 3, 7, 14 and 28. Since 2010, the United States Center for Disease Control and Prevention (CDC) has recommended a 4-dose regimen for immunocompetent individuals with single vaccine doses administered on days 0, 3, 7 and 14. Those who are immunocompromised should continue to receive the 5-dose regimen.

The efficacy of the combined use of RIG with a vaccine was first established in animal studies during the 1940s and subsequently confirmed by studies in rhesus monkeys, goats, sheep, cattle and dogs during the 1970 and 1980s. These studies demonstrate that an anti-rabies immunoglobulin/ vaccine combination provided nearly complete protection compared with animals receiving only vaccine. Since deliberately exposing subjects to rabies is not practical, a field study was commissioned by the WHO to assess a new hyperimmune serum-vaccine (nerve tissue) regimen in Iran beginning in 1950. However, there were insufficient numbers of exposed patients treated through 1954 to draw definitive conclusions. In August of 1954, a rabid wolf bit 29 persons in an Iranian village over several hours. The mortality rate among those receiving vaccine alone was similar to what had been seen previously, with a mortality rate of 60% (3 of 5 subjects). However, the addition of RIG to the vaccine treatment reduced the rate to 8% (1 of 12 subjects); one of seven subjects administered one RIG injection and vaccine while there were no deaths in the five subjects administered two RIG injections and vaccine. These encouraging findings were corroborated by a report from Russia in 1959 where 0 of 36 patients who were bitten by rabid wolves and received RIG and vaccine developed rabies while two children who received only the vaccine developed clinical disease. Subsequent

to this, the effectiveness of a RIG/rabies vaccine combination for PEP has been repeatedly demonstrated with a variety of different human and non-human RIGs and cell culture and embryonated egg-based vaccines.

There are three classes of biologic products that are available for passive immunization around the world: equine rabies immunoglobulin (ERIG), human rabies immunoglobulin, and highly purified F(ab')2 fragments produced from equine immunoglobulin. ERIGs are safe, potent and considerably less expensive than HRIG. The risk of anaphylaxis with ERIG is low (<0.001%) although serum sickness may develop one week after administration in <1-3% of recipients. Therefore, HRIG is the preferred product although it is in short supply and available primarily in the developed world. The recommended dose of HRIG is 20 IU/kg body weight and 40 IU/kg body weight for the equine products as the former are more potent.

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 studies in animals. It should be recognized that a protective rabies antibody titer has never been determined in humans as this would require unethical challenge studies. However, there has never been a single reported case of PEP failure in the United States since the introduction of RIG and modern cell culture vaccines in the 1980s. Treatment failures are very rare among the estimated 20 million people per year who receive proper therapy in a timely manner. The few who have died are from developing countries and most involved deviations from the WHO-recommended prophylaxis protocol. Common deviations resulting in death include delay in seeking rabies prophylaxis; lack of or improper administration of rabies immunoglobulin; lack of or improper primary wound care; and/or poor quality rabies vaccine or RIG.

2.2.3 Treatment

Rabies encephalitis is associated with the highest case fatality rate of any infectious disease with approximately 50,000 worldwide deaths annually. Treatment is generally supportive as attempts at the use of antiviral agents and immuno-modulators have proven futile. Deaths due to rabies result from secondary complications rather than any primary process attributable to the virus. Several groups have hypothesized that death results from a combination of neurotransmitter, cerebral vasospasm, and autonomic imbalance since there is little viral or immune-mediated cytopathic changes noted in the brain at autopsy. As of 2004, there had been only five documented survivors of rabies encephalitis. All of them had received immune-prophylaxis suggesting that vaccination may have prevented a fatal outcome.

In 2004, a 15-year old girl survived rabies encephalitis without receiving immune-prophylaxis. The medical team at the University of Wisconsin at Milwaukee designed an aggressive regimen to protect her brain while waiting for the host immune response to clear the virus. This protocol has come to be known as the "Milwaukee Protocol" and includes induction of therapeutic coma through γ–aminobutyric acid receptor agonism with benzodiazepines and barbiturates along with N-methyl-D-aspartate (NMDA) receptor antagonism with ketamine and amantadine. Although another patient was successfully treated with this protocol, the majority of patients have died with at least 28 published reports.

2.3 Safety and Efficacy of Pharmacologically Related HRIGs

HRIG is an important biologic therapy for patients following exposure to an animal suspected of having rabies. The use of HRIG is particularly beneficial in patients who are immunocompromised as they are highly susceptible to the development of clinical disease. Currently there are no alternative therapies on the market. Although Equine Rabies Immune Globulin could be used for prophylaxis, it is not available in the United States nor is it well tolerated due to the risks of allergic reactions.

There are two human rabies immunoglobulins that have been approved for marketing in the United States. They are 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 date there have been no efficacy or safety risks identified for either of these two human rabies immune globulin products for the approved indication. A cumulative review of post-marketing safety surveillance data of the two products does not identify any changes in the benefit/risk profile of the products. Therefore, the benefit-risk balance for HyperRAB™ S/D and Imogam® Rabies-HT remains favorable. Although there is no information suggesting a change in the benefit-risk profile concerning pregnancy outcomes and lactating women, they continue to be a population where relatively very little information is available. Nonetheless, neither pregnancy nor lactation is considered contraindications for rabies post-exposure prophylaxis since the disease is fatal.

2.3.1 HyperRAB™ S/D

HyperRAB™ S/D (solvent/detergent) is the trade name for a human rabies immune globulin prepared from the plasma of donors who were hyperimmunized with rabies vaccine. The immune globulin fraction is treated with 0.3% tri-n-butyl phosphate (a solvent that inactivates viruses) and 0.2% sodium cholate (a detergent that inactivate viruses) before the application of heat (30^{o}C for 6 hours). The final product is a 15-18% protein solution in glycine. It is distributed as a sterile, preservative-free solution for intramuscular administration. It was approved for marketing in the United States on June 12, 1974 and is currently approved in 18 countries worldwide. There were no new registrations or withdrawals, dosage modifications, changes in targeted populations or indications, and no formulation changes for the most recent Periodic Safety Update Report period that ended on April 26, 2016.

Information on cumulative clinical experience of Rabies Immune Globulin (Human) in clinical trials is not readily available due to the long existence of the product in the market and acquisition of the product by multiple companies. The package insert cites one clinical study conducted in eight healthy adults who received 20 IU/kg intramuscular dose of HyperRAB S/D. Passive rabies antibody titers were detected in the serum of all subjects by 24 hours post-injection and persisted through the 21 day study period. These results are consistent with prior studies with non-solvent/detergent treated product.

Additionally, the current Market Authorization Holder, Grifols Therapeutics Inc, completed one clinical study in 2014: An Open-label, Single-arm Study to Evaluate the Safety and Antibody Titers Specific to the Rabies Virus in Healthy Subjects after Receiving a Single Dose of Intramuscularly Administered Human Rabies Immune

Globulin. This was a phase 1 study in 12 healthy volunteers that was conducted in a phase 1 unit in the United States. All 12 healthy volunteers received a single IM injection of Rabies Immune Globulin (Human), (b) (4) (20 IU/kg). There were no deaths, SAEs, or subject discontinuations due to AEs in the study. A single 20 IU/kg IM dose of RIG-C was safe and well tolerated in the study.

The current Market Authorization Holder cannot provide an accurate figure for the number of patients treated but estimates that over 600,000 patients may have been treated since January 2006. The safety profile of HyperRAB™ S/D is well established since it has been approved in the USA since 1974. The important identified risk is hypersensitivity reactions including anaphylaxis while potential risks include transmission of infectious disease since the product is derived from human plasma. The overall reporting frequency of the former is estimated at 1 in 41,944 doses (0.002%). There have been no reports of infectious disease transmission since donors are screened for prior exposure to certain viruses and tested for current virus infections. Furthermore, the product is inactivated to further prevent viral transmission.

2.3.2 Imogam® Rabies-HT

Sanofi Pasteur also markets a version of HRIG in the United States that was first approved on April 27, 1984. A pasteurization step was added to the manufacturing process in 1996 and this is the product currently marketed in the US, Imogam® Rabies-HT, where the HT stands for heat-treated. The product is prepared from the cold ethanol fraction of pooled venous plasma, stabilized with glycine before heat treatment (58-60^{o}C) for 10 hours. The final product is 10-18% protein and is currently approved and marketed in 19 countries worldwide including the United States. The non-pasteurized version was phased out of use in early 1998.

The safety and efficacy of Imogam® Rabies-HT is also well established since over 600,000 patients have been treated worldwide since January 1997. Sanofi has conducted five clinical trials that administered Imogam® Rabies-HT to 1125 subjects in conjunction with an investigational rabies vaccine for post-exposure prophylaxis. Another 40 subjects were treated with Imogam® Rabies-HT as a control for an investigational rabies monoclonal antibody. There were no new safety signals noted in these six studies.

Like other HRIGs, the major safety concern is anaphylaxis. Sanofi estimates the frequency of anaphylaxis following administration is 0.4 cases per 100,000 vials (2 mL). There have also been no reports of infectious disease transmission.

2.4 Previous Human Experience with KamRAB (Including Foreign Experience)

It is estimated that over 250,000 individuals worldwide have been treated with Kamada-HRIG to date. Kamada-HRIG has been in use outside of the US for 10 years. It is approved and marketed in El Salvador, India, Israel, Mexico, Russia and Thailand. In three additional countries, Australia, Georgia, and South Korea, Kamada-HRIG is administered in named patient programs. Kamada-HRIG is being prescribed to children in India, Israel, Russia and South Korea. The formulation of Kamada-HRIG proposed for approval in the US is identical to the formulation of the product distributed in Israel since 2012.

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

A brief summary of the clinical development history of Kamada-HRIG follows.

- The 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.
- 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.
- An Investigational New Drug (IND) application was submitted by Kamada in March, 2007 to conduct a Phase 2/3 study (KAMRAB-003) in the US (IND 13333, the current IND). This IND was based on a previous IND (13193) application that was withdrawn at the recommendation of the FDA. The FDA provided comments on IND 13333 in May 2007 and notified Kamada that the proposed clinical study could proceed.
- In January, 2010, in response to a Type C meeting request, the 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 (see Section 6.2).
- There were four amendments to Study 003 submitted to and approved by the FDA between April, 2012 and March, 2014.The most clinically relevant amendments are listed in Table 2.

Table 2: Summary of KAMRAB-003 Amendments
(Applicant's Table)

Protocol Version	Date	Changes
Version 2	11/26/12	Changed rabies vaccine due to market shortage
Version 4	8/29/13	Hemolysis workup added to safety evaluation

- 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.
- Kamada submitted a Pediatric Study Plan (PSP) to FDA in December 2015. The Sponsor 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 KamRAB in children ages 0 months to <17 years when administered as part of PEP.
- Kamada had a face-to-face Type B pre-Biologics License Application (BLA) meeting with FDA in March 2016.
- Kamada submitted a BLA for Kamada-HRIG to the FDA on August 29, 2016.

The primary endpoint selected for the Phase 2/3 study (KAMRAB-003) was the proportion of subjects with anti-rabies IgG titer ≥ 0.5 IU/mL antibody measured on Day 14. 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).

Reviewer's comments: The rationale for the selection of Day 14 as the time-point for the readout of efficacy (≥0.5 IU/mL) is unclear. 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.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was well organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The conduct, evaluation, and documentation of the KAMRAB-003 study were designed to ensure that the Sponsor and Principal Investigator abide by International Council for Harmonisation (ICH) – Good Clinical Practice (GCP) guidelines, United States (US) Code of Federal Regulations Title 21, Parts 50 & 56, applicable local laws and regulations, and under the guiding principles detailed in the Declaration of Helsinki. The study was conducted under Investigational New Drug (IND) application #13333. The ClinicalTrials.gov identifier for this study is NCT02040090.

The Division of Inspections and Surveillance conducted Biomedical Monitoring (BIMO) inspections of single clinical sites, accounting for all of the subjects enrolled in the Phase 3 study. The data audit portion of the inspections focused on the verification of the safety and efficacy study data for 100% of the enrollees at this site. The BIMO inspections of the clinical investigators did not reveal substantive problems that would impact integrity of the data submitted in this BLA.

3.3 Financial Disclosures

Covered clinical study (name and/or number): RD 154/23630: A clinical trial to evaluate the safety and efficacy of KamRAB (rabies immune globulin) in healthy male and female volunteers.		
Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 1 (Dr. Jacob Atsmon)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): RD 154/24061 A clinical trial to evaluate the safety and efficacy of KamRAB (Rabies Immune Globulin) coadministered with active vaccine in healthy male and female volunteers		
Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 1 (Dr Jacob Atsmon)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		

Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): 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.		
Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 1 (Dr. Mark A Matson)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

There were no significant DMC issues that would prevent this BLA from being approved. The Applicant has committed to the following post-marketing activities:

1. Kamada commits to: (a) Improve the (b) (4) method which includes quantification of (b) (4) and submit Standard Operating Procedure and method validation report; (b) Establish a specification and provide supporting data for (b) (4) for the (b) (4) the Drug Product by using the improved (b) (4) method. Kamada will submit a Post-marketing Commitment – Final Study Report as a Prior Approval Supplement (PAS) by January 31, 2018.
2. Two additional full-scale lots will be manufactured, (b) (4) of the critical operating parameter (b) (4), with in-process testing for (b) (4) at each manufacturing step and additional characterization tests. Kamada will submit a validation protocol outlining the operating parameters for each lot and testing/characterization along with the acceptance criteria as a Post-marketing Commitment – Product Correspondence prior to manufacture of these lots. The final report will be submitted as a Post-marketing Commitment – Final Study Report by August 31, 2018.

4.2 Assay Validation

There were no assay validation issues as the assay for determining anti-rabies activity (RFFIT) is universally accepted in the field as the "gold-standard".

4.3 Nonclinical Pharmacology/Toxicology

There were no pharmacology and toxicology issues that would prevent this BLA from being approved. A single toxicology study was conducted in female (b) (4) rats that were randomized to receive 60 or 120 IU/kg of IM KamRAB. There were no toxicities noted and thus the no-observed-adverse effect level was 120 IU/kg, or 6 times higher than the clinical dose. No animal studies were conducted to evaluate carcinogenesis, mutagenesis or impairment of fertility.

4.4 Clinical Pharmacology

The concerns of the Clinical Pharmacology Reviewer were similar to those of the Medical Reviewer. Therefore, the two Reviewers collaborated closely during the review of this BLA and their concerns are reflected in Sections 6 and 7 of this review.

4.4.1 Mechanism of Action

There were no issues related to the mechanism of action of KamRAB.

4.4.2 Human Pharmacodynamics (PD)

The primary concern of the Clinical Pharmacology Reviewer was the appropriateness of a pharmacodynamic endpoint (anti-rabies immunoglobulin) as the endpoint for demonstrating clinical efficacy. Please refer to Section 5.4.2 for details.

4.4.3 Human Pharmacokinetics (PK)

The primary concern of the Clinical Pharmacology Reviewer was that KamRAB was not bioequivalent to the two Comparator HRIGs. Please refer to Section 5.4.2 and 6.1.11 for additional details

4.5 Statistical

There were no issues raised by the Statistical Reviewer. The conclusions and recommendations of the Reviewer were: "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."

4.6 Pharmacovigilance

As per the Office of Biostatistics and Epidemiology Reviewer, the pharmacovigilance plan proposed by the Applicant is adequate for the sought indication. The Applicant will capture post-marketing safety surveillance data with suspected adverse drug reactions entered into Kamada's safety database. Important potential risks such as hypersensitivity reactions, transmission of infectious agents, thrombosis and hemolysis will be closely monitored. The data to date do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy or a post-marketing study to evaluate safety

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

5.1 Review Strategy

A quick refresher and tutorial on rabies was obtained from UpToDate followed by a literature search of the topic on PubMed. The latter turned up monographs on rabies authored by expert panels convened by the World Health Organization (WHO) and United States Center for Disease Control and Prevention (CDC). For example, the WHO has published periodic position papers, expert consultation and expert committee reports on rabies. Details relating to specific issues were then garnered by accessing the primary source references. After familiarizing himself with rabies and its challenges, the clinical reviewer focused attention on the BLA and IND documents, and in particular on the three clinical studies that comprise this application. Throughout the review process, there were numerous discussions with the clinical pharmacology reviewer (Xiaofei Wang), clinical

team leader (Bruce Schneider), branch chief (Ilan Irony) and another medical reviewer with experience in rabies products (Leland Ross Pierce).

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

The documents that were reviewed for this BLA include submissions under BLA 125613 and IND 13333. These include meeting minutes, correspondence between the FDA and Kamada, FDA review memos, and documents submitted by Kamada. There were additional requests for information which were presented to Kamada prior to the mid-cycle teleconference on Feb 23, 2017.

5.3 Table of Studies/Clinical Trials

Table 3: KamRAB Development Program
(Reviewer's Table)

Study	Country	Study Design	Test Agent	Endpoints
RD 154/23630	Israel	Phase 1, randomized, double blind, two-treatment, single-dose, crossover (N=26)	KamRAB vs BayRAB (20IU/kg)	Safety & Tolerability RVNA titer by RFFIT PK: C_{max}, T_{max}, AUC, $t_{1/2}$, k_{el}
RD 154/24061	Israel	Phase 1, randomized, double blind, single-dose, parallel group (N=16)	KamRAB (20IU/kg) vs Saline (+ Imovax)	Safety & Tolerability RVNA titer by RFFIT PK: C_{max}, T_{max}, AUC, $t_{1/2}$, F_{rel}, k_{el}
KAM RAB-003	USA	Phase 3, randomized, double-blind, single-dose, parallel group (N=118)	KamRAB vs HyperRAB (20IU/kg) (+ RabAvert)	RVNA titer by RFFIT Safety & Tolerability PK: C_{max}, T_{max}, AUC, $t_{1/2}$

5.4 Consultations

5.4.1 Advisory Committee Meeting

An Advisory Committee was not convened since the treatment of rabies is well established by the CDC and WHO. Similarly, the efficacy and safety profile of HRIGs is well established and the profile of KamRAB does not differ from that of the other HRIGs. The study design of the clinical studies in this BLA is also similar to that of the other HRIGs. Furthermore, if approved, this would be the third HRIG marketed in the US.

5.4.2 External Consults/Collaborations

A consultation was obtained from Dr Brett W. Petersen of the National Center for Emerging and Zoonotic Infectious Diseases, Center for Disease Control and Prevention, Atlanta, GA. Dr. Petersen is an expert in rabies with numerous publications on the subject. A briefing packet was sent to Dr. Petersen two weeks prior to the consultation.

A teleconference was held with Dr. Petersen on March 10, 2017. The attendees from the FDA included Drs. Bruce Schneider, Ilan Irony and Winson Tang. The following issues were discussed:

1. The WHO has stated that "a protective RVNA concentration has not been established, concentrations of at least 0.5 IU/mL are widely accepted as

adequate." However, the review team has not been able to ascertain the rationale for selecting Day 14 as the time-point for the assessment of efficacy since the C_{max} and T_{max} of HRIGs occur between Days 3 and 5 following administration. Given that the half-life of HRIGs is ~21 days, serum RVNA from KamRAB would have decreased to ~60-65% of peak levels by Day 14. Since HRIG is administered with rabies vaccine, host antibody production begins to take effect on Days 7-10. Therefore, one is no longer assessing the activity of HRIGs on Day 14 but a combination of the passive and active anti-rabies antibody response, with the majority of the RVNA on Day 14 due to host response to the vaccine.

Dr. Petersen explained that a protective threshold for a rabies RVNA titer is variable with the WHO recommending a titer of 0.5 IU/mL while the ACIP recommends a level of ~0.11 IU/mL. The rationale for the selection of Day 14 for the assessment of HRIG efficacy is historical and has been lost with the passage of time. Dr. Petersen agrees with our assessment that the best interval for measuring the RVNA of a HRIG is during the first seven days following administration. RVNA on day 14 is more representative of the effects of the vaccine. Nonetheless, this has been the precedent that has been established for the evaluation of HRIGs.

2. In Studies 23630 and 003, neither KamRAB nor HyperRAB/BayRAB administration (20 IU/kg BW) resulted in therapeutic serum RVNA levels on Day 3. A review of the literature for other HRIGs suggest that the accepted protective RVNA $\geq$0.5 IU/mL also cannot be achieved on Days 3-5 when HRIGs are administered at a dose of 20 IU/kg. Dr. Petersen confirms that the importance of a RVNA $\geq$0.5 IU/mL at early time-points (initial week) is difficult to ascertain as there are no data. These levels represent a surrogate (serum concentration) of a surrogate (tissue concentration). Nonetheless, there have been almost no documented failures when the current PEP regimen is administered appropriately.
3. In Study 23630, KamRAB was not bioequivalent to BayRAB. The lower bound of the 90% CI for C_{max} (75.3%), AUC_{0-t} (77.4%), and AUC_{∞} (79.5%) fall below 80%. In Study 003, the geometric mean RVNA on Day 3 was significantly lower in the KamRAB group when compared to HyperRAB (0.176 vs 0.216 IU/mL, $p<0.0003$). Furthermore, the AUC_{0-28} is significantly greater for the KamRAB group suggesting that there was less interference with the vaccine. Finally, the only subject who did not achieve a RVNA $\geq$0.5 IU/mL by Day 14 in this study belonged to the KamRAB group although the failure is more likely due to the vaccine rather than KamRAB. Dr. Petersen agreed that the pharmacokinetic profile of KamRAB is not equivalent to that of the Comparator HRIGs. However, these small differences are not likely to be clinically meaningful.

In summary, Dr Petersen believes that KamRAB would be equally effective as the Comparator HRIGs for PEP.

5.5 Literature Reviewed

A literature search was performed on PubMed with the search term "rabies" and the relevant articles were reviewed.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The Applicant conducted three clinical trials in support of this licensing application; all of them were in normal healthy volunteers. The three studies were:

1. RD 154/23630: A clinical trial to evaluate the safety and efficacy of KamRAB (rabies immune globulin) in healthy male and female volunteers.
2. RD 154/24061: A clinical trial to evaluate the safety and efficacy of KamRAB (Rabies Immune Globulin) coadministered 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.

6.1 Trial #1: RD 154/23630 - A clinical trial to evaluate the safety and efficacy of KamRAB (rabies immune globulin) in healthy male and female volunteers.

6.1.1 Objectives

1. To monitor the subjects for safety and adverse events after the administration of an intramuscular injection of KamRAB.
2. To compare the pharmacokinetic profile of rabies antibody in the blood of healthy subjects receiving KamRAB and a positive control (BayRAB®) in a double-blind crossover mode

6.1.2 Design Overview

This was a randomized, single-dose, two-period, two-treatment, two-sequence, double-blind crossover study that treated 26 subjects. Subjects were randomized to receive a single IM injection of 20 IU/kg RIG on two separate occasions (HRIGs A or B). Subjects received the second treatment (A or B) following the 42-day test period and a 21-day washout period. The latter was selected in order to minimize any carryover effects based upon the pharmacokinetic characteristics of other HRIGs.

Admin 1 (A): KamRAB 20 IU/kg IM (Kamada, Israel; Test)
Admin 2 (B): BayRab® 20 IU/kg (Talecris, USA, Reference)

Each in-house study period lasted approximately 3 hours post-dose. Time 0 blood sample for baseline immunoglobulin level determination before dosing in Period 1 was drawn at screening, and time 0 before dosing in Period 2 was drawn on the day of RIG administration (i.e. Day 1). Subjects also returned to the CRC for bleeds at: 3, 7, 14, 28, 35 and 42 days post-dose in each of the administration period.

The original study protocol called for a two part study. The second part of the study was an open label, one period, single dose KamRAB with five doses of rabies vaccine design in which the safety and pharmacokinetics of co-administration of the KamRAB and Imovax® Rabies Vaccine (Aventis-Pasteur) was to be examined. Due to the withdrawal of the Imovax® vaccine from the market, the second arm of the study could not be completed. The study protocol was subsequently amended to require only Part 1 of the study.

