Summary Basis for Regulatory Action

Date: August 23, 2017

From: Michael C. Kennedy, PhD, Chair of the Review Committee

STN#: 125613/0

Applicant Name: Kamada Ltd.

Date of Submission: August 29, 2016

Goal Date: August 29, 2017

Proprietary Name/Established Name: KEDRAB/Rabies Immune Globulin (Human)

Indication: KEDRAB is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority: Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	• Winson Tang, MD • David Manschik, MD, MPH Alvandi Firoozeh, MD • Erin McDowell
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Shuya Lu, PhD

CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	• Ewa Marszal, PhD; Lu Deng, PhD; Malgorzata Norton, MS; Olga Simakova, PhD; Lilin Zhong • Pankaj Amin
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Evi Struble, PhD
Clinical Pharmacology Review(s)	Xiaofei Wang, PhD
Labeling Review(s) • *APLB (OCBQ/APLB)*	Alpita Popat, PharmD
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	• Method Validations – Simleen Kaur; Noel Baichoo; Hsiaoling Wang, PhD; Varsha Garnepudi, MS • N/A
Advisory Committee Transcript	N/A

1. Introduction

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 infection is universally fatal once clinical symptoms have developed. The annual global mortality of human rabies was estimated to be between 26,400 and 61,000 in 2010, with the majority of deaths in Asia and Africa. 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 goal of therapy following exposure is to prevent the development of clinical disease. Partly because of the long incubation period following exposure, post-exposure prophylaxis (PEP) has been extremely effective in preventing clinical disease. The current PEP regimen in the United States consists of passive immunization (i.e., local infiltration of human rabies immunoglobulin (HRIG) into and around the wound) followed immediately by active immunization with rabies vaccine. Infiltration of HRIG around the wound provides immediate passive protection while awaiting the patient's immune response to take effect. A major concern is HRIG binding with antigens within the vaccine, thereby decreasing rabies antibody production in response to vaccination. This concern should be addressed in clinical trials for approval of an anti-rabies immunoglobulin product.

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

Precedents for the approval of HRIGs were established in 1974 and 1984 with the FDA approval of two currently marketed HRIGs. However, the clinical team concentrated on two issues in the review of this KEDRAB BLA: the appropriate rabies vaccine neutralizing antibody (RVNA) concentration and the time-point at which this concentration is measured.

2. Background

The effectiveness of the RIG/vaccine combination has never been rigorously tested in randomized placebo-controlled trials, since deliberately exposing subjects to rabies is not ethical. The current recommendations are based upon refinement of a field study conducted in Iran in 1954. 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. Treatment failures are very rare among the estimated 20 million people per year who receive proper therapy in a timely manner. There has never been a single reported case of PEP failure in the United States since the introduction of HRIG and modern cell culture vaccines in the 1980s. The few who have died are from developing countries and most involved deviations from the WHO-recommended prophylaxis protocol.

The two major regulatory issues that were identified during the clinical review of this application were the surrogate marker for efficacy (plasma RVNA $\geq$0.5 IU/mL) and the Day 14 time-point for the assessment of efficacy. In evaluating the efficacy of HRIG, the clinical relevance 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. The issue is that the optimal tissue RVNA is unknown since placebo-controlled clinical studies are not possible in this universally fatal disease for which there is abundant evidence supporting the effectiveness of anti-rabies immunotherapy. In addition, the origin and rationale for the selection of this threshold "therapeutic" concentration (0.5 IU/ml) is unclear but may represent a consensus concentration agreed to by a panel of experts in the field in the 1970s. Nonetheless, a serum RVNA titer $\geq$ 0.5 IU/mL has been recommended by the World Health Organization (WHO) since the 1980s, and served as the basis for approval of the HRIGs in the US.

The second issue is the time-point selected for assessing RVNA. The optimal time-point for evaluating the activity of the HRIG (administered alone) is likely between Days 3 and 7, when the serum RVNA peaks. However, FDA approval of HRIGs has traditionally been based upon achieving a serum RVNA of $\geq$ 0.5 IU/mL on Day 14, a time-point consistent with the current recommendation of the WHO and Centers for Disease Control and Prevention (CDC). It is unclear why the Day 14 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 the T_{max} for the

vaccine-immunoglobulin combination is approximately Day 14. Given that the half-life of HRIGs administered intravenously is ~21 days, serum RVNA from KEDRAB has already 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, the Day-14 antibody titer is not due solely to the HRIG, but rather reflects a combination of the passive and active anti-rabies antibody response.
KEDRAB has been in use outside of the U.S. for 10 years and has been administered to more than 250,000 individuals worldwide. The KEDRAB formulation proposed for use in the U.S. is (b) (4) to the formulation of the product distributed in Israel since 2012. The product distributed or marketed in other countries has a wider pH range.