6.1.3 Population

Important Inclusion Criteria

1. Healthy males and females between 18 and 45 years of age.
2. Normal IgA levels.
3. Negative for rabies antibodies by Rapid Fluorescent Focus Inhibition Test (RFFIT).

Important Exclusion Criteria

1. A history of previous administration of rabies vaccine or RIG.
2. Seropositive for HIV Ab, HCV Ab and HBsAg
3. Females who reported being pregnant, or had positive urine pregnancy test, or were lactating.
4. Any finding in the physical examination or laboratory tests which, in the opinion of the Principal Investigator or the study physician, contraindicated the subject's participation in this study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

There were two test articles administered to each subject in this study, KamRAB and BayRAB®.

KamRAB (Study material): KamRAB is a Rabies Immune Globulin manufactured by Kamada Limited from hyperimmune plasma using ion exchange chromatography. The source of the hyperimmune plasma for the KamRAB material used in this study was collected in the United States at FDA-approved facilities. The concentration of rabies antibody was 150 IU/mL. The product is presented as a clear, preservative free, liquid formulation stabilized with 0.3M glycine in 2 and 10 ml vials. The product underwent 3 specific viral inactivation/ removal steps: Solvent detergent treatment, pasteurization ((b) (4)), and nanofiltration using a (b) (4) during the manufacturing process. KamRAB is approved for manufacturing at Kamada's production facility and export overseas.

BayRab® (Reference material): BayRab® is a Rabies Immune Globulin manufactured by Talecris Biotherapeutics, PO Box 110526, 4101 Research Commons, 79 T.W. Alexander Drive, Research Triangle, North Carolina, USA 27709, using a (b) (4) (a method that utilized cold ethanol precipitation) from hyperimmune (b) (4) plasma collected at FDA approved facilities. The concentration of rabies antibody was 150 IU/ml. The product is presented as a clear, preservative free, liquid formulation containing 0.21-0.32M glycine with a pH of 6.4-7.2 in 2 and 10 ml vials. During manufacture, the product underwent two viral inactivation/elimination steps: Heat treatment (30°C for 6 hours) and solvent detergent treatment. BayRab® was FDA-approved and is sold in the Unites States and throughout the world.

6.1.5 Directions for Use

Both RIGs were injected IM into the gluteus. If more than 5 ml were administered, the product was divided into 2 or more syringes and injected at different sites.

6.1.6 Sites and Centers

The clinical aspect of the study was conducted at the Simbec-TASMC Clinical Research Center at the Tel-Aviv Sourasky Medical Center under full medical and nursing

supervision. The immunoglobulin samples were tested by the (b) (4) . The raw data were managed by Kamada and the quality assured results were transmitted back to Simbec Research Ltd, U.K.

6.1.7 Surveillance/Monitoring

Table 4: Schedule of Study Activities
(Applicant's Table)

TIME[1]	ACTIVITY[2]
Days (-)21 – (-)1	• Informed Consent (first study period only) • Pre-study safety screening • Urine tests for pregnancy (female subjects) • "Time-0" blood for rabies antibodies
Day 1	• Admission to CRC • Body weight • Urine tests for drugs of abuse and breath alcohol • Urine tests for pregnancy (female subjects) • Pre-dose blood for rabies antibodies[3] • KamRAB/BayRab® injection • Release from CRC at 3-5h post-dose
Day (+)3	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF
Day (+)7	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF
Day (+)14	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF
Day (+)28	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF
Day (+)35	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF
Day (+)42	• Blood for rabies antibodies • Urine tests for pregnancy (female subjects) • Interim/post-study[4] blood and urine safety tests (including serology[4]) • Recording AEs in the CRF • Post study physical examination and ECG[4]

[1]Dosing day is designated as "Day 1". Time-point prior to dosing day is prefixed with (-). Time-point after dosing day is prefixed with (+).
[2]Reports on adverse events and concomitant medications will be recorded in the CRF throughout the study.
[3]In Period 2 only
[4]At the end of Phase II only

6.1.8 Endpoints and Criteria for Study Success

This was a pharmacokinetic study that compared the investigational product, KamRAB, with a reference product, BayRAB®. Therefore, the criteria for study success would be a pharmacokinetic, safety and tolerability profile for KamRAB that was not different from that of BayRAB®.

The primary endpoints were pharmacokinetic endpoints including C_{max}, T_{max}, AUC_T and AUC_I. The timing of the serial blood collection for determination of rabies antibody was determined based upon the pharmacokinetic data generated in studies with similar HRIGs such as BayRAB® and Imogam®.

Safety and tolerability were assessed by surveillance for adverse event and monitoring of clinical chemistry, hematology and urinalysis.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The sample size of this study, 26 volunteers, was considered by the sponsor to be appropriate to obtain reliable pharmacokinetic information. Subjects who did not complete both phases of the study were excluded from the efficacy evaluation. All subjects were included for the safety evaluation, including those who did not complete the study.

The following pharmacokinetic parameters, calculated from the plasma antibody profiles, were subjected to statistical analysis: C_{max}, T_{max}, AUC_T and AUC_I. Following logarithmic transformation, C_{max}, AUC_T and AUC_I values were subjected to analysis of variance (ANOVA) techniques, including terms for sequence, subject nested within sequence, treatment session and formulation. For comparison, point estimates and 90% confidence intervals using the residual mean square error obtained from the ANOVA were calculated. These point and interval estimates were then back-transformed to give estimates of the geometric means and 90% confidence intervals for the ratios of the two formulations. T_{max} was analyzed using a Wilcoxon rank sum test. There were no adjustments for covariates.

The safety assessment was descriptive in nature due to the small sample size.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

This study was conducted in young, healthy, normal volunteers.

6.1.10.1.1 Demographics

A total of twenty-six (26) healthy subjects were entered into the study and twenty-three (23) completed both doses of the study. The twenty-six (26) subjects enrolled were predominantly males (n=22) with only 4 females. They ranged in age from 18 to 37 years with a mean age of 27.0 $\pm$ 4.2 years (SD). Their mean weight was 66.9 $\pm$ 10.5 kg with a mean height of 1.73 $\pm$ 0.07 meters.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

This study was conducted in young, healthy, normal volunteers.

6.1.10.1.3 Subject Disposition

A total of twenty-six (26) subjects were entered into the study; 23 subjects completed both phases of this study as planned. Three (3) subjects did not receive the second dose of the study drug due to adverse events.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

This was a study to compare the pharmacokinetic profile of two HRIGs, KamRAB and BayRab®, with each administered at a dose of 20 IU/kg. All 26 subjects had more than one blood collection that deviated from the schedule prescribed by the protocol (either early or late). However, all deviations were within 24 hours of the prescribed sampling time with the exception of subject 3 whose Day 42 sample was actually collected on Day 43.2. For this subject, the blood sampling time was taken to the nearest day in the pharmacokinetic calculations or Day 42. For the purpose of calculation of the mean plasma titers, the nominal sampling times were used. A summary of the pharmacokinetic data are presented in Table 5. Data are presented as arithmetic mean ± SD and geometric least square (LS) mean.

Table 5: Pharmacokinetics – Study RD154/23630
(Reviewer's Table)

Parameter (units)	KamRAB		BayRAB		KamRAB/BayRAB	
	Arithmetic Mean	Geometric LS Mean	Arithmetic Mean	Geometric LS Mean	Geometric LS Mean Ratio	90% CI
C_{max} (IU/mL)	0.249 (0.063)	0.241	0.302 (0.068)	0.295	81.71	(75.34, 88.62)
AUC_T (day*IU/ml)	5.222 (1.297)	5.081	6.266 (1.236)	6.170	82.35	(77.39, 87.63)
AUC_∞ (day*IU/ml)	6.898 (1.361)	6.786	8.017 (1.364)	7.901	85.89	(79.45, 92.86)

The arithmetic mean Anti-Rabies Antibody Titer C_{max} for KamRAB and BayRab® were 0.249 ± 0.063IU/mL and 0.302 ± 0.068 IU/mL, respectively. The point estimate for the ratio of Anti-Rabies Antibody Titer C_{max} values of the test formulation and reference formulation was 81.71 (90% confidence interval 75.34% - 88.62%).

The arithmetic mean Anti-Rabies Antibody Titer AUC_T for IM Inj. KamRAB and BayRab® were 5.222 ± 1.297 Day*IU/mL and 6.266 ± 1.236 Day*IU/mL, respectively. The point estimate for the ratio of Anti-Rabies Antibody Titer AUC_T values of the test formulation and reference formulation was 82.35 (90% confidence interval 77.39% - 87.63%).

The arithmetic mean Anti-Rabies Antibody Titer AUC_I for KamRAB and BayRab® 20 IU/kg were 6.898 ± 1.361 Day*IU/mL and 8.017 ± 1.364 Day*IU/mL, respectively. The point estimate for the ratio of Anti-Rabies Antibody Titer AUC_I values of the test formulation and reference formulation was 85.59 (90% confidence interval 79.45% - 92.86%)

The median Anti-Rabies Antibody Titer Tmax for the IM Inj. KamRAB 20 IU/kg and for the IM Inj. BayRab® 20 IU/kg were 7.0 days and 3.0 days, respectively. This difference was not statistically significant (p=0.4491).

There is a marginally statistically significant sequence effect seen in Cmax (p=0.0415) and AUC_T (p=0.0329). This is essentially a treatment by period interaction.

Reviewer's comments

1. ***The PK data revealed that the KamRAB formulation was inferior to reference product BayRAB. The lower bound of the 90% confidence interval for $C_{max,}$ AUC_T, AUC_I were all below 80%.***
2. ***Since efficacy studies cannot be performed in this fatal disease, the anti-rabies antibody titers serves as a surrogate marker of efficacy***

6.1.11.2 Analyses of Secondary Endpoints
There were no secondary endpoints in this study.

6.1.11.3 Subpopulation Analyses
There was no subpopulation analysis since the study subjects were all young, healthy, normal volunteers.

6.1.11.4 Dropouts and/or Discontinuations
There were 3 subjects who did not receive the second dose of study drug due to adverse events (See Section 6.1.12.7 Dropouts and/or Discontinuations below). However, they were included in the PK (i.e.; efficacy) and safety analysis.

6.1.11.5 Exploratory and Post Hoc Analyses
There were no exploratory and post hoc analyses in this study.

6.1.12 Safety Analyses
6.1.12.1 Methods
A formal analysis of AEs was not performed due to the small sample size. The Applicant provided descriptions of each of the AEs. All 26 subjects were included for the safety evaluation, including the 3 subjects who did not complete the study.

6.1.12.2 Overview of Adverse Events
There were no severe adverse events reported in this study. There were sixty-eight (68) AEs reported (Table 6). Twenty-eight (28) AEs were reported by subjects when KamRAB (20 IU/kg) was administered and forty (40) AEs were reported by subjects when the reference BayRab® (20 IU/kg) was administered. All the adverse events following the administration of both formulations were either mild or moderate in severity, suggesting that both formulations were equally well tolerated.

Table 6: Severity of AEs
(Applicant's Table)

	KamRAB (20 IU/kg)		**BayRAB® (20 IU/kg))**	
	N	%	N	%
Mild	28	100%	37	92.5%
Moderate	0	0	3	7.5%
Total	28	100%	40	100%

There were twenty-eight (28) AEs reported by 7 subjects following the administration of KamRAB; 7 AEs (25.00%) were considered by the Investigator to be unrelated, 9

(32.14%) unlikely to be related, 11 (39.29%) possibly related and 1 (3.57%) probably related to KamRAB. There were 7 subjects who had a total of 12 AEs that were considered either possibly or probably relationship to the administration of KamRAB. They were subjects 5, 7, 10, 11, 12, 15 and 17.

Following BayRAB® administration, 7 subjects reported 40 AEs (Table 7). Eleven (11) AEs (27.50%) were considered to be unrelated, 19 AEs (47.50%) were unlikely to be related, 5 AEs (12.50%) were possibly and five (5) AEs (12.50%) were probably related to BayRAB® administration. There were 7 subjects who experienced 10 AEs that were considered to have either a possible or probable relationship to the administration of IM Inj. BayRab®. They were subjects 3, 6, 11, 13, 15, 18 and 24.

Table 7: Relationship of AEs to Study Drug
(Appplicant's Table)

	KamRAB (20IU/kg)		**BayRAB® (20 IU/kg))**	
	N	%	N	%
Unrelated	7	25.0%	11	26.5%
Unlikely	9	32.1%	19	41.2%
Possibly	11	39.3%	5	23.5%
Probably	1	3.6%	5	8.8%
Total	28	100%	40	100%

The three most common AEs were microhematuria (n=9), leukocyturia (n=7), and headaches (n=6). Seven subjects had nine episodes of hematuria with two subjects developing hematuria following both KamRAB and BayRAB® administration. Four of the episodes were noted in four subjects after KamRAB administration while the remaining five were detected in five subjects after receiving BayRAB®. Similarly for leukocyturia, five subjects were noted to have this AE with two subjects developing it after both KamRAB and BayRAB® administration. Three episodes occurred after receiving KamRAB and the remaining 5 after BayRAB®. For headaches, four of the six subjects reported this AE after receiving KamRAB.
Reviewer's comment: A more thorough analysis of hematuria and leukocyturia was requested from Kamada Ltd. at the mid-cycle review. The analysis was provided on April 21, 2017. Please see Section 8.4.5 for details.

6.1.12.3 Deaths
There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events
There were no serious adverse events reported in this study.

6.1.12.5 Adverse Events of Special Interest (AESI)
Injection-site reactions were uncommon in this study with only 3 subjects reporting pain at the injection site. All 3 episodes were reported as mild and probably related to study drug. Two of them occurred after BayRAB® administration and the other after KamRAB.

6.1.12.6 Clinical Laboratory Test Results

There were eight (8) AEs recorded where the laboratory parameters were out of range and were considered clinically relevant following the administration of KamRAB (20 IU/kg). These AEs were a mildly elevated blood bilirubin in one subject, increased white blood cell count in two subjects, leukocyturia in one subject, and hematuria in four subjects. Following the administration of BayRab® (20 IU/kg), fourteen (14) AEs were recorded where the laboratory parameters were out of range and were considered clinically relevant. These were increases in alanine aminotransferase (2 subjects), lactate dehydrogenase (1 subject), neutrophil count (1 subject), red blood cell count (3 subjects), white blood cell count (2 subjects), leukocyturia (3 subjects) and hematuria (2 subjects).

All ECG results were within normal range or where they deviated was not considered to be clinically significant by the investigating physician.

6.1.12.7 Dropouts and/or Discontinuations

There were 3 subjects who did not receive the second dose of study drug due to adverse events. Two subjects were withdrawn from the study after developing microhematuria following KamRAB (Subject (b) (6)) and BayRAB® (Subject (b) (6)) administration. The latter was graded as mild in intensity and possibly related to BayRAB® injection. A third subject (Subject (b) (6)) was withdrawn from the study because of an upper respiratory infection that was moderate in intensity and was considered unrelated to BayRAB® administration.

6.1.13 Study Summary and Conclusions

This was a Phase 1 study to compare the safety, tolerability, and pharmacokinetic profile of KamRAB with a positive control (BayRAB®) in a double-blind crossover design. The study enrolled 26 young healthy Caucasian subjects with a mean age of 27 $\pm$ 4.2 years. Twenty-three of the subjects completed the study; three subjects did not receive both study drug because of AEs (erythrocyturia in two subjects and viral respiratory infection in the remaining subject. One subject was withdrawn following KamRAB administration and the other two following BayRAB.

KamRAB was generally safe and well tolerated. There were no deaths or SAEs reported. A total of 68 AEs were reported, 28 by subjects after receiving KamRAB. The majority of the AEs were mild in severity (95.6%) with only 3 AEs that were of moderate severity, all following BayRAB administration. Of the 28 AEs reported following KamRAB administration, 7 AEs (25%) were considered by the Investigator to be unrelated, 9 AEs (32.1%) were unlikely related, 11 AEs (39.3%) were possibly related and one AE (3.6%) was probably related to KamRAB.

The pharmacokinetic profile of KamRAB was inferior to that of BayRAB. The lower bound of the 90% CI for the point estimate of the ratio of C_{max}, AUC_T, and AUC_I of KamRAB relative to BayRAB all fell below 80% (75.3%, 77.4%, and 79.5%, respectively). There was a treatment by period interaction as there was a statistically significant sequence effect seen in C_{max} (p=0.04) and AUC_T (p=0.03).

Reviewer's comments:

1. ***The priamry concern is that the PK profile of KamRAB was inferior to that of BayRAB since anti-rabies protection prior to Days 7-10 is dependent upon these passively transferred antibodies. However, upon further review of the literature***

and consultation with Dr Petersen of the CDC, it was felt that these minor PK differences will not impact upon the clinical effect of KamRAB.

2. ***KamRAB or BayRAB at a dose of 20IU/kg did not produce serum levels that are considered therapeutic (≥0.5IU/mL) according to the standards of the WHO. This is consistent with data from other HRIGs in the literature. However, the clinical experience (per the literature) suggests that these levels are not necessary for effective post-exposure prophylaxis. Indeed, the CDC has established a therapeutic RVNA that is equivalent to ~0.10-0.12 IU/mL.***
3. ***Kamada confirmed that the potency of KamRAB and BayRAB were tested prior to administration in response to our inquiry during the mid-cycle review. Thus, the differences in serum concentrations between the two test agents could not be attributed to differences in potency between the two agents.***

6.2 Trial #2: RD 154/24061 - A clinical trial to evaluate the safety and efficacy of KamRAB (Rabies Immune Globulin) coadministered with active vaccine in healthy male and female volunteers.

6.2.1 Objectives

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

6.2.2 Design Overview

This was a randomized, double blind, parallel study design. Subjects received either a single intramuscular dose of KamRAB injection (20 IU/kg) or placebo (NaCl 0.9% 0.133ml/kg) followed by three intramuscular injections of an active rabies vaccine (Rabipur®) on days 0, 7 and 28.

Sixteen healthy males and females were randomized to receive either KamRAB or placebo. Subjects received either treatment A plus C or B plus C according to a randomization code produced by Simbec Research Limited.

(A): KamRAB 20 IU/kg IM Inj. (Kamada, Israel; Test)
(B): NaCl 0.9% 0.133 ml/kg IM Inj. (Placebo)
(C): Rabipur® Rabies Vaccine 1.0 ml IM x 3 IM Inj. (Days 0, 7 and 28).

There was an in-house study period of approximately 3 hours after each dosing (KamRAB/placebo + Rabipur® on Day 1, Rabipur® only on days 7 and 28). A predose (time 1) blood sample for baseline immunoglobulin level determination was drawn at pre-study screening. Subjects returned to the study center for blood sampling at: 3, 7, 14, 28, 35 and 42 days after KamRAB/placebo + Rabipur® Rabies Vaccine injection.

Each study period was forty-two (42) days in duration.

This study did not follow the WHO recommended post-exposure regimen of RIG plus five doses of vaccine on Days 0, 3, 7, 14 and 28. Rather, the vaccination regimen selected was the standard 3 doses pre-exposure prophylaxis regimen (i.e. vaccination on Days 0, 7 and 28). This was due to a world-wide shortage of the human diploid cell culture vaccine necessitating a switch to a purified chick embryo cell vaccine. The latter is associated

with a possibly higher (albeit rare) incidence of Guillain-Barré Syndrome. The local IRB considered it unethical to expose healthy volunteers to a sham post-exposure prophylaxis regimen. However, since the chick embryo-derived vaccine is currently still being used routinely for pre-exposure prophylaxis in persons involved with animal care (veterinary doctors and students, zoo workers, etc.) the IRB approved the participation of this subject population in the study, provided they receive the acceptable pre-exposure prophylaxis regime (i.e. vaccination on Days 0, 7 and 28).

Reviewer's comments: The absence of the additional boosters on Days 3 and 14 will alter the geometric mean titers (GMT) of rabies antibody serum levels seen with a PEP regimen. However, both the WHO and CDC had subsequently advocated a 4-dose vaccination schedule. The WHO 4-dose regimen consists of two doses administered on day 0 followed by single doses on days 7 and 21 while the United States Center for Disease Control and Prevention recommends single vaccine doses administered on days 0, 3, 7 and 14.

6.2.3 Population

Important Inclusion Criteria

1. Males and females between 18 and 45 years of age who are likely to receive pre-exposure rabies immunization due to their occupation, and were not vaccinated previously.
2. Normal IgA levels.
3. Negative for rabies antibodies by Rapid Fluorescent Focus Inhibition Test (RFFIT).

Important Exclusion Criteria

1. History of previous administration of rabies vaccine or RIG.
2. Seropositive for HIV Ab, HCV Ab and HBsAg
3. Females who reported being pregnant, or had positive urine pregnancy test, or were lactating.
4. Any finding in the physical examination or laboratory tests which, in the opinion of the Principal Investigator or the study physician, contraindicates the subject's participation in this study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

There were three test articles in this study, KamRAB, sterile NaCl (0.9%) and Rabipur® rabies vaccine.

KamRAB (Study material): KamRAB is a Rabies Immune Globulin manufactured by Kamada Limited from hyperimmune plasma using ion exchange chromatography. The source of the hyperimmune plasma for the KamRAB material used in this study was collected in the United States at FDA-approved facilities. The concentration of rabies antibody was 150 IU/ml. The product is presented as a clear, preservative free, liquid formulation stabilized with 0.3M glycine in 2 and 10 ml vials.

Sterile NaCl 0.9% (Placebo): This is a marketed product routinely used at the Tel-Aviv Sourasky Medical Center.

Rabipur® (Rabies Vaccine): The Rabipur® vaccine was produced by Chiron Behring. It is a sterile, freeze-dried substance, containing ≥ 2.5 I.U. of inactivated rabies antigen (virus multiplied in chicken fibroblast cell cultures). A clear colorless

solution results after reconstitution of the white lyophilized powder with the diluent (1 ml water for injection). The excipients included: sodium chloride, polygeline, TRIS-(hydroxymethyl)-aminomethane, disodium edetate (Titriplex III), potassium-L-glutamate and sucrose. The antibiotics (Neomycin, Chlortetracycline, Amphotericin B) added during cell and virus propagation were removed to the greatest possible extent by purification steps and could not be detected with currently used methods in the final vaccine product. It is approved for routine use in Europe and in the U.S. as Rabavert®.

Reviewer's comments: The dose of the RIG, 20 IU/kg, is based on the CDC recommendations for prophylactic passive immunization together with active vaccination. Similarly, in clinical trials with previously unimmunized subjects, almost all subjects achieve a protective antibody titer by day 28 after a primary series of vaccinations with three injections of Rabipur® when given according to the recommended schedule by the intramuscular route.

6.2.5 Directions for Use

All KamRAB injections were given in the gluteal region. No more than 5 ml of RIG was given at each injection site. The Rabipur® rabies vaccine was administered to the deltoid region of either arm.

6.2.6 Sites and Centers

The clinical aspect of the study was conducted at the SIGILY-TASMC Clinical Research Center (CRC) at the Tel-Aviv Sourasky Medical Center under full medical and nursing supervision. The immunoglobulin samples were tested by the (b) (4) . The raw data was managed by Kamada. Following Kamada QA review and approval, they were transmitted back to Simbec Research Ltd, U.K. for unblinding and analysis.

6.2.7 Surveillance/Monitoring

Table 8: Schedule of Study Activities
(Applicant's Table)

TIME[1]	ACTIVITY[2]
Days (-)21 – (-)1	• Informed Consent • Pre-study safety screening • Urine tests for pregnancy (female subjects) • "Time-0" blood for rabies antibodies
Day 0	• Admission to CRC • Body weight • Temperature • Urine tests for drugs of abuse and breath alcohol • Urine tests for pregnancy (female subjects) • KamRAB or Placebo injection • Rabipur® Rabies Vaccine injection • Release from CRC at approximately 3h post-dose
Day (+)3	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF

Day (+)7	• Admission to CRC • Temperature • Pre-dose blood for rabies antibodies • Interim blood and urine safety tests • Urine tests for drugs of abuse and breath alcohol • Urine tests for pregnancy (female subjects) • Rabipur® Rabies Vaccine injection • Release from CRC at 3h post-dose • Recording AEs in the CRF
Day (+)14	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF
Day (+)28	• Admission to CRC • Temperature • Pre-dose blood for rabies antibodies • Interim blood and urine safety tests • Urine tests for drugs of abuse and breath alcohol • Urine tests for pregnancy (female subjects) • Rabipur® Rabies Vaccine injection • Release from CRC at 3h post-dose • Recording AEs in the CRF
Day (+)35	• Blood for rabies antibodies • Interim blood and urine safety tests • Recording AEs in the CRF
Day (+)42	• Blood for rabies antibodies • Urine tests for pregnancy (female subjects) • Post-study blood and urine safety tests (including serology) • Recording AEs in the CRF • Post study physical examination and ECG

[1]Dosing day was designated as "Day 0". Time-point prior to dosing day is prefixed with (-). Time-point after dosing day is prefixed with (+).
[2]Reports on adverse events and concomitant medications were recorded in the CRF throughout the study.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint of this study is to assess the safety and tolerability of a single intramuscular injection of KamRAB when co-administered with three injections of an active rabies vaccine (Rabipur®). Therefore, the criteria for study success would be a safety and tolerability profile for KamRAB and Rabipur® that was not different from that of Rabipur® alone. Safety and tolerability were assessed by surveillance for adverse events and monitoring of clinical chemistry, hematology and urinalysis.

RIG is known to interfere with rabies antibody production when co-administered with a rabies vaccine for post-exposure prophylaxis of rabies. This study was conducted to determine the effect of KamRAB on rabies virus neutralizing antibody production following immunization with Rabipur®. The primary "efficacy" endpoints were pharmacokinetic endpoints including C_{max}, T_{max}, AUC_T and AUC_I. The timing of the serial blood collection for determination of rabies antibody was determined based upon the pharmacokinetic data generated in studies with other similar HRIGs and rabies vaccines.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The hypothesis tested in this study was that there was no difference in "bioavailability" (rate of antibody production) between the KamRAB + Rabipur® administration and

Placebo + Rabipur® administration with respect to plasma anti-rabies antibody concentrations. Sixteen (16) volunteers were randomized in this study. The number of subjects (8 each in the KamRAB and Placebo arms) was considered by the sponsor to be appropriate to obtain reliable pharmacokinetic information. All subjects who were dosed and completed the study (including blood analyses) were included in the pharmacokinetic population.

Pharmacokinetic parameters, calculated from the plasma antibody profiles, were subjected to statistical analysis: C_{max}, T_{max} and AUC_T. Following logarithmic transformation, C_{max} and AUC_T values were subjected to an unpaired t-test for a difference between treatments. Point estimates and 95% confidence intervals using between subject variations were calculated for comparison. The point and interval estimates were then back-transformed to give estimates of the geometric means and 95% confidence intervals for the ratios of the point estimates of the two formulations.

Some of the pharmacokinetic samples were not taken exactly on time although all deviations were within 24 hours with the exception of three subjects. Subject (b) (6) (43.1 days), subject (b) (6) (43.0 days) and subject (b) (6) (43.1 days). For the purpose of mean daily titer calculations these deviations were ignored and the nominal time of collection used. As the study period following each dose administration lasted for forty-two (42) days, only bleed time deviations greater than 24 hours were taken into consideration during the pharmacokinetic analysis. For the purpose of pharmacokinetics analysis bleed time deviations greater than 24 hours were taken to the nearest day in the pharmacokinetic calculations.

6.2.10 Study Population and Disposition

6.2.10.1 Population Enrolled/Analyzed

A "high-risk" group of subjects (veterinary students and surgeons, animal keepers, animal handlers, and personnel in rabies research laboratories) was enrolled in this study as described in Section 6.2.2. The Rabipur® vaccine used in this study is derived from rabies virus cultured in chicken fibroblasts and is associated with a greater risk of nervous system adverse reactions (paresis or Guillain-Barré-Syndrome). Therefore, a "high-risk" group of subjects were enrolled in this study since their health would not be compromised as they were destined to receive the chick embryo vaccine.

Reviewer's comments:

This study excluded pediatric, pregnant, lactating and immunocompromised subjects from participation. There is a lack of information on the use of RIG and post-exposure prophylaxis in these populations.

6.2.10.1.1 Demographics

A total of sixteen (16) subjects were treated in this study. There were 9 males and 7 females. Their mean age was 27.3 $\pm$ 4.3 years (SD) with a range of 19 to 35 years. They had a mean weight of 69.7 $\pm$13.5 kg (range: 53.4 – 110.3 kg) and a mean height of 1.71 $\pm$ 0.11 meters.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

See comments above under Section 6.2.10.1.

6.2.10.1.3 Subject disposition

Of the sixteen (16) subjects enrolled and immunized in this study, only 15 subjects completed the study as planned. One subject (subject (b) (6) in the KamRab cohort) was discontinued from the study because of a positive urine test for cannabinoids on Day 7. The subject went on to receive the two remaining vaccinations on Days 8 and 28 for ethical reasons. The subject refused to undergo post-study testing.

6.2.11 Efficacy Analyses

Rabies immune globulin should be used in conjunction with active rabies vaccine as part of the post-exposure prophylaxis of rabies in patients bitten by and/or exposed to animals suspected of being rabid, provided the patient was not previously vaccinated with the rabies vaccine. Following intramuscular administration and infiltration around the wound, rabies immune globulin provides immediate passive antibodies for a short period of time. This protects the patient until the patient can produce neutralizing antibodies from the rabies vaccine. This study was undertaken to assess the inhibitory effect of KamRAB on rabies antibody production in response to vaccination.

6.2.11.1 Analysis of Primary Endpoint(s)

In this study, subjects who received either KamRAB or placebo injections did not develop antibody levels above 0.5 IU/mL until 14 days after vaccination (Table 9). These data are consistent with two previous studies that also showed that protective antibody titers (≥0.5 IU/mL) were detected in most subjects only on Day 14 after vaccination and concomitant RIG administration (Lang J et al, *Biologicals 1998; 26:7*, Helmick CG et al, *J Biol Stand 1982; 10:357*).

Table 9: Plasma anti-rabies immunoglobulin concentration (IU/mL) over time
(Reviewer's Table)

		D0	D3	D7	D14	D28	D35	D42
Placebo + RabiPUR	**Arithmetic Mean**	0	0	0	5.05	2.19	16.49	22.27
	Geometric Mean	--	---	--	3.00	1.54	9.48	13.08
KamRAB + RabiPUR	**Arithmetic Mean**	0	0.11	0.10	1.39	0.93	3.22	9.36
	Geometric Mean	--	---	--	---	---	2.72	6.13

On Day 14, the arithmetic mean titers were above the threshold values of 0.5 IU/mL in both groups (1.39 IU/mL in the KamRAB group and 5.05 IU/mL in the Placebo group). As stated in the Rabipur® Product information leaflet "Administration of rabies immunoglobulin… may attenuate the effects of concomitantly administered vaccine." It is therefore not surprising that antibody titers were lower in the group receiving concomitant KamRAB RIG when compared with the placebo group. Indeed, a previous study (Helmick CG et al, *J Biol Stand 1982; 10:357*) has reported an essentially similar pattern. The GMT on Day 14 was lower in vaccinees who received concomitant human RIG on Day 0 (3.95 IU/mL) than in subjects who received only the human diploid cell rabies vaccine (9.24 IU/mL). It should be noted that, unlike the volunteers in the current study, these subjects received an active vaccine injection on Day 3, which may account for the higher titers on Day 14.

The plasma concentration of Anti-Rabies Antibody Titer following administration of

KamRAB (20 IU/kg) and saline placebo formulation (0.133ml/kg) showed a mean C_{max} concentration of 9.358 IU/ml (SD 10.72) at a median of 42 days (range 42 – 42) and 23.98 IU/mL (SD 21.11) at a median of 42 days (range 14 – 42) respectively. The C_{max} for KamRAB is substantially lower than that of the placebo formulation (42.93%).

The mean Anti-Rabies Antibody Titer AUC_T for KamRAB and for placebo were 85.17 (SD 92.16) and 276.3 (SD 204.7) Day*IU/mL, respectively. The point estimate ratio of anti-Rabies Antibody Titer AUC_T values of KamRAB and placebo formulation was 31.91 (95% confidence interval 10.14 –100.42%).

The median Anti-Rabies Antibody Titer T_{max} (from the nominal sampling times) for KamRAB 20 IU/kg and placebo were 42 days (range 42 - 42) and 42 days (range 14 - 42), respectively.

Reviewer's comments: As shown in a first study (RD 154/23630), when a single dose of KamRAB or the reference BayRAB® (20 IU/kg) were injected to healthy volunteers, neither produced titers ≥0.5 IU/mL at any time during a 42-days follow-up. Hence it is likely that the contribution of the KamRAB antibodies to the overall GMT in the current study was small. More importantly, KamRAB does decrease anti-rabies antibody production in response to vaccination but the interference does not prevent formation of protective titers.

6.2.11.2 Analyses of Secondary Endpoints

There were no secondary endpoints in this study as it was a pharmacokinetic study.

6.2.11.3 Subpopulation Analyses

There was no subpopulation in this study as it was a pharmacokinetic study conducted in a homogeneous population of young, healthy, normal volunteers.

6.2.11.4 Dropouts and/or Discontinuations

One subject (subject (b) (6) in the KamRAB cohort) was discontinued from the study because of a positive urine test for cannabinoids on Day 7. The subject went on to receive the vaccine on Days 8 and 28 for ethical reasons but refused to undergo post-study testing.

6.2.11.5 Exploratory and Post Hoc Analyses

There was no exploratory and post hoc analysis performed in this study as it was a pharmacokinetic study.

6.2.12 Safety Analyses

6.2.12.1 Methods

A formal analysis of AEs was not performed due to the small sample size. The Applicant provided descriptions of each of the AEs.

6.2.12.2 Overview of Adverse Events

The definition assigning causality to adverse events was inconsistent between the Protocol and CRF, with 'Almost definite' being used in the CRF in addition to those defined in the Protocol. This causality was attributed to four adverse events. Subject 03 was withdrawn from the study following the detection of marijuana on a urine test.

A total of twenty (20) AEs were reported during this study (Table 10). Four subjects who were administered KamRAB (20 IU/kg) and vaccine reported a total of nine AEs while eleven AEs were reported by five subjects receiving the placebo and vaccine. All AEs in

the KamRAB test product group were mild in severity, suggesting that the formulation was reasonably well tolerated. All the AEs following the administration of the placebo were either mild or moderate in severity. There were no severe adverse events reported in this study.

Table 10: Severity of Adverse Events
(Applicant's Table)

AE Grade	KamRAB (20IU/kg)		Placebo (0.9% NaCl)	
	N	%	N	%
Mild	9	100%	10	90.9%
Moderate	0	0	1	9.1%
Total	9	100%	11	100%

Seven of the nine (9) AEs reported following the administration of KamRAB were considered by the Investigator to be unrelated to the test dose and/or rabies vaccine (77.78%) while the two remaining AEs (22.22%) were considered to be unlikely related to the test dose and/or rabies vaccine (Table 11). Similarly, in the group that received placebo, 7 of the 11 AEs (63.64%) were considered by the investigator to be unrelated to the placebo and/or rabies vaccine while four AEs (36.36%) were considered to have an almost definite relationship to the placebo administration and/or rabies vaccine.

Table 11: Relationship of AEs to Study Drug
(Applicant's Table)

AE Relation	KamRAB (20IU/kg)		Placebo (0.9% NaCl)	
	N	%	N	%
Almost Definite	0	0%	4	36.4%
Unlikely	2	22.2%	0	0%
Unrelated	7	77.8%	7	63.6%

There were two subjects who experienced two AEs each that were considered to have an almost definite relationship to the placebo and/or rabies vaccine. Subject (b) (6) experienced pain and swelling at the injection site that was considered definitely related to the administration of placebo/vaccine. Both of these AEs occurred 28.4 days after dosing and lasted for 1.0 day. These AEs were recorded as being mild in intensity and were completely recovered with no intervention. Subject (b) (6) also experienced pain at the injection-site and headache; both AEs were considered to be definitely related to the administration of placebo/vaccine. Both of these AEs occurred 7.2 days after dosing and lasted for 1.8 days. These AEs were recorded as being mild in intensity and were completely recovered with no intervention.

6.2.12.3 Deaths

There were no deaths reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events

There were no serious adverse events reported in this study.

6.2.12.5 Adverse Events of Special Interest

There were only two subjects who reported pain at the injection sites, both subjects were in the placebo group. The pain was mild in severity and was assessed by the Investigator as "almost definitely" related to study drug.

6.2.12.6 Clinical Laboratory Test Results

There were several laboratory test values (clinical chemistry, hematology and urinalysis) that were outside of the normal reference range but were not considered to be clinically relevant by the Investigator (See Table 15.3.4 in study report). Only three of the laboratory values that were out of the reference range were considered by the Investigator to be clinically relevant and listed as AEs. Three subjects had four episodes of leukocyturia that were reported as AEs; two of the subjects received KamRAB + vaccine and the remaining subject received placebo + vaccine. Three of the AEs were considered unrelated by the Investigator and the remaining AE was unlikely to be related to study drug.

All ECG results were within normal range or where they deviated was not considered to be clinically significant by the investigating physician.

Reviewer's comments: This Reviewer's agrees with the Applicant's safety assessments of this study.

6.2.12.7 Dropouts and/or Discontinuations

There were no dropouts from this study but one subject who received KamRAB + rabies vaccine was discontinued from the study because he tested positive for cannabis on study day 7.

Reviewer's comments: The discontinuation of one subject should not significantly impact the findings of this study even though the number of subjects enrolled in each cohort is small (n=8).

6.2.13 Study Summary and Conclusions

This was a Phase 1 placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of a single injection of KamRAB when co-administered with three injections of an active rabies vaccine (Rabipur®). Since RIG is known to interfere with rabies antibody production following rabies vaccination, the effect of KamRAB on rabies virus neutralizing antibody production following immunization with Rabipur® was also examined.

The study enrolled 16 young healthy Caucasian subjects. Fifteen subjects completed the study with one subject (Subject (b) (6) in the KamRAB group) withdrawn from the study because of a positive urine test for cannabinoids. The combination of KamRAB and Rabipur® was safe and well tolerated. There were no SAEs or deaths during the study. A total of 20 AEs was reported during the study with 9 AEs in the KamRAB group and 11 AEs in the placebo group. Of the nine AEs reported following KamRAB administration, 7 AEs (77.78%) were considered by the Investigator to be 'unrelated' and 2 AEs were considered by the Investigator to be 'unlikely' to be related to KamRAB and Rabipur®. No subjects in the KamRAB group reported injection-site pain or swelling while mild

Injection-site pain was reported by two subjects and mild local swelling by one subject in the placebo control group. These events were transient and resolved completely.

The pharmacokinetic profile of the two groups demonstrates that KamRAB interferes with RVNA production following rabies vaccination. The RVNA titer on Day 14 was 1.22 IU/mL in the KamRAB group versus 5.05 IU/mL in the Placebo group. Although the RVNA titer in response to the vaccine was lower with KamRAB co-administration, a therapeutic level (> 0.5 IU/mL) was still achieved. Similarly, the mean AUC_T for KamRAB is statistically significantly lower than mean AUC_T for the placebo formulation (95% CI: 10.14 – 100.42).

Reviewer's comments: These data are consistent with what has been demonstrated for other RIGs. That is, KamRAB interferes with the host immune response to rabies vaccination. However, despite the interference, Subjects were still able to mount an adequate immune response (RVNA ≥0.5 IU/mL) in response to the vaccine. Nonetheless, the applicability of this study to rabies PEP may be challenged by the purist since subjects received the vaccine according to a 3-dose PREP schedule.

6.3 Trial #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

6.3.1 Objectives

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

6.3.2 Design Overview

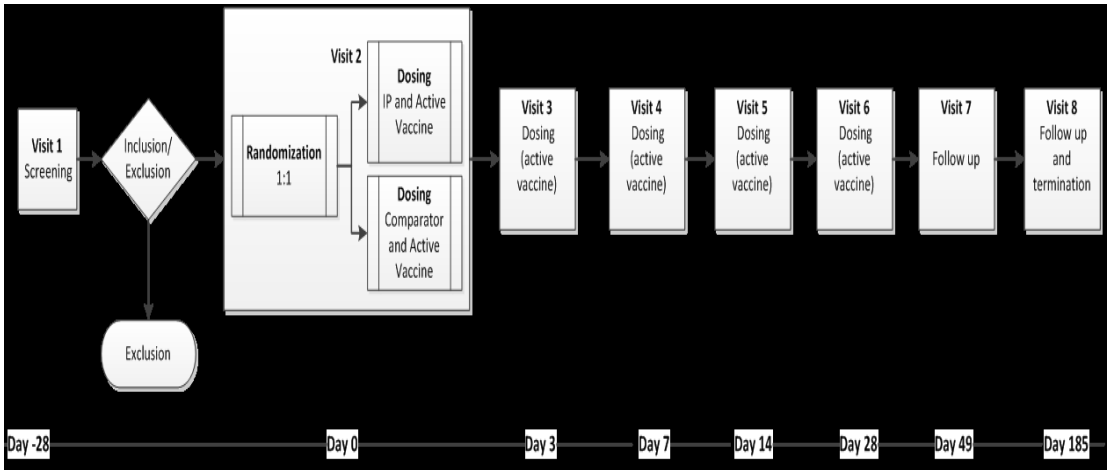
This was a single-center, prospective, randomized, double-blind, parallel-group study evaluating the safety and effectiveness of Kamada HRIG (KamRAB) compared with an HRIG commercially available in the US (HyperRAB®, Grifols Therapeutics Inc.) when co-administered with an active rabies vaccine (RabAvert® rabies vaccine, Novartis Vaccines and Diagnostics GmbH) in healthy male and female volunteers.

This study evaluated the non-inferiority of KamRAB to a HyperRAB, based on a pre-specified non-inferiority margin of -0.1 (i.e., -10%). A total of 118 healthy subjects who passed medical screening (Visit 1) and continued to meet the eligibility criteria at Visit 2 (Baseline and Randomization Visit, Day 0) were randomized to 1 of 2 treatment groups (59 subjects per group) to receive a single dose of KamRAB or HyperRAB (20 IU/kg). The Sponsor, Principal Investigator, and other staff members at the study site who may have had contact with the subject were blinded as to which HRIG product the subject received. Blinding of the study drugs (KamRAB and HyperRAB) was performed by a pharmacist who did not have contact with study subjects at the study site.

At Visit 2, blood samples were collected (to establish baseline efficacy and immunogenicity) and body weight was measured prior to dosing. KamRAB or HyperRAB and the first dose of the rabies vaccine (1.0 mL [≥2.5 IU/mL]) were

administered. Subjects were then observed for 1 hour for systemic and local reactions. Subjects subsequently received 4 more doses of rabies vaccine during the treatment period at Visit 3 (Day 3), Visit 4 (Day 7), Visit 5 (Day 14), and Visit 6 (Day 28). Follow-up visits were to be scheduled at Day 49 (± 4 days) and Day 185 (± 7 days) (Visits 7 and 8 [Termination Visit], respectively) (See Figure 1).

Figure 1: Study Design
(Applicant's Figure)



Serum samples for rabies immunoglobulin G (IgG) titer, immunogenicity markers (C3, C4, CH50), hematology, clinical biochemistry, and hemolysis assessment were collected at various time-points throughout the study as detailed below:

Days	**-28**	**0**	**3**	**7**	**14**	**28**	**49**	**185**
Rabies IgG		X	X	X	X	X	X	X
C3, C4, CH50	X	X			X		X	X
Hematology	X			X		X	X	X
Biochemistry	X			X		X	X	X
Urinalysis	X			X		X	X	X
Hemolysis		X	X	X	X	X		

At-home diary cards were completed by subjects (to record adverse events [AEs], concomitant medications and any additional information deemed relevant by the subject) for 14 days from the start of treatment (Day 0 to Day 14) and collected on Visit 5 (Day 14), or at the Early Discontinuation Visit (if discontinuation occurred during the 14 days of diary completion). AEs and concomitant medications were to be recorded throughout the study at all study visits.

Reviewer's comments

A placebo-controlled study of rabies post-exposure prophylaxis is unethical since it is a fatal disease with a therapy that is essentially 100% effective. Furthermore, HRIG must be administered in conjunction with a rabies vaccine as a component of the post-exposure prophylaxis that has been demonstrated to be safe and efficacious. The

vaccination doses and schedule were chosen as per the recommendations for the post-exposure rabies prophylaxis regimen of the CDC. Finally, effectiveness has to be assessed with surrogate markers such as the ability of the HRIG/vaccine combination to induce circulating anti-rabies antibody level of ≥0.5 IU/mL.

6.3.3 Population

Important Inclusion Criteria

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 judgment.
4. Non-pregnant, non-lactating female subjects, whose screening pregnancy test was negative and who were using contraceptive methods deemed reliable by the Principal Investigator, or who were more than 5 years post-menopausal or surgically sterilized.

Important Exclusion Criteria

1. History or laboratory evidence of immunoglobulin A (IgA) deficiency.
2. History of previous administration of rabies vaccine or HRIG.
3. History of live virus vaccine administration, e.g., measles vaccine, within the last 3 months.
4. Weight >93.75 kg
5. Previous organ transplant recipient.
6. Evidence of ongoing infection with HAV, HBV, HCV, HIV1, HIV2

Reviewer's comments

There are a number of patient populations that are excluded in this study including the pediatric, pregnant and lactating women, obese patients, immunocompromised and those co-infected with other chronic viral infections Therefore, care should be taken in the extrapolation of these data to these patient populations in the postmarketing setting.

6.3.4 Study Treatments or Agents Mandated by the Protocol

HRIG must be administered together with a rabies vaccine since the current therapy paradigm is to provide active and passive immunization consisting of localized infiltration of HRIG into and around the wound followed by immunization with rabies vaccine. The WHO recommends either a 4-dose or 5-dose vaccination schedule. The 4-dose regimen consist of two doses administered on day 0 followed by single doses on days 7 and 21. The five-dose regimen provides for single doses administered on days 0, 3, 7, 14 and 28. Since 2010, the CDC has recommended a 4-dose regimen for immunocompetent individuals with single vaccine doses administered on days 0, 3, 7 and 14. Those who are immunocompromised should continue to receive the 5-dose regimen. This study employs CDC's previously recommended 5-dose vaccine regimen. The study drugs administered in this study are presented in Table 12.

Table 12: Study Drugs
(Applicant's Table)

Treatment	Vial Size	Lot Number	Expiration Date	License Number
KamRAB	2 mL 10 mL	RA5020113A RA3131111B	Jan 2016 Nov 2014	138-88-31771
HyperRAB	2 mL 10 mL	26NL9R1 26NL431	Apr 12 2015 May 10 2014	1871
RabAvert	1 mL	517011A 519011C 524011C	Jun 2016 And Sep 2016	1754

6.3.5 Directions for Use

KamRAB or HyperRAB was administered as a single dose of 20 IU/kg body weight via IM injection on Day 0. The first 5 mL of the KamRAB or HyperRAB dose was to be administered to the left leg lateral muscle; the remainder (up to 5 mL) was to be administered to the right leg lateral muscle. Additional amounts up to 2.5 mL (for a subject >75 kg but ≤93.75 kg) were to be administered to the left arm deltoid muscle. The right arm deltoid muscle was to be utilized for the administration of the rabies vaccine. KamRAB or HyperRAB was never to be administered into the same anatomical site as vaccine, because it could partially suppress active production of antibody.