3. Clinical/Statistical/Pharmacovigilance

a) Clinical Program

The clinical development of KEDRAB began in February 2004, with the initiation of a 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 the same Israeli site in November 2004 and was completed in December 2004. Neither of these studies was conducted under a U.S. IND. Kamada submitted an IND in March 2007 to conduct their Phase 2-3 study (KAMRAB-003), which was not initiated until April 2013. This study was completed in August 2014, and the BLA was submitted in August 2016.

This BLA consists of three clinical studies: two Phase 1 studies and a single Phase 2-3 study. A total of 91 subjects were treated with KEDRAB in these three clinical studies. The two Phase 1 studies were conducted at a single site (Simbec-Tel-Aviv Sourasky Medical Center) while the Phase 2-3 study was conducted at a single site in the U.S. (Prism Research, St Paul, MN). The studies were conducted under International Council for Harmonisation – Good Clinical Practice guidelines.

The three clinical trials individually addressed a different question but in aggregate, complemented each other. The first Phase 1 study (23630) suggests that KEDRAB is not bioequivalent to BayRAB® (an HRIG marketed in Israel). The lower bound of the 90% CI for the point estimate of the ratio of C_{max}, AUC_T, and AUC_I of KEDRAB relative to BayRAB were all below 80% (75.3%, 77.4%, and 78.6%, respectively). As expected, the second Phase 1 study (24061) supports that KEDRAB inhibits rabies antibody production following immunization with a rabies vaccine (Rabipur®). This inhibition is well described and has been reported for all other HRIGs. The Phase 2-3 study (KamRAB-003) provides evidence that KEDRAB is not inferior to HyperRAB (another HRIG licensed in the U.S.) when administered in combination with a rabies vaccine (RabAvert®) for post-exposure prophylaxis. The difference between the proportion of subjects with RVNA titer ≥0.5 IU/mL on Day 14 in the KEDRAB 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 supporting that KEDRAB was non-inferior to HyperRAB.

In general, the three studies comprising this BLA were well-executed. Kamada successfully achieved the prospectively defined primary endpoint of non-inferiority to HyperRAB for PEP in the Phase 2-3 study. Nonetheless, the clinical review team was

initially concerned about the pharmacokinetic profile of KEDRAB since it was not equivalent to those of two other marketed HRIGs. However, 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. Despite these concerns, it is likely that plasma RVNA levels greater than 0.5 IU/mL are protective and these minor differences in pharmacokinetic parameters are unlikely to be clinically relevant.

Because of concerns relating to the RVNA concentration and the time-point at which it was assessed, Dr. Brett Petersen of the CDC was consulted and confirmed that the rationale for the selection of Day 14 for the assessment of HRIG efficacy is based on historical precedent with little objective scientific basis. The best interval for measuring the RVNA is during the first seven days following HRIG administration. The RVNA on Day 14 is more reflective of the effects of the vaccine. Nonetheless, this has been the precedent that has been established for the evaluation of HRIGs. The importance of an RVNA level $\geq$0.5 IU/mL at early time-points (initial week) is difficult to ascertain as there are no data to link these levels with clinical effectiveness. RVNA represents 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. Finally, Dr. Petersen confirmed that the pharmacokinetic profile of KEDRAB is not equivalent to the comparator HRIGs, but these differences are small and are unlikely to be clinically meaningful.

There are 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 primarily to young Caucasians. As with other marketed HRIGs, there is a paucity of information regarding the use of HRIGs in more racially diverse and in the pediatric, geriatric, immunocompromised, pregnant, and lactating segments of the population. However, KEDRAB has been administered to over 250,000 patients outside of the U.S. over the last decade, and it is likely that a diverse population has been treated, with no reports of treatment failures.

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 (b) (4) , issue evaluation, updating of labeling and generating risk-benefit assessments) will be continuously performed by Kamada post-marketing. Topics of special interest such as the development of allergic-type reactions and the possibility of transmission of infectious agents will be closely monitored.

In support of this application, KEDRAB 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 Kamada's HRIG was provided by the Israeli Ministry of Health (IMoH). 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 Kamada's HRIG, and were actively followed at one of the sixteen regional IMoH public health offices. The suspected animals were tested by (b) (4) tests 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 Kamada's HRIG.

Please refer to Section 7 for an overview of the safety profile of KEDRAB. The clinical review team recommends the approval of KEDRAB to be used in conjunction with rabies vaccine for the post-exposure prophylaxis of rabies, given the favorable benefit-risk profile of KEDRAB.

A bioresearch monitoring (BIMO) inspection of the single clinical investigator site for clinical study KAMRAB-003 was conducted in support of this Biologics License Application (BLA). The BIMO inspection did not reveal substantive problems that impact the data submitted in this BLA.

b) Pediatrics

Kamada submitted their initial Pediatric Study Plan (PSP) to the FDA in December 2015 and submitted a revised PSP in April 2016 incorporating all of the FDA recommendations. The revised PSP was agreed to by the FDA on May 20, 2016. The PSP and the study were approved by the Pediatric Review Committee (PeRC) during a meeting held on July 12, 2017, with a date for the submission of the final pediatric study report set to October 15, 2019.

The study (KamRAB-004) is entitled "**Open-label Post-marketing Study of KEDRAB 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. This 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 KEDRAB 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 KEDRAB and rabies vaccine according to US CDC Advisory Committee on Immunization Practices (ACIP) recommendations for PEP
- To evaluate the efficacy of KEDRAB, 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. Subjects will receive a single dose of 20 IU/kg KEDRAB on Day 0 and four doses 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 84 days after treatment. Efficacy evaluation will include RVNA titer at Day 14 assessed by a validated Rapid Fluorescent Focus Inhibition Test (RFFIT), and the number of cases of active rabies

infection in subjects treated with KEDRAB and rabies vaccine. Safety data will be collected for local and systemic Adverse Events 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.

c) Statistical Review

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

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

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

d) Pharmacovigilance

The pharmacovigilance plan proposed by the applicant appears adequate for the sought indication. Class effect adverse events (e.g., thrombotic events) seen in other immune globulin products could potentially present in association with this product. The applicant's aforementioned plan for conducting routine pharmacovigilance appears reasonable in view of available KEDRAB safety data. The review team has not identified any clinical safety concern related to the administration of KEDRAB to date that would warrant additional pharmacovigilance measures.

Summary of Safety Concerns and Planned Pharmacovigilance Actions

Safety concern	Planned action(s)
Important Potential Risk: Hypersensitivity reaction in patients with selective IgA deficiencies who have known antibodies against IgA and patients hypersensitive to the product or to any of its component	Routine pharmacovigilance activities: • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form) • Search of the biomedical literature for case reports relevant to Kamada-HRIG
Important Potential Risk: 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) • Monitoring of literature to identify new potential sources of blood-borne infection
Important Potential Risks: Thrombosis and hemolysis	Routine pharmacovigilance activities: • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form)
Important Missing Information: Pediatric use	An open-label study of Kamada-HRIG product administered as a single dose with active rabies vaccine in children exposed to rabies will be conducted. A total of 30 children between the ages of 0 months to <17 years will be enrolled.

Abbreviations: ADR: adverse drug reaction; AE: adverse event; HRIG: human rabies immune globulin; IgA: immunoglobulin A

4. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

KEDRAB is a sterile liquid formulation rabies immunoglobulin product available in two single-use fill sizes: 2 mL (4ml vial size) and 10 mL (13.5ml vial size). Each vial contains not less than 150 IU/mL of anti-rabies immunoglobulins. The product is stabilized with 0.3 M Glycine.

KEDRAB is manufactured from human hyperimmune plasma of healthy adult donors who have been immunized with rabies vaccine and have developed high titers of rabies antibody. The manufacturing process includes (b) (4) and three virus inactivation/reduction steps. Kamada's control on plasma, final excipients, primary packaging materials and processing reagents (chemicals, (b) (4) and filters) is acceptable. The Drug Substance (DS) stability results support Kamada's proposed DS shelf life of (b) (4) with currently set DS release specifications. The Drug Product (DP) stability results support

Kamada's proposed DP shelf life of 30 months at 5±3°C with currently set DP release specifications.