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

6.3.6 Sites and Centers

This study was conducted at a single study center: Prism Research located at 1000 Westgate Drive, Suite 149 in St Paul, MN.

6.3.7 Surveillance/Monitoring

Please refer to Table 5 Schedule of Events on page 32-33 of the KAMRAB-003 Clinical Study Report.

6.3.8 Endpoints and Criteria for Study Success

The standard treatment for a patient exposed to rabies is to provide immediate passive immunity HRIG while simultaneously vaccinating the individual with a rabies vaccine. This regimen is critical as the HRIG immediately neutralizes the virus while awaiting the host's adaptive immune response. During the initial phase of active immunity, the predominance of antibodies is of the IgM subclass, followed in days to weeks by the development of IgG antibodies. The Rapid Fluorescent Focus Inhibition Test (RFFIT), a validated assay for determining rabies virus neutralizing antibody (RVNA), measures the combined neutralizing activity of IgG and IgM antibodies, from passive and active immunity, and is considered the appropriate test to ascertain the effectiveness of rabies vaccination. By the time the primary endpoint was measured in this study (i.e., 14 days after vaccination), the subject's RVNA reflects the combined activity of both passive and

active immunity, with the major contribution due to the subject's immune response to vaccination and only a minor contribution conferred by the passive HRIG.

The primary endpoint was a dichotomous (0-1) variable, defined by reaching an anti-rabies IgG concentration ≥ 0.5 IU/mL on Day 14. Subjects treated with HRIG and rabies vaccine are expected to develop a relatively high rabies antibody titer with a concentration ≥ 0.5 IU/mL deemed protective. The criterion of response was the proportion of subjects with anti-rabies IgG titer ≥ 0.5 IU/mL antibody measured on Day 14. The primary hypothesis was that the proportion of subjects treated with KamRAB + vaccine with anti-rabies concentration ≥0.5 IU/mL on Day 14 would not be less than 90% of the proportion of subjects treated with HyperRAB + vaccine. The upper limit of the 90% binomial confidence interval would be 0.1 or 10%..

The secondary endpoints that were evaluated included

1. Pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty,}$ and $t_{1/2}$ of anti-rabies IgG concentrations.
2. Safety and tolerability as assessed by
    - local and systemic reactions classified according to timing after injection and relationship to treatment
    - hematology, serum chemistry, serology and urinalysis
    - unsolicited AEs

Reviewer's comments: There was an error in the terminology used in the protocol, SAP, and source tables for this study. The anti-rabies IgG antibody concentrations cited in the primary efficacy and PK results are more accurately described as RVNA titers. These were assessed with the RFFIT test which measures both anti-rabies IgG and IgM and is the gold standard for the detection of RVNA titer in serum. RFFIT was the test pre-specified in the protocol for the evaluation of the primary endpoint. Therefore, the anti-rabies IgG antibody concentration cited in this BLA actually represents RVNA titer.

The optimal time-point for evaluating the activity of HRIGs is likely between Days 3 and 7 when the serum RVNA from the HRIG is at its peak. In Study 23630, the geometric mean titer of C_{max} for KamRAB was 0.21 IU/mL on Day 7; a titer that is only 40% of the recommended level of 0.5 IU/mL. However, it should be noted that the two comparator HRIGs (BayRAB and HyperRAB) administered in these studies also did not achieve this target level. A review of the literature reveals that other HRIGs when administered at 20 IU/kg are also unable to produce a RVNA of 0.5 IU/mL. In fact, one group suggested that the dose of HRIGs should be increased to 40 IU/kg but this recommendation was never adopted because there was greater interference with the effect of the rabies vaccine. Finally, it should be emphasized that HRIG acts locally where the tissue levels would be expected to be much higher than plasma levels.

6.3.9 Statistical Considerations & Statistical Analysis Plan

6.3.9.1 Sample size determination

The primary analysis was based on a concentration proportion (Cp), the difference between KamRAB and control in the proportions of subjects with serum anti-rabies concentration ≥ 0.5 IU/mL at Day 14. The null hypothesis was that Cp would be ≤ -0.1.

In the KamRAB003 PK study as well as a published study of HRIG given with rabies vaccine, 100% of subjects reached an anti-rabies IgG concentration of at least 0.5 IU/mL.

It is conservatively assumed that since a reference group achieves a proportion of at least 0.95, the power of this study can be computed based on the premise that the true proportion for the treatment group is also 0.95. A sample size of 53 in each group achieves 80% power to conclude non-inferiority (NI) using a NI margin (tolerable difference between groups proportions) of -0.10. This power calculation assumes that under the null hypothesis of inferiority, the treatment group proportion is 0.85. The test statistic was to be the one-sized Z test with a significance level of 0.05. Allowing for 10% loss, the sample size was increased to 59 in each group.

6.3.9.2 Demographics and baseline characteristics Analysis

The demographic characteristics of the study population including age, sex, race, ethnicity, height, weight, and BMI were analyzed. All demographic data were to be summarized and listed. Medical history data were also to be listed. An analysis of variance (ANOVA) was used to assess homogeneity regarding demographic characteristics in the various treatment groups. Sex and race differences were not expected to influence the PK pattern. For quantitative variables, number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum were to be presented. For qualitative data, n, number of occurrences, and percentage were to be provided. The Wilcoxon Rank Sum Test was used in the case of skewed data; otherwise, a t-test was used. For categorical data, the Pearson Chi-square test was used.

6.3.9.3 Study populations

Analysis of the study was performed on the following three populations:

1. Safety Population: The Safety Population was to include 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.
2. As-Treated Population: The As-Treated Population was to include all randomized subjects who received at least three vaccine doses (until Day 14 before the serum sample was taken) and one dose of the HRIG. Per protocol, the analysis of the primary efficacy endpoint was to be performed on the As-Treated Population.
3. Pharmacokinetic Population: The PK Population was to include all subjects in the Safety Population who had at least one PK parameter available.

6.3.9.4 Dropouts and imputation of missing data

Enrolled subjects who did not receive study medication were considered dropouts. Enrolled subjects who received study medication and did not complete the study, including the follow-up period, for any reasons that led to subject discontinuation, were also considered dropouts. Dropouts were not replaced.

There was no imputation of missing data. In the case of determining baseline values, the last non-missing measurement prior to the first dose was to be used.

A total of 7 subjects either discontinued treatment (n=5) or did not receive all 5 doses of vaccine (n=5) during the study; 3 of these subjects (2 KamRAB,1 HyperRAB) were excluded from the As-Treated Population. A summary of dropouts and missing data for these subjects are presented in Table 13.

Table 13: Summary of Subjects who Missed Vaccination(s) or Discontinued from Study
(Applicant's Table)

ID #	Tx Group	Missed Vaccine Dose (Day)					Subject D/C	Subject Included in As-Treated Population	IgG Titer (Day)	
		0	3	7	14	28			0	14
0021	KamRAB			X			N	N	0.04	0.32
0054	KamRAB						Y	Y	0.04	24.5
0062	HyperRAB			X	X	X	Y	N	1.74	724.1
0076	KamRAB						Y	N	0.04	---
0087	HyperRAB						Y	Y	0.04	65.4
0108	HyperRAB					X	N	Y	0.04	61.2
0114	KamRAB				X	X	Y	Y	0.04	25.6

There were 3 subjects with missing data who either discontinued the study after Day 14 (**Subject 0054** and **Subject 0087**) or did not receive all 5 doses of vaccine (**Subject 0108**). All of these subjects met the criteria for inclusion in the As-Treated Population and were included in the evaluation of the primary endpoint at Day 14.

The 3 subjects who were not included in the As-Treated Population are as follows:

- **Subject 0021**, in the KamRAB group, did not arrive for the Day 7 visit and missed this dose of vaccine. The subject did receive vaccine at baseline and Days 3, 14, and 28. Nonetheless, this subject did not meet the definition for the As-Treated Population and was excluded.
- **Subject 0062**, in the HyperRAB group, met the definition required for the As-Treated Population (i.e., received HRIG and all 5 doses of vaccine) but had a higher than expected level of plasma anti-rabies antibody level at baseline (as well as on Days 3, 7, and 14). Prior to unblinding, the experts at the Kansas State Veterinary Diagnostic Laboratory were consulted and it was determined that the most probable explanation was previous exposure to rabies or rabies vaccine.
- **Subject 0076**, in the KamRAB group, received only 2 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.

An additional subject (**Subject 0114**) discontinued participation in the study before Day 14, and thus the Day 14 data were treated as missing in the primary efficacy analysis. However, this subject had data from the Early Discontinuation Visit on Day 14. A post-hoc sensitivity analysis was conducted using these available data for Day 14, instead of treating it as missing; these results indicate that the exclusion of the subject's data from the primary efficacy analysis did not change its outcome.

6.3.9.5 Anti-Rabies Antibody Concentration Analysis

The concentration-time courses of anti-rabies antibody titers were summarized separately for each treatment group in the As-Treated Population. Since multiple assayed anti-rabies antibody titers levels were reported for each PK sampling time, the geometric mean anti-rabies antibody titer (GMT) was calculated at each PK time point. However, for each PK sampling time, all of the assayed anti-rabies antibody titer levels in addition to the calculated GMT were listed for each subject. Individual and mean plasma anti-rabies antibody titers (GMT only) versus time curves were plotted by treatment group and presented on both linear and semi-logarithmic scales. The following statistics were calculated for each of the sampling points: arithmetic mean, standard deviation (SD), and coefficient of variation (CV), geometric mean, geometric SD (re-transformed SD of the logarithms) and CV, minimum, median, maximum value, and the number of measurements. A t-test was performed to compare the GMT at each scheduled PK sampling time point between the KamRAB and HyperRAB treatment groups. Log-transformation of the GMT data at each PK sampling time was to be performed as necessary during statistical testing to meet assumptions for normality.

6.3.9.6 Primary Endpoint Analysis

The primary analysis was based on the difference in the geometric mean anti-rabies antibody titers (GMT) between KamRAB and HyperRAB in the proportions of subjects with a GMT $\geq$ 0.5 IU/mL at Day 14. The null hypothesis was that the difference in the GMT would be $\leq$ -0.1. The null hypothesis would be rejected at the one-sided 5% significance level, and the difference in the GMT > -0.1 would be concluded, if the lower bound of an exact 90% binomial confidence interval (CI) was greater than -0.1.

6.3.9.7 Secondary Endpoints Analysis

6.3.9.7.1 Pharmacokinetics

Non-compartmental PK methods were utilized to calculate selected PK parameters (C_{max}, t_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$) for each subject using only the GMT calculated at each PK time point. Anti-rabies antibody titers reported as below the lower limit of quantification (LLOQ) of 0.07 IU/mL were to be assigned a value of 0.04, which represents 50% the LLOQ rounded to 2 decimal places. Dose-normalized C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$ were generated by dividing the PK parameters by the actual dose the subject received. A t-test was performed to compare the PK parameters and dose-normalized PK parameters between the KamRAB and HyperRAB treatment groups. Log-transformation of the PK parameters was performed as necessary during statistical testing to meet assumptions for normality.

6.3.9.7.2 Safety and Tolerability

All analyses of treatment emergent AEs (TEAEs) were performed using the Safety Population. The incidence of any immediate reaction was summarized by severity, relationship with study medication, group, and body system. Summary tables were presented for the frequency of immediate reactions within the 60-minute and 24-hour periods after injection in subjects from both treatment groups.

Incidence tables were presented for AEs within the first 60 minutes, the first 72 hours, the first week, and throughout the study since the administration of HRIG. The incidence of AEs occurring in more than 5% of subjects during the first 72 hours of HRIG treatment (irrespective of Principal Investigator assessment) was presented. The incidence of drug-

related AEs during the first 72 hours, the first week, and throughout the study since the time of HRIG treatment was also presented.

Local and systemic reactions were summarized for each group. The frequency of solicited local and systemic reactions was presented by each reaction, severity, relationship, and treatment group. An exact 95% CI was to be constructed for the proportion of the immediate, local, and systemic reactions for each treatment group.

Unsolicited AEs were assessed based from the time of study treatment administration through the Day 185 Follow-up Visit. The Principal Investigator was to follow a subject with any AE until the event was either resolved or determined to be stable. The investigator was to evaluate and report the onset date and time, outcome and outcome date and time, severity (intensity), relationship to study drug, actions taken, and determination of seriousness for each AE. The data were listed individually and summarized by system organ class (SOC) and preferred terms within a SOC for each treatment group. The incidence of unsolicited AEs was summarized by maximum severity and strongest relationship to study drug. If the same AE occurred on multiple occasions, the highest severity and least favorable relationship were assumed. If two or more AEs were reported as a unit, the individual terms were to be reported as separate experiences. Dates and times for AEs were not to be imputed. In the case that a missing date or time led to ambiguity in whether an AE occurred prior to or after treatment with drug, that AE was classified as an unsolicited AE.

All AEs were to be coded by using the Medical Dictionary for Regulatory Activities (MedDRA Version 16.1).

6.3.9.7.3 Laboratory Parameters

All safety laboratory results were tabulated for the Safety Population. They were tabulated by time point and type (biochemistry, hematology) by using summary statistics (number of observations, mean, SD, median, minimum, and maximum) for continuous data and by using proportion for categorical data. The change from baseline (pre-treatment) for laboratory values was tabulated as above. All laboratory results were listed for the Safety Population; any values that lie outside the normal range or were clinically significant were flagged.

All vital signs (weight, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature) and ECGs were tabulated on the Safety Population. Vital signs and ECGs were summarized by time point by using summary statistics (number of observations, mean, SD, median, minimum, and maximum). The change from baseline (pre-treatment) of vital signs and ECGs were tabulated as above. A shift table was to be used for categorical data. All vital signs and ECGs were listed for the Safety Population; any values that lie outside the normal range or were clinically significant were flagged.

Serology, immunogenicity, and physical examination were summarized by time point.

Concomitant medication data collected during the study were to be listed.

6.3.10 Study Population and Disposition

6.3.10.1 Population Enrolled/Analyzed

This study was conducted in young, healthy, normal volunteers. A total of 236 subjects were screened with 118 subjects randomized in 1:1 ratio to receive either KamRAB + rabies vaccine or HyperRAB + rabies vaccine (Table 14). Subject disposition was comparable between the treatment groups. Overall, 113 subjects (95.8%) completed the study and 5 subjects (4.2%) terminated early. The most common reason for early termination was AE in 2 subjects (1.7%); both of whom were in the KamRAB group.

Table 14: Disposition of Study Subjects
(Applicant's table)

	KamRAB + Vaccine N (%)	HyperRAB + Vaccine N (%)	Overall N (%)
Subjects Screened	---	---	236
Subjects Randomized	59	59	118
Subjects Randomized & Treated	59	59	118
Subjects Completed Study	56 (94.9)	57 (96.6)	113 (95.8)
Subjects Terminated Early	3 (5.1)	2 (3.4)	5 (4.2)
Primary Reason for Termination			
Adverse event	2 (3.4)	0	2 (1.7)
Protocol deviation	0	0	0
Withdrawal by subject	0	1 (1.7)	1 (0.8)
Lost to follow-up	0	1 (1.7)	1 (0.8)
Death	0	0	0
Investigator's discretion	1 (1.7)	0	1 (0.8)

Reviewer's comments: Kamada provided data for screening failures in the following Table during the mid-cycle review.

Table A: Reasons for Screen Failure
(Applicant's Table)

Reason For Screen Failure	***Subject #***
Concomitant medication	*1*
Failed drug/alcohol screen	*5*
Abnormal Lab results	*14*
Poor venous access	*1*
Non-qualifying creatinine clearance	*0*
Volunteer withdrew consent	*20*
Abnormal ECG	*2*
Abnormal Vital Signs	*14*
Others	*61*
Allergic reactions to vaccine	*1*
Blood draw intolerance	*1*
Medical history	*24*
Noncompliance	*2*
Scheduling issues	*7*
Weight	*3*
Screening window expired	*2*
Study hold	*19*

Enrollment completed	*2*
Total	*118*

The three most common causes of screen failure were prior medical history (24), withdrawal of consent (20), and study hold (19).The latter refers to the 19 subjects who were screened and were eligible for enrollment but were not randomized into the study because the study was placed on an administrative hold for protocol revisions.

6.3.10.1.1 Demographics

The subjects in this study 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 median BMI was 26.32 kg/m^2.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

This study enrolled a population of healthy subjects.

6.3.10.1.3 Subject Disposition

Overall, 113 of the 118 subjects (95.8%) completed the study. There were 5 subjects (4.2%) who terminated early; three subjects in the KamRAB group and two in the HyperRAB group. The most common reason for early termination was AEs in 2 subjects (1.7%); both of whom were in the KamRAB group.

6.3.11 Efficacy Analyses

6.3.11.1 Analysis of Primary Endpoint(s)

There were only 56 KamRAB subjects included in this analysis despite a total of 57 subjects in the As-Treated Population. One of the subjects (**Subject 0114**) was not included in the primary analysis because she was withdrawn from the study on Day 14 due to an AE (nipple pain). However, she was included in a post-hoc sensitivity analysis (See Section 6.3.11.5). Nonetheless, 55 of the 56 subjects in the KamRAB group (98.2%; 95%CI: 90.4, 100) and all 58 subjects (95%CI: 93.8, 100) in the HyperRAB group had an anti-rabies IgG antibody titer ≥0.5 IU/mL on Day 14. The difference between the proportion of subjects with an anti-rabies IgG antibody titer ≥0.5 IU/mL on Day 14 in the KamRAB and HyperRAB groups was -1.8% (90% CI: -8.2, 3.1). The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of -10%, thus demonstrating that KamRAB was non-inferior to HyperRAB for the primary endpoint.

One subject in the KamRAB group, **Subject 0024**, did not achieve an anti-rabies IgG antibody titer of ≥0.5 IU/mL on Day 14. This subject had a titer that was below the level of quantitation at baseline, and was 0.12 IU/mL on Days 3 and 7, 0.18 IU/mL on Day 14, 0.81 IU/mL on Day 28, 0.88 IU/mL on Day 49, and 0.38 IU/mL on Day 185. Additional details on Subject 0024 were provided during the mid-cycle review. Subject 0024 was a 62 year-old non-Hispanic white female with a previous medical history of bilateral prophylactic mastectomy and complete hysterectomy, with ongoing seborrheic keratoses, anxiety, and obesity. Her height was 163 cm, weight 82 kg, and BMI 30.7 kg/m^2. Current medications included Effexor, and previous medications included clindamycin and Vicodin. She was screened for enrollment on 10 April 2013, and received KamRAB (11 mLs, 1650 IU) and her first dose of rabies vaccine (1 mL) on 7 May 2013. Subsequent doses of rabies vaccine were administered on 10 May, 14 May, 21 May, and 4 June. Treatment-emergent adverse events which occurred during the study

were gingivitis starting on 11 May 2013 and resolving on 25 June 2013, and tenosynovitis stenosans (left de Quervain's tendonitis), starting on 20 June 2013 and resolving on 12 October 2013. Both AEs were assessed as moderate in severity and not related to treatment. She completed follow up per protocol.

Reviewer's comments: There were no apparent factors that would impact the efficacy of KamRAB in Subject 024. Her age (62 years) may have predisposed her to a lower antibody response to active rabies vaccine as compared to a younger subject. However, a review of the literature as well as communications from the Kansas State Veterinary Laboratory reflecting more recent data confirm that not all persons receiving a rabies post-exposure prophylaxis regimen will achieve a protective antibody level of 0.5 IU/ml by Day 14. Thus, the failure of one subject who was treated per protocol is not unexpected. Furthermore, it appears the failure is not due to KamRAB but more likely represents an attenuated immune response to the vaccine.

6.3.11.2 Analyses of Secondary Endpoints

The PK analysis population comprised of 117 of the 118 healthy volunteers in whom PK samples were collected. One subject (Subject 0062) in the HyperRAB group was excluded from the PK analysis population due to having a higher than expected baseline plasma HRIG concentration. Based upon examination of all the data from that subject, it was retrospectively postulated that the subject had either been previously vaccinated or exposed to rabies antigen.

The PK data for the 117 subjects are presented in Table 15. There were no statistically significant differences for the majority of the pharmacokinetic parameters ($AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, K_{el} or $t_{½}$) between the KamRAB and HyperRAB groups, even when normalized for the dose administered.

Table 15: Pharmacokinetics Parameters (Geometric Mean) – Study 003
(Reviewer's table)

Parameter (units)	KamRAB				HyperRAB			
	Mean	%CV	Min	Max	Mean	% C	Min	Max
$AUC_{0\text{-t}}$ (day*IU/ml)	2282.2	84.1	1.3	9008.3	2224	75.5	133.6	7606.1
AUC_{∞} (day*IU/ml)	2900.5	85.3	184.6	11019.9	4259.2	291.1	312.4	86435.
C_{max} (IU/ml)	67.5	142.0	0.25	655.1	54.1	100.1	1.09	328.3
T_{max}* (day)	14	-	3	49	14	-	14	49
K_{el} (day^{-1})	0.015	38.7	0.003	0.026	0.013	33.4	0.0002	0.022
$T_{1/2}$ (day)	59.1	62.9	26.5	245.6	138.2	394.8	31.20	3790.8

However, the plasma anti-rabies immunoglobulin concentration was statistically significantly lower in the KamRAB group at the Day 3 timepoint (0.176 vs 0.216 IU/mL, $p<0.0003$). Data are presented in the Table below as the geometric mean of the plasma concentration (IU/mL) in Table 16.

Table 16: Plasma anti-rabies immunoglobulin concentration over time
(Reviewer's table)

	D0	D3*	D7	D14	D28	D49	D185
KamRAB	0.041	0.176	0.241	37.2	16.5	9.10	1.59
HyperRAB	0.040	0.216	0.284	32.3	16.3	9.82	1.88

All Subjects also received RabAvert on Days 0, 3, 7, 14 and 28 *p=0.0003

Reviewer's comments
Kamada was asked at the mid-cycle review to discuss the rationale for selecting D14 as the time point for assessing this potential marker of efficacy as opposed to D3. Kamada responded that antibody levels of 0.5 IU/mL are considered protective against rabies after administration of PEP although there are no definitive human data. However, this level is not generally attained until Day 14, and even then is not attained in all PEP recipients. 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.

Day 3 serum levels are less likely to be reflective of true potency, as there has been less time for the passive immunoglobulin administered intramuscularly to be absorbed and distributed systemically. Most published studies of PEP do not assess antibody levels at Day 3. Of those studies that have reported antibody levels at Day 3, antibody levels are low and variable, with geometric means less than 0.2 IU/mL, and individual values ranging to the lower limit of quantification of the assay (0.1 IU/mL, Kansas State Laboratory; 0.07 IU/ml for assays performed for KamRAB-003). These published results are consistent with analyses performed between 2010 and 2014 at the Kansas State University Veterinary Diagnostic Laboratory for clinical studies of PEP (not with KamRAB), in which RFFIT results at Day 3 were below 0.5 IU/mL in >90% of samples, and below 0.2 IU/mL in >50% of samples; at Day 7 levels were below 0.5 IU/mL in >80% of samples and below 0.2 IU/mL in 25-64% of samples.

In the KamRAB-003 study 58/59 subjects in the KamRAB group and 59/59 subjects in the HRIG Comparator group had RNVA levels that were near the limit of quantitation of the assay on Day 3. Day 7 levels were generally higher, but mean titers are still well below 0.5 IU/mL and for many samples were below 0.2 IU/mL. At Day 14 most recipients of PEP achieve levels of 0.5 IU/mL, although some have late and low responses to vaccination and do not achieve this level until Day 28. At the Kansas State University laboratory between 1.4-13.0% of samples were below 0.5 IU/mL at Day 14. Thus, despite some "failures", Day 14 is most commonly cited in the literature as to the day by which protective target antibody levels should have been reached for those receiving PEP, even though the antibody measured on that day is a mixture of both passive and active immunity.