Control of critical steps: process parameters

Kamada was asked to narrow their process parameters to reflect what was covered by the conformance lots. A Post-Marketing Commitment (PMC) for additional (b) (4) full-scale lots at (b) (4) ranges of the operating parameters and time limits will be requested to assure that the (b) (4) and quality attributes do not change significantly at the outer limits of the operating parameters.

In-process quality attributes

Generally, the process quality attributes are monitored adequately; however, additional (b) (4) will be requested as a PMC to obtain a better idea of the (b) (4) of the manufacturing process and provide a baseline to which manufacturing changes may be compared. Therefore, FDA will request the above-mentioned PMC to manufacture (b) (4) additional full-scale lots to assess additional (b) (4) testing.

Specifications

The specifications and validation of analytical methods for quality control lot release testing have been evaluated by the review team. Revised specifications for (b) (4) will be included under a Post-marketing Commitment after Kamada finalizes the development and validation of an (b) (4) method for the determination of (b) (4) .

A (b) (4) test is used to determine anti-rabies potency in DP (b) (4) as well as (b) (4) . Identity of DP as human IgG is determined by (b) (4) . Purity of the DP as protein composition is determined by (b) (4) . The (b) (4) was evaluated by the (b) (4) method. These assays were determined to be adequately validated.

Bioburden, sterility and endotoxin test methods were qualified and performed in accordance with (b) (4) , respectively. In addition, the pyrogen test is being performed in accordance with 21 CFR 610.13(b) and (b) (4) . Therefore, these methods are acceptable for their intended purpose.

KEDRAB release specifications

Test	Acceptance criteria	Analytical procedure
General Characteristics Tests		
Clarity and Degree of Opalescence	The solution is clear to slightly opalescent	Visual inspection (b) (4)

Degree of Coloration	The solution is colorless to pale yellow	Visual inspection (b) (4)
Visible Particles	May contain some protein particles	Visual inspection
pH	5.0 – 6.0	(b) (4)
Extractable volume	Not Less Than (NLT) 2 mL for the 2 mL vials; NLT 10 mL for the 10 mL vials	(b) (4)
Identity		
Protein Identity	The main component corresponds to IgG standard	(b) (4)
Identification (b) (4)	(b) (4)	(b) (4)
Content		
Anti-Rabies Potency	150(b) (4) IU/mL	(b) (4)
Glycine Concentration	(b) (4)	(b) (4)
Protein Concentration	(b) (4)	(b) (4)
Purity and impurities		
Protein Composition	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Residual Triton X-100[1]	(b) (4)	(b) (4)
Residual TnBP[1]	(b) (4)	(b) (4)
Biological safety tests		
Sterility	Sterile	(b) (4)
Pyrogenicity	Pass	(b) (4)

Bacterial Endotoxins	(b) (4)	(b) (4)

(b) (4)

Virus safety

To support the viral clearance and viral inactivation for the KEDRAB manufacturing process, Kamada provided laboratory viral spiking study data. (b) (4) is the contract laboratory that conducted the viral clearance validation studies. The study's design and results were acceptable.

The starting material is human plasma from donors who have been hyper-immunized with rabies vaccine. Individual plasma units are tested for hepatitis B surface antigen (HBsAg) and for antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2), as well as Nucleic Acid Testing (NAT) for hepatitis B virus (HBV), HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests. Plasma is also tested by in-process NAT procedures for hepatitis A virus (HAV) and parvovirus B19. For HAV, each plasma unit must be non-reactive. For parvovirus B19 the limit in the manufacturing pool is set not to exceed 10^4 IU per mL. All plasma collection centers are FDA-licensed. All test kits are FDA-licensed.

There are three steps from the manufacturing process that Kamada claims to have viral removal/inactivation effects:

1. Solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TnBP) and Octynoxol 9;
2. Heat treatment (pasteurization) step;
3. Nanofiltration (NF) step.