6.3.11.3 Subpopulation Analyses

There was no subpopulation analysis since these were a homogeneous population of young, healthy Caucasian volunteers.

6.3.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.3.10.1.3 Subject Disposition for subject dropouts and/or discontinuations.

6.3.11.5 Exploratory and Post Hoc Analyses

A post-hoc sensitivity analysis was conducted to evaluate the primary efficacy endpoint result including data from Subject 0114. Subject 0114 was discontinued from the study on Day 7 and thus did not have a Day 14 value. Coincidentally, the subject's Early Discontinuation Visit was conducted on Day 14. Therefore, a post-hoc sensitivity analysis was conducted to evaluate the primary efficacy endpoint using the subject's Early Discontinuation Visit data for the Day 14 data, instead of treating it as missing. In this analysis, the Early Discontinuation Visit IgG concentration value was used as Visit 5 (Day 14), instead of treating it as missing. Results were consistent with the primary efficacy results, and showed that KamRAB was non-inferior to HRIG Comparator based on the difference in the proportion of subjects with an anti-rabies IgG antibody titer ≥0.5 IU/mL (-1.8% [90% CI: -8.1, 3.2]).

6.3.12 Safety Analyses

The safety and tolerability of the IP were to be evaluated using the incidence of clinically significant abnormal findings in measurements for objective tolerability, i.e., vital signs, ECG, laboratory (hematology, clinical chemistry, and urinalysis), thrombogenicity, hemolysis, and the occurrence of AEs after drug administration. A laboratory test abnormality considered clinically relevant/significant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the Principal Investigator, was reported as an AE. Each event was described in detail along with start and stop dates, severity, relationship to study drug, action taken, and outcome.

6.3.12.1 Methods

Safety and tolerability assessments were to occur based on the schedule of events in Section 6.3.7 Surveillance/Monitoring. Subjects were to be carefully monitored for AEs. The AE monitoring was to be done throughout the study, beginning at the time a subject provided informed consent and continuing until the last visit. This monitoring was to include, but was not limited to, clinical laboratory tests, physical examination, and vital signs monitoring. Adverse events were to be assessed in terms of their seriousness, severity, and relationship to the study drug.

When in the clinic, subjects were to remain at the study site for one hour after receiving study drug for observation of any local or systemic adverse effects. When out of the clinic, at-home diary cards were to be completed by subjects (to record AEs, concomitant medications, and any additional information deemed relevant by the subject) for 14 days from the start of treatment (Day 0 to Day 14) and collected on Visit 5 (Day 14), or at the Early Discontinuation Visit (if discontinuation occurred during the 14 days of diary completion).

Subjective well-being and AEs were to be assessed by asking non-leading questions at all visits. Any change in subjective well-being of the subjects was to be documented. Adverse events were to be followed up until the event resolved according to the judgment of the Principal Investigator.

6.3.12.2 Overview of Adverse Events

All 118 subjects received a single dose of KamRAB (59 subjects) or HyperRAB (59 subjects). All but 5 subjects (4 in the KamRAB group [6.8%] and 1 in the HyperRAB

group [1.7%]) received all 5 doses of rabies vaccine. **Subject 0076** in the KamRAB group received 2 doses of vaccine, **Subject 0114** in the KamRAB group received 3 doses of vaccine, and **Subject 0021** and **Subject 0054** in the KamRAB group and **Subject 0108** in the HyperRAB group each received 4 doses of vaccine.

Overview of Adverse Events (**Safety Population)**
The incidence of TEAEs (per the Investigator) was comparable between the KamRAB and HyperRAB groups (81.4% and 86.4%, respectively; p=0.62). The incidences of drug-related TEAEs, SAEs, and TEAEs leading to discontinuation of study treatment were also comparable between the KamRAB and HyperRAB groups (all p-values ≥0.46). No deaths occurred during this study. The data are presented in Table 17.

Table 17: Treatment Emergent Adverse Events
(Applicant's Table)

	Number (%) of Subjects		
	KamRAB + Vaccine (N=59)	**HyperRAB + Vaccine (N=59)**	**Overall**
ALL TEAEs	48 (81.4%)	51 (86.4%)	99 (83.9%)
Related TEAE	32 (54.2%)	27 (45.8%)	59 (50%)
Serious TEAE	1 (1.7%)	0	1 (0.8%)
TEAT precipitating Discontinuation	2 (3.4%)	0	2 (1.7%)
TEAE leading to death	0	0	0

Overview of Immediate Reactions (Safety Population)
The incidence of immediate TEAEs (i.e., AEs occurring within 60 minutes, 24 hours, or 72 hours following administration of study treatment) was comparable between the KamRAB and HyperRAB groups (all p-values ≥0.58). The data are presented in Table 18.

Table 18: Immediate Treatment Emergent Adverse Events
(Applicant's Table)

	Number (%) of Subjects		
	KamRAB + Vaccine (N=59)	**HyperRAB + Vaccine (N=59)**	**Overall**
Immediate TEAE within 60 minutes	15 (25.4%)	13 (22.0%)	28 (23.7%)
Immediate TEAE within 24 hours	26 (44.1%)	24 (40.7%)	50 (42.4%)
Immediate TEAE within 72 hours	31 (52.5%)	27 (45.8%)	58 (49.2%)

Overview of Local and Systemic Reactions (Safety Population)
The incidence of systemic reactions was comparable between the KamRAB and HyperRAB groups (p=1.00) while the incidence of local reactions was numerically

higher in the KamRAB group (42.4%) compared with the HyperRAB group (32.2%; p=0.34). The data are presented in Table 19.

Table 19: Local and Systemic Adverse Events
(Applicant's Table)

	Number (%) of Subjects		
	KamRAB + Vaccine (N=59)	**HyperRAB + Vaccine (N=59)**	**Overall**
Local Reactions	25 (42.4%)	19 (32.2%)	44 (37.3%)
Systemic Reactions	13 (22.0%)	14 (23.7%)	27 (22.9%)

Common Treatment Emergent AE – System organ Class (≥20% Frequency – Safety Population)
System organ classes with the highest TEAE incidence (i.e., ≥20% in each treatment group) during treatment in the KamRAB and HyperRAB groups, respectively, were General disorders and administration site conditions (52.5% and 45.8%), Musculoskeletal and connective tissue disorders (30.5% and 23.7%), and Nervous system disorders (25.4% and 23.7%) The incidences of TEAEs in each SOC were comparable between treatment groups.

Common Treatment Emergent AE – Preferred Term (>3% Frequency – Safety Population)
The most common TEAEs (i.e., those occurring in ≥3% of subjects overall) are presented in Table 20. The most frequently reported TEAEs in the KamRAB and HyperRAB Comparator groups, respectively, were injection-site pain (49.2% and 39.0%), headache (13.6% and 15.3%), upper respiratory tract infection (13.6% and 13.6%), and myalgia (13.6% and 10.2%).

Table 20: Common TEAE – Preferred Term (Safety Population)
(Applicant's Table)

Preferred Term	**KamRAB + Vaccine (N=59)**		**HyperRAB + Vaccine (N=59)**		**Overall (N=118)**	
	N (%)	**Events**	**N (%)**	**Events**	**N (%)**	**Events**
Any TEAE	48 (81.4)	162	51 (86.4)	160	99 (83.9)	322
Injection-site pain	29 (49.2)	59	23 (39.0)	43	52 (44.1)	102
Headache	8 (13.6)	8	9 (15.3)	10	17 (14.4)	18
URI	8 (13.6)	9	8 (13.6)	11	16 (13.6)	20
Myalgia	8 (13.6)	8	6 (10.2)	6	14 (11.9)	14
Nausea	4 (6.8)	4	2 (3.4)	3	6 (5.1)	7
Dizziness	3 (5.1)	3	2 (3.4)	3	5 (4.2)	6
Presyncope	4 (6.8)	4	1 (1.7)	1	5 (4.2)	5
Pain in extremity	2 (3.4)	2	3 (5.1)	3	5 (4.2)	5
Arthralgia	4 (6.8)	4	0	0	4 (3.4)	4
Back pain	2 (3.4)	2	2 (3.4)	2	4 (3.4)	4

Fatigue	3 (5.1)	3	1 (1.7)	1	4 (3.4)	4
Diarrhea	2 (3.4)	2	2 (3.4)	2	4 (3.4)	4
Ecchymosis	3 (5.1)	3	1 (1.7)	1	4 (3.4)	4
Laceration	2 (3.4)	3	2 (3.4)	3	4 (3.4)	6

Reviewer's comment:
The incidence of the most common TEAEs was generally comparable between the two groups, with the exception of a higher incidence of injection-site pain in the KamRAB group (49.2%) compared with the HyperRAB group (39.0%). However, injection-site pain could have been a result of either the HRIG or rabies vaccine injection in both treatment groups.

Treatment Emergent AE by Time Interval
The TEAEs occurring in at least 3% of subjects overall by time interval (i.e., the first 60 minutes, 24 hours, 72 hours, and 1 week post-HRIG administration) are presented in Table 21. The incidence of TEAEs that occurred in at least 3% of subjects overall was generally comparable between treatment groups at 60 minutes, 24 hours, 72 hours and 1 week. The only exception was a higher incidence of injection-site pain in the KamRAB group (range: 20.3% to 44.1%) compared with the HyperRAB group (range: 13.6% to 33.9%) across all time intervals.

Table 21: Time to Occurrence of TEAE
(Applicant's Table)

Preferred Term	Number (%) of Subjects		
	KamRAB + Vaccine (N=59)	HyperRAB + Vaccine (N=59)	Overall (N=118)
Within the first 60 minutes post-HRIG	15 (25.4)	14 (23.7)	29 (24.6)
Injection-site pain	12 (20.3)	8 (13.6)	20 (16.9)
Within the first 24 hours post-HRIG	31 (52.5)	30 (50.8)	61 (51.7)
Injection-site pain	22 (37.3)	17 (28.8)	39 (33.1)
Headache	3 (5.1)	2 (3.4)	5 (4.2)
Nausea	3 (5.1)	1 (1.7)	4 (3.4)
Within the first 72 hours post-HRIG	36 (61.0)	35 (59.3)	71 (60.2)
Injection-site pain	26 (44.1)	18 (30.5)	44 (37.3)
Headache	3 (5.1)	5 (8.5)	8 (6.8)
Myalgia	0	4 (6.8)	4 (3.4)
Nausea	3 (5.1)	1 (1.7)	4 (3.4)
Within the first week post-HRIG	40 (67.8)	38 (64.4)	78 (66.1)
Injection-site pain	26 (44.1)	20 (33.9)	46 (39.0)
Headache	4 (6.8)	6 (10.2)	10 (8.5)
Myalgia	2 (3.4)	4 (6.8)	6 (5.1)
Nausea	3 (5.1)	2 (3.4)	5 (4.2)
Upper respiratory tract infection	2 (3.4)	2 (3.4)	4 (3.4)

The TEAEs reported as occurring within the first 60 minutes and 24 hours post-HRIG (i.e., after receiving 1 dose of HRIG and 1 dose of rabies vaccine) in at least 3% of subjects overall included injection-site pain (16.9%) within 60 minutes post-HRIG and injection-site pain (33.1%), headache (4.2%), and nausea (3.4%) within 24 hours post-HRIG.

The TEAEs reported as occurring within the first 72 hours post-HRIG (i.e., after receiving 1 dose of HRIG and 2 doses of rabies vaccine) in at least 3% of subjects overall included injection-site pain (37.3%), headache (6.8%), myalgia (3.4%), and nausea (3.4%).

The TEAEs reported as occurring within the first week post-HRIG (i.e., after receiving 1 dose of HRIG and 3 doses of rabies vaccine) in at least 3% of subjects overall included injection-site pain (39.0%), headache (8.5%), myalgia (5.1%), pain in extremity (4.2%), nausea (4.2%), and upper respiratory tract infection (3.4%).

From within the first 60 minutes post-HRIG through the first week post-HRIG, the most frequently reported TEAE in both treatment groups was injection-site pain. Headache and nausea were reported in both treatment groups within the first 24 hours post-HRIG administration through the first week post-HRIG. Myalgia occurred only in the HyperRAB group within 72 hours of administration but was reported in both treatment groups within the first week post-HRIG.

Drug-related treatment-emergent adverse events
Drug-related (relatedness is defined as related, probable, and definite) TEAEs as determined by the Investigator occurring in at least 3% of subjects overall are presented in Table 22. The most frequently reported drug-related TEAEs in the KamRAB and HyperRAB Comparator groups, respectively, were injection-site pain (42.4% and 28.8%), headache (3.4% and 5.1%), and myalgia (1.7% and 5.1%). The incidences of the most frequently reported drug-related TEAEs were generally comparable between the two treatment groups, with the exception of a higher incidence of drug-related injection-site pain in the KamRAB group (42.4%) compared with the HyperRAB group (28.8%).

Table 22: Drug-related TEAE
(Applicant's Table)

Preferred Term	Number (%) of Subjects		
	KamRAB + Vaccine (N=59)	HyperRAB + Vaccine (N=59)	Overall (N=118)
Any related TEAE	32 (54.2)	27 (45.8)	59 (50.0)
Injection-site pain	25 (42.4)	17 (28.8)	42 (35.6)
Headache	2 (3.4)	3 (5.1)	5 (4.2)
Nausea	1 (1.7)	3 (5.1)	4 (3.4)

Drug-related treatment-emergent adverse events by time interval
Drug-related TEAEs occurring in at least 3% of subjects overall by time interval (i.e., within the first 72 hours and 1 week post-HRIG) are presented in the Table below.

The only drug-related TEAE reported as occurring within the first 72 hours post-HRIG (i.e., after receiving 1 dose of HRIG and 2 doses of rabies vaccine) in at least 3% of subjects overall was injection-site pain (34.7%).

The only drug-related TEAEs reported as occurring within the first week post-HRIG (i.e., after receiving 1 dose of HRIG and 3 doses of rabies vaccine) in at least 3% of subjects overall were injection-site pain (35.6%), headache (3.4%), and myalgia (3.4%).

The incidence of drug-related TEAEs that occurred in at least 3% of subjects overall was generally comparable between treatment groups, both within 72 hours or 1 week post-HRIG. The only exception was drug-related injection-site pain in the KamRAB group (42.4% at each time interval) compared with the HyperRAB comparator group (27.1% and 28.8%, respectively). The data are presented in Table 23.

Table 23: TEAEs within 72 Hours and First Week
(Applicant's Table)

Preferred Term	Number (%) of Subjects		
	KamRAB + Vaccine (N=59)	HyperRAB + Vaccine (N=59)	Overall (N=118)
Within first 72 hours post-HRIG	31(52.5)	27 (45.8)	58 (49.2)
Injection-site pain	25 (42.4)	16 (27.1)	41 (34.7)
Within first week post-HRIG	32 (54.2)	27 (45.8)	59 (50.0)
Injection-site pain	25 (42.4)	17 (28.8)	42 (35.6)
Headache	2 (3.4)	2 (3.4)	4 (3.4)
Myalgia	1 (1.7)	3 (5.1)	4 (3.4)

Treatment-emergent adverse events by severity
The majority of subjects in the KamRAB and HyperRAB groups experienced TEAEs that were "mild" (45.8% and 47.5%, respectively) or "moderate" (33.9% and 39.0%, respectively) in intensity. The incidence of TEAEs by intensity was comparable between treatment groups (Table 24). One subject (0.8%) experienced a "severe" TEAE during the study. **Subject 0036** in the KamRAB group experienced a "severe" TEAE of tooth fracture that was not serious, was considered "not related" to study drug by the Principal Investigator, and resolved by the end of the study.

Table 24: Severity of TEAEs
(Applicant's Table)

Severity	Number (%) of Subjects		
	KamRAB + Vaccine (N=59)	HyperRAB + Vaccine (N=59)	Overall (N=118)
Mild	27 (45.8)	28 (47.5)	55 (46.6)
Moderate	20 (33.9)	23 (39.0)	43 (36.4)
Severe	1 (1.7)	0	1 (0.8)

Local injection-site reactions
Local reactions were defined as any TEAEs considered "probably related" or "definitely related" to study drug by the Principal Investigator that were coded to "injection-site." Overall, 44 subjects (37.3%) experienced local reactions during the study. The majority of these local reactions were injection-site pain (42 subjects; 35.6%). The incidence of injection-site pain was higher in the KamRAB group (25 subjects; 42.4%) compared with the HyperRAB group (17 subjects; 28.8%). Injection-site discomfort, injection-site hematoma, injection-site hemorrhage, and injection-site pruritus were experienced by 1 subject each (0.8%) in both groups.

Overall, most local reactions were considered "probably related" to study drug by the Principal Investigator (39 subjects, 33.1%) while only 5 subjects (4.2%) experienced local reactions that were considered "definitely related" to study drug by the Principal Investigator. The majority of subjects experienced local reactions that were "mild" in intensity (41 subjects, 34.7%) with only 3 subjects (2.5%) having local reactions that were "moderate" in intensity. No subject experienced a local reaction that was "severe" in intensity.

Systemic reactions
Systemic reactions were defined as any TEAEs considered "probably related" or "definitely related" to study drug by the Principal Investigator that were not coded to "injection-site." Overall, 27 subjects (22.9%) experienced systemic reactions during the study; all systemic reactions were considered "probably related" to study drug. The most frequently reported systemic reactions were headache (5 subjects, 4.2%) and myalgia (4 subjects, 3.4%). All other systemic reactions occurred in ≤3 subjects. Overall, the majority of subjects experienced systemic reactions that were "mild" in intensity (18 subjects, 15.3%) while only 9 subjects (7.6%) experienced systemic reactions that were "moderate" in intensity. No subject experienced a systemic reaction that was "severe" in intensity. The incidence of systemic reactions by relationship to study drug and by intensity was comparable between treatment groups.

6.3.12.3 Adverse Events of Special Interest
During the conduct of the study in August 2013, the protocol was amended (amendment 4) to include a warning and risk mitigation plan regarding hemolysis and thrombosis. FDA had noted signs of hemolysis and thrombosis in subjects who received human plasma-derived normal immunoglobulin products administered intravenously, IM, or subcutaneously. Therefore, all subsequent subjects (Subjects 58 to 118) randomized under Amendment 4 underwent routine laboratory evaluations for hemolysis.

The following changes in blood test results were to be considered indicative of hemolysis: decrease in Hgb level, increase in reticulocyte count, and a decrease in the level of haptoglobin. Subjects were to be followed up for triggering signs and symptoms of thrombosis and hemolysis that included: pallor, weakness, chest pain, back pain, discolored urine or hematuria, shaking chills, and fever for hemolysis; pain, swelling, discoloration for thrombosis; or any other sign that, according to the Principal Investigator's judgment, could indicate an incident.

Hemolysis was evaluated by monitoring reticulocyte counts (baseline only), haptoglobin, hemoglobin, and LDH levels. The latter three parameters were measured on Days 3, 7,

14, and at Day 28 (only if Day 14 values were abnormal). Hemoglobin and LDH levels were also assessed as part of the routine safety assessments at Day 28 and Follow-up/Termination. There were no subjects with a simultaneous decrease in hemoglobin and haptoglobin with an increase in LDH. Furthermore, urobilinogen was assessed as a further sensitivity test for hemolysis. Urobilinogen results were found to be comparable between treatment groups with no indication of hemolysis in either treatment group. Thus, there was no evidence of hemolysis in either treatment group. Consequently, reticulocyte counts were not measured after baseline.

One subject (**Subject 0040**) who was enrolled in the study prior to the institution of the hemolysis assessment was initially suspected of having a TEAE potentially related to hemolysis. However, the subject, a 51-year-old female in the KamRAB group, was ultimately determined to have iron deficiency anemia at the Follow-up/Termination Visit that was non-serious, "moderate" in intensity, and considered "not related" to study drug by the Principal Investigator. It did not result in action taken regarding study drug, and was ongoing at the end of the study.

Thrombosis did not occur in this study.

6.3.12.4 Clinical Laboratory Test Results

If an abnormal laboratory value was considered potentially clinically significant by the Principal Investigator, the laboratory assessment was repeated. If the value was persistently abnormal and considered clinically relevant/significant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the Principal Investigator, it was reported as an AE.

Three subjects, all in the KamRAB group, developed laboratory abnormalities that were considered clinically significant during the study.

- **Subject 0061**, a 20 year old male had normal baseline ALT and AST that increased to 96 U/L (normal 0-67 U/L) and 51 IU/L (normal 0-50 U/L), respectively, on Day 7. The ALT and AST were still elevated at 83 U/L and 51 U/L on repeat testing on an unscheduled visit on Day 10. However, they had returned to the normal range by D14 and remained so for the remainder of the study. These abnormal liver enzyme levels were considered "mild" in intensity and "probably related" to study drug by the Principal Investigator.
- **Subject 0078** developed an increase in AST and CPK. Subject had normal AST and CPK at screening and on Days 7 and 28. However, the AST and CPK had increased to 71 U/L and 1974 U/L on the Day 49 visit. The subject was followed over the ensuing 12 days where the AST and CPK progressively declined to 37 and 106 U/L, respectively. The AST and CPK values for Subject 0078 at the Day 185 study termination visit were 36 and 111 U/L respectively.
- **Subject 0096** developed moderate neutropenia. Subject had a low normal neutrophil count at screening (1.94×10^9/L) that remained low throughout the study (range: $1.77 - 2.11 \times 10^9$/L) and was noted to be neutropenic on the Day 185 study termination visit (1.41×10^9/L).

All three of the remaining TEAEs related to abnormal laboratory values were non-serious, "mild" or "moderate" in intensity, were considered "not related" to study drug by

the Principal Investigator, did not result in action taken regarding study drug, and resolved by the end of the study.

6.3.12.4.1 Hematology

The mean change from baseline in hematology values at Day 28 and Follow-up/Termination were small and there were no meaningful differences between the two groups. The hematology variables that were evaluated include total leukocyte counts with differential (basophil, eosinophils, lymphocytes, monocytes and neutrophils), erythrocytes, hematocrit, and platelet count.

6.3.12.4.2 Clinical Chemistry

The mean change from baseline in clinical chemistry values at Day 28 and Follow-up/Termination were small and there were no meaningful differences between the two groups. The chemistry variables that were evaluated include ALT, albumin, alkaline phosphatase, total and direct bilirubin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatine kinase, creatinine, GGT, glucose, lactate dehydrogenase, potassium, protein, and sodium.

6.3.12.4.3 Urinalysis

The mean change from baseline in urinalysis values at Day 28 and Follow-up/Termination were small and there were no meaningful differences between the two groups. There were two TEAEs related to urinalysis findings that were reported during this study. **Subject 0105** in the KamRAB group reported a TEAE of dysuria that was non-serious, "mild" in intensity, considered "not related" to study drug by the Principal Investigator, did not result in action taken regarding study drug, and resolved by the end of the study. **Subject 0017** in the HyperRAB Comparator group reported a TEAE of calculus ureteric that was non-serious, "moderate" in intensity, considered "unlikely related" to study drug by the Principal Investigator, did not result in action taken regarding study drug, and resolved by the end of the study.

6.3.12.4.4 Serology

Subjects in this study were tested for exposure to a variety of viruses including HAV, HBV, HCV, HIV-1, HIV-2 and Parvo B-19. Subjects were negative for all serology (HAV Ab, HCV Ab, HIV-1 Ab, HIV-2 Ab) and virology (HBsAg) parameters at baseline and at the Follow-up/Termination visit. The exception was Parvo B19 IgG antibody (index) and Parvo B19 IgM antibody. No subject in either treatment group shifted from negative serology parameters at baseline to positive serology parameters at Follow-up/Termination or the Early Discontinuation Visit.

Twenty nine of 33 subjects (87.9%) in the KamRAB group and 24 of 33 subjects (72.7%) in the HRIG Comparator group were positive for Parvo B19 IgG antibody (index) at baseline. At the Follow-up/Termination visit, 44 of 56 subjects (78.6%) in the KamRAB group and 45 of 57 subjects (78.9%) in the HRIG Comparator group were positive. These results were comparable between the two treatment groups.

Of note, for Parvo B19 IgG antibody, **Subject 0114** in the KamRAB group shifted from positive at Screening to equivocal at Early Discontinuation and **Subject 0117** in the HRIG Comparator group shifted from positive at Screening to negative at Follow-up/Termination. For Parvo B19 IgM antibody, **Subject 0100** in the KamRAB group shifted from equivocal at Screening to negative at Follow-up/Termination.

None of the serology results were considered clinically significant by the Principal Investigator.

6.3.12.4.5 Immunity

Complement levels (C3, C4, CH50) were tested at baseline, Day 49 and Follow-up/Termination. The incidences of changes from baseline in C3, C4 and CH50 were comparable between groups; differences between treatment groups in the incidence of high CH50 levels at baseline were not considered clinically meaningful.

6.3.12.5 Dropouts and/or Discontinuations

There were two subjects in the KamRAB group who reported TEAEs that led to discontinuation from the study. These subjects received KamRAB but did not complete the requisite five rabies vaccinations.

- **Subject 0054** was discontinued from the study after receiving the fourth dose of the vaccine because of an intraductal proliferative breast lesion. The SAE was graded as "moderate" in intensity, considered "not related" to study drug by the Principal Investigator, and was ongoing at the end of the study. Please see the brief narrative in Section 6.3.12.4 Nonfatal Serious Adverse Events
- **Subject 0114** discontinued study treatment after the third dose of rabies vaccine due to a TEAE of nipple pain that was non-serious, "moderate" in intensity, considered "unlikely related" to study drug by the Principal Investigator, and resolved by the end of the study

There were no subjects in the HyperRAB group that were discontinued from the study because of a TEAE.

6.3.13 Study Summary and Conclusions

This was a single-center, prospective, randomized, double-blind, parallel-group, non-inferiority study to evaluate the safety and effectiveness of KamRAB relative to another US FDA registered and commercially available HRIG (HyperRAB®) when co-administered with a rabies vaccine (RabAvert®). The study was designed based upon the Advisory Committee on Immunization Practices guidelines (endorsed by the CDC and WHO) for rabies post-exposure prophylaxis.

The study enrolled 118 subjects who were randomized to receive KamRAB (N=59) or HyperRAB (N=59). The demographic characteristics between the two groups were comparable, with the majority of subjects being White (93.2%) and female (63.6%). The median age was 47.5 years. All but 5 subjects (4 KamRAB [6.8%] and 1 HyperRAB [1.7%]) received all 5 doses of rabies vaccine during the study.

The Efficacy Analysis was performed on the As-Treated Population. This was defined as all randomized subjects who received at least 3 vaccine doses (until Day 14) and 1 dose of the HRIG, in order to ensure sufficient vaccinations to mount an active immune response. There were 3 subjects (2.5%) excluded from this analysis; two subjects in the KamRAB group who received only two vaccinations before Day 14. A third subject in the HyperRAB group was excluded because the subject may have been previously exposed to rabies or rabies vaccine. An additional subject was excluded from the primary efficacy analysis because she was withdrawn from the study on Day 14 for an AE despite receiving 3 doses of the vaccine.

The analysis of the primary endpoint in the As-Treated Population demonstrated that KamRAB was non-inferior to HRIG Comparator. Nearly all subjects in the KamRAB group (55 of 56 subjects; 98.2%) and all subjects in the HRIG Comparator group had an anti-rabies IgG antibody titer ≥0.5 IU/mL on Day 14. The difference between the proportion of subjects with an anti-rabies IgG antibody titer ≥0.5 IU/mL on Day 14 in the KamRAB and HRIG Comparator groups was -1.8% (90% CI: -8.2, 3.1). The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of -10%. However, one subject (**Subject 0024**) did not achieve an anti-rabies IgG antibody titer of ≥0.5 IU/mL until Day 28 (0.81 IU/mL) and the peak level was only 0.88 IU/mL on Day 49.

In general, KamRAB was well tolerated and had a safety profile comparable to that of HyperRAB. The overall incidence of TEAEs was comparable between the two groups. The most frequently reported TEAEs in the KamRAB and HRIG Comparator groups were injection-site pain (49.2% and 39.0%), headache (13.6% and 15.3%), upper respiratory tract infection (13.6% and 13.6%), and myalgia (13.6% and 10.2%). There were no deaths during the study and only one SAE. One subject who received KamRAB reported an SAE of intraductal proliferative breast lesion that resulted in discontinuation of study treatment.

Reviewer's Comments

1) ***Similar to the initial Phase 1 study, the PK data on Day 3 for this study again shows that KamRAB is not bioequivalent to the HRIG comparator. This is potentially important since HRIGs provide the only anti-rabies protection during this early time period. However, subsequent discussions with Dr. Petersen of the CDC affirms our belief that these minor differences in serum concentration will not impact the protective effect of KamRAB against rabies exposure.***
2) ***The Applicant should be able to tease out the role of HRIG vs vaccine on local adverse reactions since HRIG and vaccine are administered at different sites. These data were subsequently provided by Kamada during the mid-cycle review (See Table B in Section 8.4.7).***

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication

KamRAB is 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.

7.2 Methods of Integration

The applicant conducted a clinical development program with three clinical trials; each addressed a different question but in aggregate, the trials complemented each other. In the first study (RD 154/23630), the applicant sought to demonstrate that KamRAB is bioequivalent to BayRAB® (a HRIG marketed in Israel). The second study (RD 154/24061) assessed the inhibitory effect of KamRAB on active rabies antibody production following immunization with a rabies vaccine (Rabipur®). The third and final study (KamRAB-003) combined elements from the two earlier trials to demonstrate the

efficacy of KamRAB in combination with a rabies vaccine (RabAvert®) for post-exposure prophylaxis. The last trial compared the antibody response to KamRAB and RabAvert® with that of HyperRAB and RabAvert®.

Each study was controlled, with an active comparator in the first and third trial (RD 154/23630 and KamRAB-003) and a placebo control in the second study (RD 154/24061). There was a parallel comparator group in the last two studies but subjects served as their own controls in the first study as this was a two-period, two-treatment, two-sequence, crossover study in which subjects received both KamRAB and BayRAB®. All three studies were double-blind, randomized trials. Pharmacokinetic sampling and analysis was an important component of all three studies. Each of the three studies was conducted at a single center: Simbec-TASMC Clinical Research Center, Tel-Aviv Sourasky Medical Center, Israel for the first two trials and Prism Research, St Paul, MN, USA for KamRAB-003.

Depending upon the study, subjects in the three clinical studies received either saline placebo, KamRAB, and/or a comparator HRIG. The latter two groups received a single 20 IU/kg IM injection. Subjects in Study RD 154/24061 and KamRAB-003 also were vaccinated with a rabies vaccine. Since Study RD 154/23630 was a two-treatment crossover study, the 26 enrolled subjects were scheduled to receive both KamRAB and BayRAB. However, because of the development of AEs following the first dose of study drug, only 24 subjects received KamRAB and 25 subjects received BayRAB. Table 25 provides a by-study and overall summary of the study treatments that were administered in the three studies.

Table 25: Summary of Subject Treatment by Study
(Applicant's Table)

Study Number	Treatment Groups				
	All KamRAB	**KamRAB + Vaccine**	**Other HRIG**	**Other HRIG + Vaccine**	**Saline Placebo + Vaccine**
RD 154/23630	24	--	25	--	--
RD 154/24061	8	8	--	--	8
KAMRAB-003	59	59	59	59	--
Total	91	67	84	59	8

7.3 Demographics and Baseline Characteristics

The three studies enrolled 160 healthy volunteers since a placebo controlled efficacy study in subjects exposed to rabies would be unethical. However, the volunteers in the second study were restricted to individuals at risk of contracting rabies due to occupational hazards, ie: animal care providers. This was due to a world-wide shortage of the human diploid cell culture vaccine necessitating a switch to a purified chick embryo cell vaccine. The latter is associated with a possibly higher (albeit rare) incidence of Guillain-Barré Syndrome. The subjects in the three studies were overwhelmingly Caucasian (95%) and young; 54% were female.

7.4 Subject Disposition

There were no data presented for screen failures, but this information was provided at the mid-cycle review at the request of this Reviewer.

A total of 160 subjects were enrolled in the three studies with 151 subjects (94.4%) completing their study. There were 3 subjects (11.5%) who did not receive the second study drug due to AEs after receiving the first study drug; 2 subjects did not receive KamRAB and one subject did not receive BayRAB. One subject (6.3%) in the second study was discontinued from the study on Day 7 because of a positive cannabinoid test on Day 3. The subject received the last two vaccinations on Days 8 and 28 for ethical reasons but refused to undergo post-study testing. Five subjects in the third study were (4.2%) terminated early. The most common reason for early termination was AE in 2 subjects (1.7%); both of whom were in the KamRAB group. Of the remaining three subjects, one subject was terminated per Investigator discretion for medication use, another withdrew from the study and a third was lost to follow-up. Table 26 provides a by-study and overall summary of the study treatments for the subjects that were included in the Efficacy database.

Table 26: Subject Treatment by Study (Efficacy Database)
(Applicant's Table)

Study Number	Treatment Groups				
	All KamRAB	KamRAB + Vaccine	All Other HRIG	Other HRIG + Vaccine	Saline Placebo + Vaccine
RD 154/23630	24	--	25	--	--
RD 154/24061	7	7	--	--	8
KAMRAB-003	56	56	57	57	--
Total	87	63	82	57	8

7.5 Analysis of Primary Endpoint(s)

The primary hypothesis of this application is that the proportion of KamRAB and vaccine recipients with anti-rabies concentration ≥0.5 IU/mL on Day 14 would not be less than the corresponding proportion of HyperRAB and vaccine subjects by as much as 0.1. The criterion of response is the proportion of subjects with anti-rabies IgG titer ≥ 0.5 IU/mL antibody measured on Day 14.

In the first study (RD 154/23630), the primary efficacy endpoint was to compare the pharmacokinetic profile of two HRIGs, KamRAB and BayRab®, with each administered at a dose of 20 IU/kg (Table 27). There was a marginally statistically significant sequence effect seen in Cmax (p=0.0415) and AUC_T (p=0.0329) that was essentially a treatment by period interaction.

Table 27: Pharmacokinetic Profile - KamRAB vs BayRAB
(Reviewer's Table)

	KamRAB	BayRab®	90% CI
C_{max} (IU/mL)	0.249 ± 0.063	0.302 ± 0.068	75.3 - 88.6%
T_{max} (days)	7	3	---

AUC_T (Day*IU/mL)	5.222 ± 1.297	6.266 ± 1.236	77.4 - 87.6%
AUC_I (Day*IU/mL)	6.734 ± 1.274	7.972 ± 1.362	78.6 - 90.7%

Nonetheless, the pharmacokinetic profile of KamRAB is inferior to that of BayRAB. However, as stated previously, these minor differences are unlikely to be clinically meaningful as rabies is an aviremic infection and the function of HRIG is to neutralize rabies virus at the inoculation site.

The second study was conducted to assess the potential inhibitory effect of KamRAB on anti-rabies Ab production following vaccination with a rabies vaccine. This is a well-known side effect of all RIGs and is postulated to arise from binding of RIG to rabies immunogens within the vaccine. The hypothesis tested in this study was that there was no difference in anti-rabies antibody production between KamRAB and placebo when coadministered with a rabies vaccine (Rabipur®). As expected, the average titers on Day 14 were 1.22 IU/mL and 5.05 IU/mL in the KamRAB and placebo groups, respectively, clearly demonstrating that KamRAB inhibits active antibody production. These data are consistent with what has been demonstrated for other licensed RIGs. However, there was one extraneous factor that may complicate the interpretation of this study. Because of a worldwide shortage of rabies vaccine during the conduct of this study, the Sponsor had to substitute a 3-dose pre-exposure vaccination schedule for the currently recommended 4 or 5 dose PEP schedule. Therefore, subjects were not vaccinated on Day 3, which likely led to lower antibody levels on Day 14. Nonetheless, this should not affect the conclusion that KamRAB interferes with anti-rabies antibody production in response to vaccination.

Study KamRAB-003 demonstrates that KamRAB was non-inferior to a HRIG Comparator, HyperRAB for rabies PEP. In the As-Treated Population (115 subjects), almost all subjects (55 of 56 subjects (98.2%; 95%CI: 90.4, 100) in the KamRAB group and all 58 subjects (95%CI: 93.8, 100) in the HyperRAB group had an anti-rabies antibody titer ≥0.5 IU/mL on Day 14. The difference between the proportion of subjects with an anti-rabies IgG antibody titer ≥0.5 IU/mL on Day 14 in the KamRAB and HyperRAB groups was -1.8% (90% CI: -8.2, 3.1). The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of -10%, thus demonstrating that KamRAB was non-inferior to HyperRAB for the primary endpoint.

There were 2 subjects with outlying results in KamRAB-003. One subject (Subject 0024) in the KamRAB group did not achieve an anti-rabies antibody titer of ≥0.5 IU/mL on Day 14. This subject had a titer that was below the level of quantitation at baseline, and titers of 0.12, 0.12, 0.18, 0.81, 0.88 and 0.38 IU/mL on Days 3, 7, 14, 28, 49, and 185. Another subject (Subject 0062 in the HyperRAB group) had an antibody titer of 724.11 IU/mL on Day 14 that was considerably higher than for other subjects. After consulting with experts at the Kansas State Veterinary Diagnostic Laboratory, it was determined that the most probable explanation for the high value was that this was an anamnestic response to previous rabies or rabies vaccine exposure.

An important finding is that the geometric mean titer (GMT) for anti-rabies antibody on Day 3 is lower in the KamRAB group than in the the HyperRAB group. The GMT on Day 3 was 0.176±1.32 and 0.216±1.37 IU/mL in the KamRAB and HyperRAB groups, respectively. This difference was statistically significant (p=0.0003). This may be important since the concentration on Day 3 reflects the neutralizing activity of passive

immunization since response to the vaccine is not seen until days 7-10. Thus, the serum rabies neutralizing activity for KamRAB on Day 3 is lower when compared with two other licensed HRIGs, BayRAB and HyperRAB.

A major weakness of these studies is that they were not conducted with the same HRIG or rabies vaccine as the comparator, thereby complicating evaluation across studies. Nonetheless, the following can be concluded:

- KamRAB is not bioequivalent to other HRIGS
  - PK profile (Cmax, AUC_T, AUC_I) is inferior to BayRAB
  - Anti-rabies neutralizing activity on Day 3 is lower than that of HyperRAB
- KamRAB interferes with host anti-rabies antibody production when administered with Rabipur® for rabies PEP although the RVNA was higher in the KamRAB group suggesting that it may be less potent than HyperRAB.
- KamRAB is not inferior to HyperRAB when administered with RabAvert® for rabies PEP on D14.

7.6 Analysis of Secondary Endpoint(s)

The secondary endpoints relate to the pharmacokinetic profile of KamRAB. These data were discussed in Section 7.5 since the primary efficacy endpoints were based upon serum anti-rabies antibody concentrations.

7.7 Subpopulations

The three studies in this application were conducted primarily in young Caucasians. There were a number of segments of the population that were excluded from these three studies including the pediatric, minority ethnic groups, pregnant and lactating women, obese, immunocompromised and those co-infected with other chronic viral infections (See Section 9.1).

7.8 Persistence of Efficacy

Similar to other human immunoglobulins, the half-life of KamRAB is approximately 21 days. The C_{max} for KamRAB was achieved seven days following administration and would be expected to decline thereafter. However, since KamRAB is administered in conjunction with a rabies vaccine, serum rabies neutralizing activity actually peaks on Day 14 and declines thereafter through the last timepoint examined in this study, Day 185. Please refer to Section 7.1.4.

7.9 Product-Product Interactions

KamRAB, similar to other RIGs, is intended to be administered in conjunction with a rabies vaccine for post-exposure prophylaxis following exposure to rabies. As with all other HRIGs, KamRAB interferes with the immune response of the vaccinee to rabies vaccination. Please refer to Section 6.2.

7.10 Efficacy Conclusions

In conclusion, the primary efficacy endpoint selected by this and other HRIG applicants does not assess the clinical efficacy of rabies immunoglobulins. The plasma pharmacokinetic parameters of AUC and C_{max} may bear little relevance to the mechanism of action of RIGs, i.e.; local tissue inactivation of rabies. In addition, rabies is an aviremic

infection; thereby, further suggesting that serum concentrations are at best a surrogate of a surrogate biomarker for tissue concentrations. Finally, an assessment of serum rabies neutralizing activity ≥0.5 IU/mL on Day 14 is not measuring the effect of KamRAB but rather, that it does not significantly interfere with the ability of the rabies vaccine to stimulate host antibody production.

Reviewer's comments: Given the concern with the selection of RVNA on D14 as the primary efficacy endpoint, the clinical review team asked Kamada at the mid-cycle review to provide an analysis of PEP outcomes for Israel, South Korea, and Australia. Kamada contacted the Ministries of Health in Israel, South Korea, and Australia to obtain as much clinical outcome information as possible to support the efficacy of KamRAB. However, detailed information was not available from these countries. Kamada has requested the collection of clinical outcomes data in Australia going forward, but retrospective data are not available.

Israel was able to provide available information on clinical outcomes following KamRAB administration. The Director of Public Health Services of the Israeli Ministry of Health (IMoH) has provided a summary of the clinical experience with KamRAB in Israel from 2010 to 2015. All subjects received treatment in accordance with WHO guidance including KamRAB, the only rabies immune globulin administered in Israel. During this period, 84,287 people approached the IMoH to receive treatment due to suspected exposure to rabies. All subjects with suspected or confirmed rabies were actively followed during the treatment period at one of the 16 regional IMoH public health offices. Of these, 1,863 were confirmed to have been exposed to a rabid animal. The suspected animals were tested by (b) (4) ***for Rabies virus in brain samples at the*** (b) (4) ***and confirmed to be rabid. The latter is the only laboratory in the country that provides this service. During this period, none of the subjects progressed to clinical rabies, and there were no reports of serious adverse events related to the administration of KamRAB. This data supports the efficacy of KamRAB when used in combination with a rabies vaccine for post-exposure prophylaxis.***

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety assessments for each subject included AEs, SAEs, laboratory tests (hematology, biochemistry, virology and serology, pregnancy testing for female subjects of reproductive potential, and urinalysis), vital signs, body temperature, and ECG findings. Blood was collected for clinical chemistry and hematology and urine for urinalysis on Days 3, 7, 14, 28, 35 and 42 for the first two studies. For study KAMRAB-003, tests were performed for clinical chemistry, hematology, and urinalysis on Days 7, 28, 49 and 185. Subjects were also sent home with diary cards for the recording of AEs for the first 14 days of the study.

For the pooled Integrated Summary of Safety (ISS) database, adverse event (AE) and laboratory datasets from each study were converted to a uniform format and appended together into a unified database. Adverse event data from Studies 23630 and 24061 were up-coded from the Medical Dictionary for Regulatory Activities (MedDRA) version 7.1

to MedDRA version 16.1. A listing showing the mapping of each verbatim AE term to MedDRA System Organ Class (SOC) and Preferred Term (PT) was produced. Data on adverse event action, outcome, and relationship to study treatment from each individual study were harmonized.

Laboratory data were combined into a single, uniform dataset in order to comply with the Study Data Tabulation Model Analysis Data Model standard. Laboratory values were converted to standardized values, and values were categorized as low/normal/high according to the laboratory standard.

8.2 Safety Database

The Integrated Summary of Safety was based on the pooled Safety Population, which includes all subjects who received at least one dose of study medication (i.e., KamRAB, comparator HRIG, or placebo. Data summaries were produced for two study populations that were referred to as "pool" by the Applicant.

- **The All Studies Pool** includes data for all subjects treated in the studies of KamRAB. In these summaries, data were displayed for the following treatment groups:
  - The **All KamRAB** group, comprising all 91 subjects who received KamRAB with or without rabies vaccine in the 3 clinical studies
  - The **All Comparator HRIG** group, comprising all 84 subjects who received Comparator HRIG (BayRAB or HyperRAB) with or without rabies vaccine in Studies KAMRAB-003 and 23630
  - The **Placebo + Vaccine** group, comprising 8 subjects from Study 24061
- **The Test Article or Comparator with Vaccine (TACV) Pool** includes data for subjects who received KamRAB, comparator HRIG (BayRAB or HyperRAB), or saline placebo with rabies vaccine. The purpose of this pool is to allow for the comparison of AEs in subjects who received both test article (i.e., HRIG or placebo) and rabies vaccine. Data from Study 23630 which did not include rabies vaccination are not included in this pool. Data summaries for the TACV Pool include the following treatment groups:
  - The **KamRAB + Vaccine** group, comprising the 67 subjects who received KamRAB with rabies vaccine in Studies KAMRAB-003 and 24061
  - The **Comparator HRIG + Vaccine** group, comprising the 59 subjects who received HyperRAB with rabies vaccine in Study KAMRAB-003.
  - The **Placebo + Vaccine** group, comprising 8 subjects from Study 24061.

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

There were three studies used for the safety analysis (See Section 5.3). A total of 160 subjects were enrolled in the three studies and all 160 subjects are included in the safety evaluation.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A by-study and overall summary of the study treatments that were administered to subjects in the safety database is presented in Table 28. Although 160 subjects were included in the safety evaluation, the number of subjects exposed to test article is greater than 160 since Study 23630 was a two-treatment crossover study. However, only 24 and

25 of the 26 subjects received KamRAB and BayRAB, respectively, because of the development of AEs following their first dose of study drug.

Table 28: Subject Treatment by Study (Safety Database)
(Applicant's Table)

Study Number	Treatment Groups				
	All KamRAB	KamRAB + Vaccine	All Other HRIG	Other HRIG + Vaccine	Saline Placebo + Vaccine
RD 154/23630	24	--	25	--	--
RD 154/24061	8	8	--	--	8
KAMRAB-003	59	59	59	59	--
Total	91	67	84	59	8

Subjects in Study 24061 received three doses of rabies vaccine on Days 0, 7, and 28 while subjects in Study KAMRAB-003 received 5 vaccinations on Days 0, 3, 7, 14 and 28. The latter vaccination schedule is consistent with the current WHO recommendation for rabies post-exposure prophylaxis. The three-dose vaccination is recommended by the WHO for pre-exposure prophylaxis but was used in this study because of a world-wide shortage of the human diploid cell culture vaccine necessitating a switch to a purified chick embryo cell vaccine (See Section 6.2.2).

The duration of follow-up (mean $\pm$ SD) in days for each of the three studies and for the pooled analysis are presented in Table 29.

Table 29: Duration of Follow-up in Days
(Reviewer's Table)

	All KamRAB	All Other HRIG	Saline Placebo + Vaccine
RD 154/23630	58.8 (8.8) N=24	58.4 (14.3) N=25	--
RD 154/24061	38.0 (12.5) N=8	--	42.5 (0.5) N=8
KAMRAB-003	177.3 (34.2) N=59	186.8 (10.3) N=59	--
All Studies Pool	133.8 (65.9) N=91	148.6 (60.2) N=84	42.5 (0.5) N=8
TACV Pool	160.7 (55.8) N=67	186.8 (10.3) N=59	42.5 (0.5) N=8

The demographics of the All Studies pool population are presented in Table 30.

Table 30: Demographics –All Studies Pool Population
(Reviewer's Table)

	All KamRAB (N=91)	All Other HRIG (N=84)	Saline Placebo + Vaccine (N=8)
Age (yrs)	37.6 (15.3)	40.7 (15.1)	26.9 (3.4)
Sex			
Male	46	42	5
Female	45	42	3
Race			
Asian	1	0	0
Black	0	4	0
White	89	78	8
Other	1	2	0
Weight (kg)	72.9 (11.5)	73.7 (12.0)	67.0 (8.0)

Data for age and weight is presented as mean (SD)

The demographics of the TACV pool are presented in Table 31.