The following table is the Log_{10} Virus Reduction table from the package insert:

Process Step	**Enveloped Viruses**				**Non-enveloped Viruses**	
	HIV-1	**BVDV**	**PRV**	**WNV**	**EMCV**	**PPV**
S/D treatment	>4.99	>5.70	>4.38	>5.46	Not tested	Not tested
Heat treatment	>6.21	>5.67	Not tested	>6.33	3.30	Not tested
Nanofiltration	Not tested	Not tested	>6.58	Not tested	>7.66	3.41
Global Log_{10} Reduction Factor	**>11.20**	**>11.37**	**>10.96**	**>11.79**	**>10.96**	**3.41**

The viral clearance studies provided were reviewed and found to appropriately justify the values listed in the virus reduction table.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. For routine lot release, the applicant will submit final container samples together with lot release protocols. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of Rabies Immune Globulin (Human) (KEDRAB) is listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraph that follows.

Manufacturing Facilities Table for KEDRAB

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Drug substance and drug Product Manufacturing, Labeling, and Testing Kamada Ltd. MP Negev Beit Kama, Israel 8532500	1000630279	600251631	Pre-license inspection	CBER March/April 2017 VAI

CBER conducted a pre-license inspection (PLI) of Kamada Ltd. from March 26-April 5, 2017. At the end of the inspection CBER issued a Form FDA 483 with six observations related to the manufacture of KEDRAB. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

d) Environmental Assessment

The BLA included a request for a categorical exclusion from an environmental assessment under 21 CFR 25.31 (c). FDA concluded that the request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

Kamada provided adequate characterization to support comparability of all product lots (clinical, engineering, conformance). Kamada has committed to supply additional data to support comparability of in-process intermediates which will be provided post-approval.

f) Container Closure System

Kamada-HRIG drug product is supplied as a ready to use sterile solution for intramuscular injection in two presentations, 2 mL fill in 4 mL vials and 10 mL fill in 13.5 ml vials. For the 4 ml vial presentation, the container/closure material consists of clear, colorless, (b) (4) glass s that are closed with (b) (4) rubber stoppers and (b) (4) flip (b) (4) caps. For the 13.5 ml vial presentation, the container/closure material consists of clear, colorless, (b) (4) glass that are closed with (b) (4) rubber stoppers and (b) (4) flip (b) (4) caps. The container closure integrity testing was validated by (b) (4) testing, however there was (b) (4) . Kamada has agreed to a postmarketing commitment to perform a validation with a (b) (4) .

5. Nonclinical Pharmacology/Toxicology

A GLP toxicology study was conducted in healthy rats. The animals received a single intramuscular injection of 60 or 120 IU/kg/injection (3-fold and 6-fold higher than the recommended human dose). No toxicities were observed for the duration of the study. Additionally, the formulation and impurity profile is judged safe for human administration when used according to the recommended indication and dose.

6. Clinical Pharmacology

KEDRAB is a human rabies immune globulin product indicated for passive, transient PEP of rabies infection, when given immediately after contact with a rabid or possible rabid animal and concomitantly with a rabies vaccine. The proposed dose regimen is a single dose of intramuscular injection at the dose of 20 IU per kilogram of body weight in combination with rabies vaccine.

The pharmacokinetic profile of KEDRAB was compared with a comparator HRIG that is currently on the market, in 26 healthy subjects. In a single-dose, two-way crossover study comparing KEDRAB to the corresponding reference comparator HRIG product, at the dose of 20 IU/kg in healthy subjects, KEDRAB showed lower Cmax and AUC of rabies virus neutralizing antibody (RVNA) than the comparator HRIG. The bioequivalence (BE) assessment results did not meet bioequivalence criteria. The point estimate of the ratios of ln-transformed Cmax, AUC_{0-t}, and AUC_{∞} for RVNA were within the acceptable bioequivalence limits of 80- 125% (81.71%, 82.35%, and 84.44%for Cmax, AUC_{0-t}, and AUC_{∞} respectively). However, the lower bound of the 90% confidence interval (CI) of Cmax, AUC_{0-t}, and AUC_{∞} were below the bioequivalence limit of 80-125% (75.34 – 88.62%, 77.39 - 87.63%, and 78.63 – 90.68% for Cmax, AUC_{0-t}, and AUC_{∞} respectively).