Table 31: Demographics – TACV Pool Population
(Reviewer's Table)

	KamRAB + Vaccine (N=67)	Comparator HRIG + Vaccine (N=59)	Saline Placebo + Vaccine (N=8)
Age (years)	41.4 (16.1)	46.3 (14.5)	26.9 (3.4)
Sex			
Male	26	21	5
Female	41	38	3
Race			
Asian	1	0	0
Black	0	4	0
White	65	53	8
Other	1	2	0
Weight (kg)	75.0 (11.1)	76.6 (11.5)	67.0 (8.0)

Data for age and weight is presented as mean (SD)

8.2.3 Categorization of Adverse Events

The common AEs for the Pooled Population, defined as all System Organ Class (SOC) in which events occurred in ≥10% of subjects, are presented in Table 32.

Table 32: Adverse Events Categorization –All Studies Pool Population
(Reviewer's Table)

	All KamRAB (N=91)	All Other HRIG (N=84)	Saline Placebo + Vaccine (N=8)
General Disorder & Administration site	35 (38.5%)	36 (42.9%)	2 (25%)
Nervous System	21 (23.1%)	18 (21.4%)	3 (37.5%)

Musculoskeletal/ connective tissue	19 (20.9%)	14 (16.7%)	1 (12.5%)
Gastrointestinal	14 (15.4%)	8 (9.5%)	1 (12.5%)
Respiratory, Thoracic & Mediastinal	11 (12.1%)	(11.9%)	0 (0%)

At the Preferred Term level reported in >3% of the subjects, the most common AEs occurring in the KamRAB and Comparator HRIG groups were the same in the All Studies Pool. These included injection-site pain, headache, myalgia, and upper respiratory tract infection.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The pooling of data from the three studies for an integrated safety analysis seems appropriate since the studies complement each other. For example, a safety profile of KamRAB administered as a single agent can only be discerned from Study 23630 since this was the only study in which the agent was administered without a vaccine. Study 24061 enrolled only 16 subjects and thus, its overall contribution to the safety data base is minor. Indeed, there were no SAEs reported in either Study 23630 or 24061. The major contributor to the safety database is KAMRAB-003 which enrolled the majority of the subjects (73.8%). Furthermore, the latter study was the only study in which the treatment schedule mimicked the planned use of the agent, i.e. post-exposure prophylaxis.

8.4 Safety Results

8.4.1 Deaths

There were no study subject deaths during the conduct of the three clinical trials.

8.4.2 Nonfatal Serious Adverse Events

There was only one SAE reported in the three studies. This was Subject 0054 in Study KAMRAB-003. The subject was a 63 year old female who was administered KamRAB. She developed an intraductal proliferative breast lesion that was “moderate” in intensity, considered “not related” to study drug by the Principal Investigator, and was ongoing at the end of the study. The subject discontinued study treatment after only 4 doses of rabies vaccine due to this SAE. Please refer to Section 6.3.12.4 Nonfatal Serious Adverse Events for a narrative of the SAE.

8.4.3 Study Dropouts/Discontinuations

There were 9 subjects (5.6%) who were withdrawn from the study; five of the subjects were withdrawn for an AE. Five of the subjects who were withdrawn from the study were enrolled in Study KAMRAB-003 while three subjects were from Study 23630 and the remaining subject was in Study 24061.

Study KAMRAB-003

1. **Subject 0054** – withdrawn for Serious Adverse Event (intraductal proliferative breast lesion) – See Section 6.3.12.4 for narrative
2. **Subject 0114** – withdrawn for Adverse Event (nipple pain)
3. **Subject 0062 -** Withdrew consent. Subject is a 37-year-old black male who received HyperRAB and 5 doses of rabies vaccine. The subject had a higher than

expected level of plasma HRIG concentration at baseline (as well as on Days 3, 7, and 14). Prior to unblinding, the experts at the Kansas State Veterinary Diagnostic Laboratory were consulted and it was determined that the most probable explanation was previous exposure to rabies or rabies vaccine. The subject withdrew consent for continued participation in the study. The last study visit date was 13-May-2014 (Day 161)

4. **Subject 0076** - Withdrawn for Prohibited Prescribed Medication Use. Subject is a 50-year-old white woman who received KamRAB and two doses of rabies vaccine on 20-Dec-2013 and 31-Dec-2013. On 13-Jan-2014, the subject did not receive rabies vaccine and was withdrawn from the study because she was using prohibited medications (prednisone, naproxen, and hydrocodone). The last three doses of rabies vaccine were not administered, and the subject was removed from the study per protocol.
5. **Subject 0087**- Lost to Follow-up. Subject is a 24-year-old woman who received HyperRAB and five doses of rabies vaccine. However, the subject did not attend the Day 49 study visit or any subsequent visits. There were no further contact with the subject and she was deemed lost to follow-up.

Study 23630

1. **Subject** (b) (6) – Withdrawn for Adverse Event (Hematuria). Subject is an 18-year-old man who received KamRAB. One week later, mild microhematuria was found on urinalysis. This AE was assessed as mild and possibly related to study treatment. The subject was withdrawn from the study because of the event, which was ongoing at the last study contact.
2. **Subject** (b) (6) – Withdrawn for Adverse Event (Viral upper respiratory tract infection). Subject is a 28-year-old man who received BayRab as the first study treatment on 16-Feb-2004. On 15-Apr-2004, the subject developed a viral upper respiratory tract infection that was assessed as moderate and unrelated to study treatment. The subject was withdrawn from the study because of the AE, which resolved on 20-Apr-2004. The subject did not receive KamRAB.
3. **Subject** (b) (6) - Withdrawn for Adverse Event (Hematuria). Subject is a 26-year-old man who received BayRab as the first study treatment. Mild erythrocyturia was found on urinalysis three days later. The AE was assessed as possibly related to study treatment. The subject was withdrawn from the study because of the event, which resolved in approximately two months.

Study 24061

1. **Subject** (b) (6) - Withdrawn for Prohibited Drug Use (Cannabinoid] Use). Subject is a 27-year-old white man randomized to receive KamRAB and rabies vaccine. On 08-Nov-2004, the subject received KamRAB and rabies vaccine. On Day 7, the subject's urine tested positive for cannabinoid and the subject was withdrawn from the study on Day 7. The remaining two doses of vaccine were administered on Days 8 and 28 for ethical reasons. The subject declined to undergo post-study testing.

8.4.4 Common Adverse Events

The percentage of subjects with AEs was slightly lower in subjects administered KamRAB (+ vaccine) than in the Comparator HRIG (+ vaccine) group in the All Studies

Pool (70.3% vs. 78.6%) and TACV Pool (77.6% vs. 86.4%). In the All Studies and TACV Pools (Table below), a similar proportion of subjects in the KamRAB (± vaccine) and Comparator HRIG (± vaccine) groups had related AEs, injection-site AEs, related injection-site AEs, AEs occurring within 72 hours of administration, and related AEs occurring within 72 hours of administration (Table 33). The proportion of subjects in the KamRAB (± vaccine) and Comparator HRIG (± vaccine) groups with mild AEs was similar, while the percent of subjects with moderate AEs was lower in the KamRAB (± vaccine) group.

Table 33: Overall Summary of Adverse Events for All Pools
(Reviewer's table)

Pool	All Studies		Placebo	TACV	
MedDRA Preferred Term	All KamRAB (N=91)	Other HRIG (N=84)	Saline + Vaccine (N=8)	KamRAB + Vaccine (N=67)	HRIG + Vacccine (N=59)
Adverse Event	64 (70.3)	66 (78.6)	5 (62.5)	52 (77.6)	51 (86.4)
Related Adverse Event	39 (42.9)	34 (40.5)	2 (25.0)	32 (47.8)	27 (45.8)
Injection-site AE	30 (33.0)	28 (33.3)	2 (25.0)	29 (43.3)	24 (40.7)
Related injection-site AE	26 (28.6)	23 (27.4)	2 (25.0)	25 (37.3)	19 (32.2)
AE within 72 hours	44 (48.4)	41 (48.8)	1 (12.5)	38 (56.7)	35 (59.3)
Related AE within 72 hrs	34 (37.4)	33 (39.3)	0	31 (46.3)	27 (45.8)
AE - greatest severity:					
Mild	43 (47.3)	40 (47.6)	4 (50.0)	31 (46.3)	28 (47.5)
Moderate	20 (22.0)	26 (31.0)	1 (12.5)	20 (29.9)	23 (39.0)
Severe	1 (1.1)	0	0	1 (1.1)	0
Serious Adverse Event	1 (1.1)	0	0	1 (1.1)	0

Common AEs are defined as all MedDRA Preferred terms reported in >3% of subjects. These data are reported in Table 34. In the All Studies and TACV Pools, the most common AEs were similar as were those occurring in the KamRAB (± vaccine) and Comparator HRIG (± vaccine) groups. They included injection-site pain, headache, myalgia, and upper respiratory tract infection.

Table 34: Common AE Occurring in >3% of Subjects
(All Studies and TAVC Pools)
(Reviewer's Table)

Pool	All Studies		Placebo	TACV	
MedDRA Preferred Term	All KamRAB (N=91)	Other HRIG (N=84)	Saline + Vaccine (N=8)	KamRAB + Vaccine (N=67)	HRIG + Vacccine (N=59)
Injection-site pain	30 (33.0)	26 (31.0)	2 (25.0)	29 (43.3)	23 (39.0)
Headache	14 (15.4)	11 (13.1)	3 (37.5)	10 (14.9)	9 (15.3)
Myalgia	8 (8.8)	6 (7.1)	0 (0.0)	8 (11.9)	6 (10.2)
URI	8 (8.8)	8 (9.5)	0 (0.0)	8 (11.9)	8 (13.6)
Arthralgia	5 (5.5)	0 (0.0)	1 (12.5)	4 (6.0)	0 (0.0)
Dizziness	5 (5.5)	3 (3.6)	0 (0.0)	3 (4.5)	2 (3.4)

Fatigue	5 (5.5)	2 (2.4)	0 (0.0)	3 (4.5)	1 (1.7)
Abdominal pain	4 (4.4)	1 (1.2)	0 (0.0)	2 (3.0)	1 (1.7)
Hematuria	4 (4.4)	2 (2.4)	0 (0.0)	---	---
Nausea	4 (4.4)	3 (3.6)	0 (0.0)	4 (6.0)	2 (3.4)
Presyncope	4 (4.4)	1 (1.2)	0 (0.0)	4 (6.0)	1 (1.7)
Ecchymosis	3 (3.3)	1 (1.2)	0 (0.0)	3 (4.5)	1 (1.7)
Sunburn	3 (3.3)	0 (0.0)	0 (0.0)	3 (4.5	0 (0.0)
Leukocyturia	3 (3.3)	4 (4.8)	0 (0.0)	2 (3.0)	0 (0.0)

8.4.5 Clinical Laboratory Test Results

The clinical laboratory results for the three studies were not pooled since they were so infrequent (Table 35). There were a total of 11 abnormal blood tests reported as AEs; 6 in Study 23630 and 5 for Study KAMRAB-003. The number of abnormal urinalysis reported as AEs were slightly more frequent at 19 with 16 of them reported in Study 23630.There was no observed safety signal related to laboratory abnormalities in any study. The Abnormal laboratory values reported as AEs in the individual studies are displayed in Table E.

Table 35: Abnormal Laboratory Test Results Reported as AEs (Per Study Summary)
(Applicant's Table)

	Study 23630		**Study 24061**		**Study 003**	
System Organ Class Preferred Term	**All Kam RAB**	**Other HRIG**	**Kam RAB + Vaccine**	**Saline + Vaccine**	**Kam RAB + Vaccine**	**HRIG + Vacccine**
	N=24	N=25	N=8	N=8	N=59	N=59
Abnormal Blood Test						
ALT increase	0 (0.0)	2 (8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Bilirubin increase	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CPK increase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
LDH increase	0 (0.0)	1 (4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iron deficient anemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
LFT Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Neutrophilia	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
WBC increase	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Urine Test						
Hematuria	4 (16.7)	2 (8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukocyturia	0 (0.0)	0 (0.0)	2 (25)	1 (12.5)	0 (0.0)	0 (0.0)
Urine RBC positive	0 (0.0)	3 (12)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine WBC positive	3 (12.5)	4 (16)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as number of subjects (percent of subjects).

Reviewer's comments: An integrated summary of urinary abnormalities was requested from Kamada by this Reviewer at the mid-cycle review. Most of the occurrence of

hematuria and leukocyturia occurred in one study (Study 23630) with 16 of the 19 events reported in this study. The frequency was similar in the KamRAB and Comparator HRIG groups. This difference may be due to differences in study conduct. Although two subjects in Study 23630 were withdrawn due to hematuria, all of the events were mild. None of the subject had an elevation of their serum creatinine.

A review of the literature undertaken by Kamada suggests renal toxicity associated with the use of intravenous immune globulin (IVIG) is a rare but potentially serious event commonly associated with excipients, particularly sucrose. The incidence and prevalence of renal injury associated with IVIG is difficult to determine, as estimates rely on spontaneous reports, with the extent of underreporting and the number of IVIG recipients unknown. IVIG-associated renal failure mostly occurs in patients with preexisting conditions or those at increased risk such as prior renal insufficiency, diabetes, elderly (>65 years old), volume depletion, sepsis, paraproteinemia or concomitant use of nephrotoxic agents. The incidence of renal failure is highest with sucrose-stabilized products with much lower incidence with IVIGs stabilized with glucose, maltose, D-sorbitol, mannitol, glycine or L-proline. The mechanism of injury with these stabilizers is as yet unidentified but may include inhibition of renal enzymes involved in excipient metabolism, renal vasoconstriction, tubule-glomerular feedback and pigment- mediated acute renal injury secondary to hemolysis. In addition, the adverse effects of immunoglobulin are generally less frequent and milder with IM administration relative to IV, with the exception of local reactions at the administration site. This is because the volume and dose are higher with intravenous administration. Finally, IVIGs are typically administered repeatedly over time while HRIG administration is anticipated to be infrequent.

In summary, the population in which KamRAB is used is likely to be younger, healthier, and at lower risk for adverse renal reactions than the population for which IVIG is prescribed.

8.4.6 Systemic Adverse Events

There were no subjects in the clinical studies of KamRAB who had an event (e.g., anaphylaxis) or constellation of events (e.g., urticaria, shortness of breath) that could represent an immediate hypersensitivity reaction to KamRAB.

Systemic AEs occurring within the first 72 hours of KamRAB or Comparator HRIG with or without rabies vaccine were uncommon (Table 36). Headache was the most common complaint.

Table 36: Systemic Adverse Events with Onset within 72 Hours of First Injection that Occurred in One or More Subject in Any Treatment Group
(Reviewer's Table)

Pool	All Studies		Placebo	TACV	
MedDRA Preferred Term	All KamRAB (N=91)	Other HRIG (N=84)	Saline + Vaccine (N=8)	KamRAB + Vaccine (N=67)	HRIG + Vacccine (N=59)
Headache	6 (6.6)	5 (6.0)	0 (0.0)	3 (4.5)	5 (8.5)
Abdominal pain	3 (3.3)	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)

Arthralgia	3 (3.3)	0 (0.0)	0 (0.0)	3 (4.5)	0 (0.0)
Fatigue	3 (3.3)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	3 (3.3)	1 (1.2)	0 (0.0)	3 (4.5)	1 (1.7)
Back pain	2 (2.2)	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)
Dizziness	2 (2.2)	2 (2.4)	0 (0.0)	0 (0.0)	2 (3.4)
Leukocyturia	2 (2.2)	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)
Musculoskeletal stiffness	2 (2.2)	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)
Presyncope	2 (2.2)	1 (1.2)	0 (0.0)	2 (3.0)	1 (1.7)
Asthenia	1 (1.1)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	0 (0.0)	4 (4.8)	0 (0.0)	0 (0.0)	4 (6.8)
Pain in extremity	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	2 (3.4)

8.4.7 Local Adverse Events

The analysis of injection-site AEs is based on summaries of events that occurred within 72 hours of administration of study treatment (i.e., KamRAB, BayRAB, or saline placebo). These data are presented in Table 37. In the All Studies and TACV Pools, the most common adverse event overall, and the most common injection-site AE occurring within 72 hours of first study injection, was injection-site pain. The proportion of subjects in the KamRAB and Comparator HRIG groups with injection-site AEs was similar in both pools. No subject in the saline placebo with vaccine group had an injection-site AE within 72 hours of first study injection.

Table 37: Injection-Site Adverse Events within 72 Hours (All Studies and TACV Pool)
(Reviewer's Table)

Pool	**All Studies**		**TACV**	
MedDRA Preferred Term	**All KamRAB (N=91)**	**Other HRIG (N=84)**	**KamRAB + Vaccine (N=67)**	**HRIG + Vacccine (N=59)**
Injection-site pain	27 (29.7)	21 (25.0)	26 (38.8)	18 (30.5)
Injection-site hematoma	1 (1.1)	0	1 (1.5)	0
Injection-site paresthesia	1 (1.1)	0	0	0
Injection-site hemorrhage	0	1 (1.2)	0	1 (1.7)
Injection-site discomfort	0	1 (1.2)	0	1 (1.7)
Injection-site pruritus	**0**	1 (1.2)	0	1 (1.7)

Reviewer's comments: This Reviewer asked Kamada to reanalyze their AE database to differentiate between the local AEs at the HRIG and vaccine injection sites for the Phase 2/3 study. These data are presented in Table B. Injection-site pain was more frequent in subjects who received KamRAB (39.0% in the KamRAB group versus 27.1% in the HRIG comparator group for related events). There was otherwise no apparent difference in the frequency of other local AEs (hematoma, paresthesia, hemorrhage, discomfort, pruritus) between the KamRAB and HRIG comparator group as these AEs were uncommon.

Table B: Injection-Site Adverse Events
(Reviewer's Table)

	KamRAB + Vaccine (N=59)		HRIG + Vaccine (N=59)	
SOC Preferred Term	**# Events**	**N (%)**	**# Events**	**N (%)**
Injection-site pain				
HRIG	26	23 (39.0%)	20	16 (27.1%)
Vaccine	10	10 (16.9%)	7	7 (11.9%)
Injection-site hematoma				
HRIG	1	1 (1.7%)	0	0
Vaccine	0	0	0	0
Injection-site paresthesia				
HRIG	0	0	0	0
Vaccine	1	1 (1.7%)	0	0
Injection-site hemorrhage				
HRIG	0	0	1	1 (1.7)
Vaccine	1	1 (1.7%)	0	0
Injection-site discomfort				
HRIG	0	0	2	1 (1.7%)
Vaccine	0	0	0	0
Injection-site pruritus				
HRIG	0	0	1	1 (1.7%)
Vaccine	0	0	0	0

8.4.8 Adverse Events of Special Interest

The US FDA published a safety communication regarding the risks of hemolysis and thrombosis potentially related to human immune globulin products in November, 2012. Study KAMRAB-003 was amended (amendment 4) in August 2013 to include a warning and risk mitigation plan regarding hemolysis and thrombosis. Because of this, Subjects 58 to 118, who were randomized after Amendment 4 became effective, underwent routine laboratory evaluations for hemolysis.

The safety database for the All Studies Pool was searched for event terms in the Hemolytic disorders Standardized MedDRA Query (SMQ). None of the event terms in the Hemolytic disorders SMQ appear in the pooled AE data. In addition, the pooled laboratory data were searched for subjects with a constellation of treatment-emergent changes in hemoglobin, haptoglobin, bilirubin and/or reticulocyte count values suggestive of hemolysis. No such subjects were identified.

Similarly, a search of the safety database for the All Studies Pool revealed no AEs (e.g., deep vein thrombosis, pulmonary embolism) that could represent thrombosis related to administration of KamRAB.

Since KamRAB is a human plasma derived product, subjects were tested for the potential to be infected with HBV and/or parvovirus B19. Seroconversion (hepatitis B surface antigen and parvovirus B19) was assessed in Study 003. No subject in this study seroconverted during this study.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

KamRAB and the other two comparator HRIGs administered in these studies were given as a single dose of 20IU/kg as per the current WHO and CDC recommendation. Thus, there is no data on the contribution of dose to the AE profile of KamRAB.

8.5.2 Time Dependency for Adverse Events

The most common AEs occurring within 72 hours of first injection in the All Studies and TACV Pools were similar to the most common AEs overall (Table 38). By far, the most common AE occurring within 72 hours of injection was injection-site pain in the KamRAB (+ vaccine) and Comparator HRIG (+ vaccine) groups.

Table 38: Adverse Events within 72 Hours
(All Studies, Placebo and TACV Pool)
(Reviewer's Table)

Pool	All Studies		Placebo	TACV	
MedDRA Preferred Term	All KamRAB (N=91)	Other HRIG (N=84)	Saline + Vaccine (N=8)	KamRAB + Vaccine (N=67)	HRIG + Vacccine (N=59)
Injection-site pain	27 (29.7)	21 (25.0)	0	26 (38.8)	18 (30.5)
Headache	6 (6.6)	5 (6.0)	0	3 (4.5)	5 (8.5)
Myalgia	0 (0.0)	4 (4.8)	0	0 (0.0)	4 (6.8)
Arthralgia	3 (3.3)	0 (0.0)	0	3 (4.5)	0 (0.0)
Dizziness	2 (2.2)	2 (2.4)	0	0 (0.0)	2 (3.4)
Fatigue	3 (3.3)	1 (1.2)	0	1 (1.5)	1 (1.7)
Abdominal pain	3 (3.3)	0 (0.0)	0	2 (3.0)	0 (0.0)
Nausea	3 (3.3)	1 (1.2)	0	3 (4.5)	1 (1.7)

8.5.3 Product-Demographic Interactions

The three clinical studies in this Application enrolled primarily young Caucasians (See Section 9.1). Nonetheless, it is notable that the proportion of subjects in the KamRAB group with injection-site AEs, related injection-site AEs, AEs occurring within 72 hours of administration, related AEs occurring within 72 hours of administration, and moderate AEs were higher in Study 003 than in the two other studies. The reason for this difference is not known, but it may be related to cultural differences in AE reporting, or to subject demographics. Studies 23630 and 24061 were performed in Israel while Study 003 was conducted in the United States. In Studies 23630 and 24016, the mean ages of study subjects in the KamRAB groups were 27 and 28 years, respectively, whereas in Study 003, the mean age of subjects in the KamRAB group was 43 years. Finally, the proportion of women was higher in Study 003.

Reviewer's comments: Kamada was asked to provide a safety analysis by the following subgroups: age, sex, and BMI during the mid-cycle review. These data are presented in Table C. There was no effect of BMI on related TEAEs. The percentage of subjects in the KamRAB + rabies vaccine group with TEAE were 28.8% and 25.4% in subjects with BMI >26.32 and ≤26.32 kg/m^2, respectively, with a similar pattern in the Comparator HRIG+Rabies vaccine group. For sex, related TEAEs were nearly twice as

frequent in females as in males in both the KamRAB + rabies and HRIG + rabies vaccine groups (35.6% vs 18.6% in the KamRAB + rabies vaccine group). For all analyses, there were no statistically significant differences between the KamRAB + rabies vaccine and Comparator HRIG + rabies vaccine groups. With respect to age, younger subjects (age ≤47.5 years) experienced more related TEAEs than older subjects (30.5% vs. 23.7% in the KamRAB + rabies vaccine group), with a similar pattern in the Comparator HRIG + rabies vaccine group. However, the magnitude of the difference is small, and the clinical significance of this finding is unclear.

Table C: Demographic Analysis of TEAE
(Reviewer's table)

	KamRAB+Rabies Vaccine
Age	
≤47.5 years	*30.5%*
>47.5 years	*23.7%*
Sex	
Male	*18.6%*
Female	*35.6%*
BMI	
≤26.32 kg/m^2	*25.4%*
>26.32	*28.8%*

A similar subgroup analysis was performed for the PK parameters. There was a consistent pattern of higher RVNA concentrations in younger subjects (<47.5 years old), with higher geometric mean levels seen at all post-baseline time points, and with a higher magnitude difference at later time points where nearly all the antibody is due to active rabies vaccine. Other PK parameters showed a similar pattern, with higher C_{max} and higher AUCs in the younger age group. This was seen in both the KamRAB + rabies vaccine and Comparator + rabies vaccine groups. The previously seen statistically significant difference between treatment groups in RVNA level at Day 3 persists within the subgroup analyses, and another statistically significant difference (p=0.001) appears at Day 7 in the age subgroups, with higher levels for older subjects in the Comparator HRIG + rabies vaccine group (this test was borderline significant in the overall analysis; p=0.051). It should be noted that no correction was made for multiple testing in these analyses.

For the PK analysis by sex, slightly higher RVNA concentrations are seen in females as compared to males, with higher geometric mean levels at all time points. Similarly, higher C_{max} and AUCs were seen in females. The magnitude of these differences was less than that seen for age, and consistent differences by sex were seen only in the KamRAB + rabies vaccine group. This finding is not likely to be clinically significant.

There were no consistent or meaningful differences in PK parameters or in geometric mean RVNA values at post-baseline timepoints, including early time points, between subjects with BMI above and below the median value (26.32 kg/m^2).

8.5.4 Product-Disease Interactions

The clinical studies enrolled healthy normal individuals without comorbidities (See Section 9.1). There are no co-morbidities that would contraindicate the use of KamRAB and a rabies vaccine for PEP.

8.5.5 Product-Product Interactions

Rabies immunoglobulins are known to interfere with antibodies production by patients following immunization with a rabies vaccine. The effect of KamRAB on immune response following rabies vaccination was explored in Studies KAMRAB-003 and 24061. Passive immune-prophylaxis with KamRAB does decrease antibody production by the vaccine but the effect was not clinically relevant. Subjects were able to achieve effective levels of RVNA ($\geq$ 0.5 IU/mL) following co-administration of KamRAB with rabies vaccine in a PEP regimen.

KamRAB may interfere with development of an immune response to attenuated live virus vaccines. Therefore, other attenuated live virus vaccines should not be administered within 3 months of KamRAB; measles vaccine should not be administered within 4 months of KamRAB.

8.5.6 Human Carcinogenicity

Kamada-HRIG drug product is a plasma-derived purified protein; therefore, no testing of genotoxicity, carcinogenicity, or embryotoxicity was performed. However, the product has been marketed for the past 10 years and has been administered to over 250,000 individuals and there were no reports of an association with carcinogenecity.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no overdose of KamRAB reported during the conduct of the three clinical studies. One postmarketing event report of administration of six daily doses of KamRAB was received from India. No adverse events were reported in the patient. Because the vial volume (5 mL) for the product administered is not available for KamRAB, it is not certain that this patient received Kamada-HRIG.

KamRAB has no known central nervous system effects, and has no known potential for abuse. There are no anticipated withdrawal or rebound effects following a single treatment with KamRAB.

8.5.8 Immunogenicity (Safety)

KamRAB is a human plasma-derived purified protein and therefore is not expected to generate a recipient host immune response. However, KamRAB as with all other HRIGs can interfere with the active rabies antibody production in response to rabies vaccination.

8.5.9 Person-to-Person Transmission, Shedding

KamRAB is prepared from human plasma collected from healthy donors who have developed high titers of rabies antibody following immunization with rabies vaccine. The product is prepared in FDA-approved facilities in the US. Donor immunization and plasma collection are performed according to Plasma Protein Therapeutics Association and FDA guidelines. Collected plasma is processed and purified using a series of (b) (4) procedures.

To reduce the risk of transmissible disease, all individual donations are tested and must be nonreactive for antibodies to HIV 1 and 2, antibodies to hepatitis C virus, and hepatitis

B surface antigen. (b) (4) For parvovirus B19, the objective is to reduce rather than eliminate the viral challenge; therefore, only high-titer donations of (b) (4) IU/mL are interdicted.

After plasma units are pooled for manufacturing, the pool is screened and must be non-reactive for antibodies to HIV 1/2, antibodies to HCV, and HBsAg, and have a titer of not more than 10^4 copies/mL of parvovirus B19. In order to further reduce the risk of viral transmission, three specific viral removal steps are employed during manufacture: treatment with solvent detergent (S/D), heat treatment ((b) (4) [Pasteurization]) and nanofiltration using a (b) (4)).

8.6 Safety Conclusions

This BLA includes three clinical studies of KamRAB that enrolled 160 healthy adult subjects. Nine of the 160 subjects in the clinical studies withdrew prematurely. There were 5 subjects who withdrew because of an AE (3 subjects received KamRAB and 2 subjects received Comparator HRIG). Two subjects were withdrawn because of prohibited drug use (positive drug test for cannabinoids) and prohibited prescribed medication (steroids). One subject was lost to follow-up and one subject withdrew consent.

In the three clinical studies, a total of 91 subjects were exposed to KamRAB (20 IU/kg), including 67 subjects who received KamRAB and rabies vaccine; 84 subjects were exposed to comparator HRIG, including 59 subjects who received comparator HRIG and rabies vaccine; and 8 subjects were exposed to saline placebo (all with rabies vaccine). The data from these three studies were pooled to form two pools, an All Studies pool and a Test Article or Comparator with Vaccine (TACV) Pool.

In the All Studies pool, the majority of the subjects were Caucasian (>90%) while the proportion of men and women in each treatment group was similar. The mean ages of subjects in the KamRAB and Comparator HRIG groups were 38 years and 41 years, respectively. The demographics of subjects in the TACV pool were similar to those of the All Studies pool, with two exceptions: the proportion of female subjects in the KamRAB and Comparator HRIG groups was 61% and 64%, respectively, and the mean age of subjects in the Comparator HRIG group was 46 years.

The mean (median) duration of follow-up for subjects in the KamRAB group was 135 days (182 days) and in the Comparator HRIG group was 149 days (184 days) in the All Studies pool. In the TACV pool, the mean (median) duration of follow-up in the KamRAB group was 163 days (185 days) and in the Comparator HRIG group was 187 days (185 days).

There were no deaths or pregnancies during the conduct of the three studies. A single SAE (intraductal proliferative breast lesion that was assessed as not related to study treatment) occurred in a female subject who received KamRAB and rabies vaccine in Study KAMRAB-003. One severe AE, a tooth fracture assessed as not related to study

treatment, occurred in a male subject who received KamRAB and rabies vaccine in Study 003.

In the All Studies pool, the most common AEs in the KamRAB and Comparator HRIG groups were similar, and included injection-site pain (33% and 31% of subjects, respectively), headache (15% and 13% of subjects, respectively), myalgia (9% and 7% of subjects, respectively), and upper respiratory tract infection (9% and 10% of subjects, respectively). The most common AEs occurring within 72 hours of first injection in both treatment groups were similar to the most common AEs overall. Results were similar for the TACV pool. The proportion of subjects with related AEs was similar in the KamRAB and Comparator HRIG groups in the All Studies (43% and 41% of subjects, respectively) and TACV pools (48% and 46% of subjects, respectively).

The most common AE in these studies was injection-site pain. However, other injection-site related AEs such as hematoma, hemorrhage, discomfort paresthesia, pruritus were rare with report of one or fewer subjects within a group in the All Studies and TACV pools.

The most common systemic AE with onset within 72 hours of injection in the KamRAB and Comparator HRIG groups was headache (7% and 6% of subjects, respectively) in the All Studies pool. Other common systemic AEs occurring within 72 hours of injection in the KamRAB group were abdominal pain, arthralgia, fatigue, and nausea, each occurring in 3% of subjects. In the Comparator HRIG group, myalgia (5% of subjects) was also a common systemic AE that occurred within 72 hours of the first injection. Data for the TACV pool were similar to those for the All Studies pool.

The US FDA published a safety communication regarding the risks of hemolysis and thrombosis potentially related to human immune globulin products in November, 2012. A search of the pooled safety data revealed no subject with a hemolysis AE, and a search of the individual study laboratory data revealed no subject with a constellation of changes in laboratory values suggesting hemolysis. No thrombosis or embolism events were reported.

Laboratory values were not pooled for this ISS. However, there were only 11 abnormal blood tests and 16 abnormal urinalyses that were reported as AEs. No safety signal related to the laboratory abnormalities was observed in any study.

In conclusion, the data from the 160 subjects who were enrolled in the three clinical trials indicate that KamRAB is safe and well-tolerated.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

The three clinical studies that comprised this application were conducted primarily in young Caucasians. Similar to other HRIGs that are currently on the market, there is a dearth of data on the use of products of this class in the pediatric population, elderly, pregnant or lactating women, individuals with concurrent acute and chronic diseases (e.g., hypertension, diabetes, renal or hepatic impairment, cardiac disease), viral coinfection (HIV, HBV, HAV, etc.), IgA deficiency, subjects who had received blood or

plasma derivatives in the previous 12 months, and subjects who had received live virus vaccine (e.g., measles vaccine) within the last 3 months.

Kamada believes that KamRAB has been administered to over 250,000 patients outside of the US for over 10 years, and assumes that patients of diverse age groups, races, ethnicities, and health status have received KamRAB for post-exposure prophylaxis against rabies infection.

9.1.1 Human Reproduction and Pregnancy Data

There are no data on the use of KamRAB (or of any other RIG) in pregnant women. Since KamRAB is a human immunoglobulin, it would be expected to be transported across the placenta.

9.1.2 Use During Lactation

There are no data on the use of KamRAB (or of any other RIG) in nursing mothers. Since KamRAB is a human immunoglobulin, it would be expected to be transported in breast milk.

9.1.3 Pediatric Use and PREA Considerations

There are no data on the use of KamRAB (or of any other RIG) in pediatric patients. The FDA has agreed to a deferred PREA study and Kamada Ltd will conduct a Phase 4 study entitled "**Open-label Post-marketing Study of KamRAB Administered as a Single Dose with Active Rabies Vaccine in Children Exposed to Rabies.**" The study will begin enrolling subjects in 2017. The study was presented to PeRC at their July 12, 2007 meeting. PeRC concurred with the deferral of this pediatric study but corrected the deferral date to October 15, 2019. Please refer to Sec 11.6 Recommendations on Postmarketing Actions for additional details.

9.1.4 Immunocompromised Patients

There are no data on the use of KamRAB (or of any other RIG) in immunocompromised patients.

9.1.5 Geriatric Use

There are no data on the use of KamRAB (or of any other RIG) in the geriatric population. Most of the subjects enrolled in the three trials were 18 to <40 years of age. There were only 15 subjects of the 91 subjects (16.5%) who received KamRAB that were between 60 to 69 years of age but no subjects who were older than 69.

10. CONCLUSIONS

Kamada Ltd is submitting a BLA for a human rabies immunoglobulin, KamRAB (proprietary name: KEDRAB) given in combination with a rabies vaccine for passive, transient post-exposure prophylaxis of rabies infection. The proposed dose is 20 IU/kg BW that will be infiltrated locally into the wound/exposure site as per the current WHO and CDC guidelines. The BLA consists of three clinical studies, two Phase 1 studies and a single Phase 2/3 study. The three clinical trials were well executed and individually addressed a different question that in aggregate complemented each other. A total of 91 subjects were treated with KamRAB in these three clinical studies.

The two major regulatory issues that were identified during the clinical review of this application was the surrogate marker for efficacy (RVNA $\geq$0.5IU/mL) and the Day 14

time-point selected for the assessment of efficacy. Another concern intrinsic to the product was the pharmacokinetic profile of KamRAB, which was inferior to that of the Comparator HRIG. After discussions within the Clinical team and consultation with Dr Brett Petersen of the CDC, it was decided that the risk benefit profile of KamRAB favors approval of this Application. Specifically, a RVNA $\geq$0.5IU/mL on Day 14 has been the standard recommended by the WHO since the 1980's. There have been no reports of PEP failure in the United States during the intervening years. Finally, the minor differences in the pharmacokinetic profile of KamRAB relative to the Comparator HRIG are not expected to be clinically relevant. In support of this Application, the "real world" experience with KamRAB was consistent with our assessment. The Israeli Ministry of Health reported that during the period 2010 to 2015, clinical rabies did not develop in 1,863 individuals with confirmed rabies exposure who received PEP with KamRAB.

There are a number of minor issues with this BLA such as the paucity of study centers as the three studies were all single-center studies with two studies conducted at the same site. The patient population that was studied was limited to primarily young Caucasians. As with other marketed HRIGs, there is a paucity of information regarding the use of HRIGs in the ethnic, pediatric, geriatric, immunocompromised, pregnant and lactating population.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Rabies is universally fatal once clinical symptoms have developed. Therefore, the goal of therapy following exposure is to prevent the development of clinical disease. Because of the long incubation period following exposure, PEP has been extremely effective in preventing clinical disease. Indeed, documented cases of PEP failure can be traced to deviations from the WHO-recommended prophylaxis protocol. Common deviations resulting in death include delay in seeking rabies prophylaxis; lack of or improper administration of rabies immunoglobulin; lack of or improper primary wound care; and/or poor quality rabies vaccine or RIG.

The current PEP regimen results from the refinement of work dating back to Louis Pasteur in the 1880s. It consists of passive-active immunization with an anti-rabies immunoglobulin administered in conjunction with vaccination. Although never rigorously tested in controlled studies, this protocol has been successfully adopted worldwide for the past 50 years. Indeed, there has never been a single reported case of PEP failure in the United States since the introduction of RIG and modern cell culture vaccines in the 1980s.

The risk associated with the use of KamRAB is minimal. The most common AE in these studies was injection-site pain, occurring in approximately one-third of the study population. However, other injection-site related AEs such as hematoma, hemorrhage, discomfort paresthesia, pruritus were rare. The AE profile of KamRAB was similar to that of the two Comparator HRIGs (BayRAB and HyperRAB). The safety data from this BLA suggest that KamRAB is safe and well-tolerated. Given this safety profile, the benefit risk profile would seem to favor the approval of KamRAB for rabies PEP.

Please refer to Appendix 1: Risk and Benefit Analysis of KamRAB for Rabies Post Exposure Prophylaxis for additional details.

11.2 Risk Management Plan

KamRAB was administered to 91 subjects in the three clinical studies that comprise this BLA. In addition, it has been in use outside of the US for over 10 years. KamRAB has never been withdrawn from investigation or marketing in any country, and no other regulatory actions related to safety have been required by regulatory authorities. Between January 2006 and December 2015, a total of (b) (4) 2 mL vials (each equivalent to 300 IU) and (b) (4) 10 mL vials (each equivalent to 1500 IU) of KamRAB was sold. This is sufficient for treating approximately 270,000 individuals, assuming a 70 kg average body weight and the recommended dose of 20 IU/kg.

There are no important identified risks for KamRAB but there are a number of potential risks that may occur with its use. These include transmission of infectious agents, hypersensitivity, and thrombotic or hemolytic events. To date, these adverse reactions have not been identified following exposure to KamRAB in clinical trials, or reported following post-marketing use in other countries. In order to minimize these potential risks, relevant information will be included in the prescribing information, and reports of adverse events/reactions will be monitored. Additionally, searches of the literature for safety reports relevant to KamRAB will be performed at least quarterly. All reports on suspected ADRs will be entered into the Kamada Safety Database. This will consist of all information related to the case, including the presence of underlying diseases or concomitant use of other drugs or vaccines.

Routine pharmacovigilance activities such as creation and reporting of individual case safety reports, expedited ADR reports, preparation of Periodic Reports and/or other summary safety reports, and monitoring of the safety profile of Kamada-HRIG product (including signal detection, issue evaluation, updating of labeling and generating risk-benefit assessments) will be continuously performed by Kamada. Topics of special interest such as the development of allergic-type reactions and the possibility of transmission of infectious agents will be closely monitored.

Kamada has proposed the following risk management plan (Table 39):

Table 39: Risk Management Plan
(Applicant's Table)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Hypersensitivity	Routine pharmacovigilance activities: • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific Adverse Drug Reaction (ADR) follow-up)	The prescribing information addresses this risk and relevant mitigation measures.

Table 39: Risk Management Plan (Cont'd)
(Applicant's Table)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Transmission of infectious agents	Routine pharmacovigilance activities: • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form)	The prescribing information addresses this risk and relevant mitigation measures.
Thrombosis	Routine pharmacovigilance activities: • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form)	The prescribing information addresses this risk and relevant mitigation measures.
Hemolysis	Routine pharmacovigilance activities: • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form)	The prescribing information addresses this risk and relevant mitigation measures.

Reviewer's comments: This risk management plan seems appropriate given the relatively benign adverse event profile of this agent and the long duration (>40 years) that other HRIGs have been in use.

11.3 Recommendations on Regulatory Actions

In general, the three studies comprising this BLA were well executed. There were a number of issues with this BLA that were addressed during the review process as discussed in Section 10. In support of this Application, KamRAB has been administered to over 250,000 patients within the past decade. There have been no reports of PEP failure or excessive toxicity. A more thorough analysis of the "real world" experience with KamRAB was provided by the Israeli Ministry of Health. From 2010 to 2015, (b) (4) people in Israel received PEP due to suspected exposure to rabies. All subjects received treatment in accordance with WHO guidance, including the administration of KamRAB and were actively followed at one of the sixteen regional IMoH public health offices. The suspected animals were tested by (b) (4) for Rabies virus in brain samples at the (b) (4) . Of these, 1,863 individuals were confirmed to have been exposed to a rabid animal and none of them developed clinical rabies. There were no reports of serious adverse events related to the administration of KamRAB.

Therefore, this Reviewer recommends the approval of KamRAB to be used in conjunction with rabies vaccine for the post-exposure prophylaxis of rabies. Although there may be some potential controversy regarding the selection of Day 14 as opposed to an earlier time-point (Day 3 or 5) as the time-point for the evaluation of the efficacy of a HRIG, this has been standard for the assessment of efficacy established by both the WHO and CDC. The risk associated with the use of KamRAB was minimal. The most common AE in these studies was injection-site pain, occurring in approximately one-third of the study population. Furthermore, the "real world" clinical experience of KamRAB in Israel between 2010 and 2015 confirms that KamRAB is an effective agent for rabies PEP when used with a rabies vaccine.

11.5 Labeling Review and Recommendations

A brief review of the Package Insert suggests that there were two major deficiencies. First, the data presented in the Clinical Pharmacology section of the document are incomplete. For example, a discussion of the pharmacokinetics results from Study 23630 neglects to report the results of the comparator BayRAB. Second, the data presented in the Adverse Reaction section are inconsistent with those in the BLA submission.

-

11.6 Recommendations on Postmarketing Actions

As per the Pediatric Research Equity Act (21 CFR 314.55(b) and 601.27 9b), Kamada Ltd and the FDA have agreed on a protocol for the conduct of a study that will satisfy the pediatric post-marketing requirement. The study (KamRAB-004) is entitled "**Open-label Post-marketing Study of KamRAB Administered as a Single Dose with Active Rabies Vaccine in Children Exposed to Rabies**". A deferral has been granted and the study will begin enrolling subjects in 2017. The study will be conducted at one or more centers in the United States with experience administering rabies PEP to children. The objectives of the study are:

Primary: To confirm the safety of KamRAB in children ages 0 months to <17 years, when administered as part of PEP.

Secondary:

- To obtain data on anti-rabies antibody levels after treatment with KamRAB and rabies vaccine according to US 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

The study plans to enroll 30 subjects between the ages of 0 months to <17 years with exposure or possible exposure to rabies, for whom PEP against rabies infection is indicated. They will receive a single dose of 20 IU/kg KamRAB on Day 0 and four dose of a licensed rabies vaccine (RabAvert®; Novartis Vaccines and Diagnostics) on Days 0, 3, 7 and 14, according to ACIP recommendations. Telephone contacts will occur on Days 28, 56 and 84. Subjects will be followed for a total of 3 months (84 days) after treatment. Efficacy evaluation will include RVNA titer at Day 14 assessed by a validated RFFIT, and number of cases of active rabies infection in subjects treated with KamRAB and rabies vaccine. Safety data will be collected for local and systemic AEs and physical

examination findings collected during visits on Days 0, 3, 7 and 14 days and by telephone contact on Days 28, 56 and 84.

The study plans to enroll subjects between 0-2 years of age. However, Kamada will request a partial waiver for that age group if enrollment proves impossible.

Reviewer's comments: This Reviewer believes that the proposed plan is reasonable and should satisfy the requirements of the Pediatric Research Equity Act.

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APPENDIX 1: RISK AND BENEFIT ANALYSIS OF KAMRAB FOR RABIES POST-EXPOSURE PROPHYLAXIS

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Rabies infection has effectively a 100% mortality rate if PEP is not administered. • There have only been a handful of cases of survival after clinical onset of disease-almost all of these subjects received rabies vaccine. • The few patients who do recover are left with residual neurologic damage.	• Rabies is a universally fatal disease after the onset of clinical symptoms.
Unmet Medical Need	• There are two other anti-rabies immunoglobulins marketed in the US. • There is a shortage of human anti-rabies immunoglobulins in the undeveloped world but not in the US. Equine anti-rabies immunoglobulin is the predominant agent in undeveloped countries. • There are other competing products being developed in the US (polyclonal and monoclonal Abs). • The expense of the product precludes widespread adoption in the third world	• There is no unmet need in the US and Western Europe.
Clinical Benefit	• PEP has been shown to be effective in animal studies but controlled clinical studies are impractical since rabies is a fatal disease. • Clinical efficacy was first demonstrated in an uncontrolled field study in 1954. A rabid wolf bit 29 people in an Iranian village over several hours. The mortality rate among those receiving vaccine alone was 60% (3 of 5 subjects). The addition of RIG to the vaccine reduced the mortality to 8% (1 of 12 subjects); one of seven subjects administered one RIG injection and vaccine while there were no deaths in the five subjects administered two RIG injections and vaccine. • The current WHO and CDC recommendation for PEP (RIG + 4 or 5 doses of vaccine) has been successfully implemented around the world over the past 40-50 years. The goal is to attain a RVNA $\geq$0.5IU/mL on Day 14. There has never been a single reported case of PEP failure in the United States since the introduction of RIG and modern cell culture vaccines in the 1980s. • KamRAB (20IU/kg) when administered with a licensed rabies vaccine (5 dose regimen) achieved a protective level of 37.2 IU/mL on Day 14 in the current BLA.	• The evidence for the clinical benefit of rabies post-exposure prophylaxis is overwhelming. • Use in ethnic, geriatric, immunocompromised, pregnant and lactating population has not been formally examined. However, KamRAB has been administered to over 250,000 subjects in the last decade without reports of failure or toxicity.
Risk	• The most substantial risks of KamRAB are theoretical, i.e., infection, hemolysis, thrombosis. None of these AEs occurred in the three studies that served as the basis of this review. • Anaphylaxis is unlikely given that it is a human protein. • The most common risk associated with the use of KamRAB is injection-site reactions. However, they are generally mild in severity, and resolve relatively quickly and without sequelae. • No other safety signals were apparent in the adult population.	• All the evidence indicates that the risk of KamRAB administration is minor.
Risk Management	• The most common risks of KamRAB are associated with injection-site reactions. However, they are brief in duration, self-limiting, and resolve spontaneously and without sequelae. • There are potential theoretic concerns such as hypersensitivity reactions, transmission of infectious agents, hemolysis and thrombosis. To date, these adverse reactions have not bee n identified following exposure to KamRAB in clinical trials, or reported following postmar keting use in countries outside of the United States.	• If KamRAB were approved for the general population including pediatrics, routine measures, such as the package insert and the current pharmacovigilance plan would be adequate to manage the risks. • The Applicant plans to conduct a pediatric study (ages 0 to <17 years) beginning in 2017 to identify new potential risks.