HRIGs have the potential to attenuate the vaccinee's immune response to rabies vaccine. In a double-blind, randomized study, 16 healthy subjects were administered either KEDRAB (20 IU/kg IM) or saline placebo followed by three doses of a rabies vaccine on Days 0, 7 and 28. None of the subjects in either group developed a RVNA

≥0.5 IU/mL until Day 14. Compared to the placebo + vaccine group, subjects in the KEDRAB + vaccine group had lower RVNA titers on Day 14. This observation supports that KEDRAB, similar to other HRIGs, has a limited effect in interfering with the host immune response to rabies vaccine.

The pharmacokinetic profile of KEDRAB was also compared with the comparator HRIG in a single-dose, parallel study when co-administered with five doses of a rabies vaccine on Days 0, 3, 7, 14, and 28 in 118 healthy subjects. KEDRAB was not bioequivalent to the comparator HRIG when co-administered with a five-dose rabies vaccine regimen: the 90% confidence interval (CI) of Cmax, AUC_{0-t}, and AUC_{∞} were out of the bioequivalence limit of 80-125% (90.62 – 171.28%, 79.03 – 134.98%, and 80.48 – 141.54% for Cmax, AUC_{0-t}, and AUC_{∞} respectively). The mean RVNA titer on Day 3 was lower in the KEDRAB with rabies vaccine group than in the comparator HRIG with vaccine group (0.188±0.051 vs. 0.229±0.054, P=0.0005). However, these pharmacokinetic differences are not expected to affect clinical outcomes.

7. Safety

The safety profile associated with the use of KEDRAB was favorable. There were no deaths during the conduct of the three studies. There was only a single Serious Adverse Event reported in the three studies. A woman who received KEDRAB and rabies vaccine in Study KAMRAB-003 was found to have an intraductal proliferative breast lesion that was probably not related to study treatment. The most common Adverse Event (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, and pruritus were rare. The AE profile of KEDRAB was similar to that of the two Comparator HRIGs (BayRAB and HyperRAB). The safety data from this BLA suggest that KEDRAB is safe and well tolerated.

There are a number of potential risks that may occur with KEDRAB. These include transmission of infectious agents, hypersensitivity, and thrombotic or hemolytic events. To date, these adverse reactions have not been identified following exposure to KEDRAB 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 KEDRAB 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.

The favorable safety profile of KEDRAB in the three clinical studies that constitute this BLA is consistent with the post-marketing experience of this agent. Kamada's HRIG has been in use outside of the U.S. 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's HRIG is administered in named patient programs. Kamada's HRIG is being prescribed to children in India, Israel, Russia and South Korea. The formulation of KEDRAB proposed for approval in this BLA is (b) (4) to the

formulation of the product distributed in Israel since 2012. Kamada estimates that over 250,000 individuals worldwide have been treated with Kamada's HRIG, and there have been no safety issues to date.

8. Advisory Committee Meeting

The efficacy and safety profiles of HRIGs are well established since the FDA has already approved two HRIGs (HyperRAB and Imogam) that are currently marketed in the United States. The efficacy and safety profiles of KEDRAB do not differ from these other HRIGs. The designs of the three studies submitted in this BLA are also similar to the studies for the other HRIGs. Therefore, the review team did not have any substantial questions for consideration by an Advisory Committee.

9. Other Relevant Regulatory Issues

None.

10. Labeling

The proposed proprietary name, KEDRAB, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on November 1, 2016, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on November 14, 2016.

The APLB found the prescribing information (PI) and carton/container labels to be acceptable from a promotional and comprehension perspective. The review committee negotiated revisions to the PI, including CLINICAL PHARMACOLOGY and ADVERSE REACTIONS. All issues were acceptably resolved after exchange of information and discussions with the applicant. No issues were identified with the proposed carton and container labeling.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The review team recommends approval of KEDRAB for passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and concurrently with a full course of rabies vaccine.

b) Risk/Benefit Assessment

Rabies is a fatal disease and passive, transient post-exposure prophylaxis with HRIGs (including KEDRAB) administered concurrently with a full course of rabies vaccine immediately after contact with a rabid animal is the only effective therapy. The risk associated with the use of KEDRAB is minimal with injection-site pain the most common Adverse Event. Therefore, the benefit risk profile favors the approval of KEDRAB for post-exposure prophylaxis. The quality, efficacy, and safety of KEDRAB

have been reviewed and have been determined to be acceptable for use as indicated in the label.

c) Recommendation for Post marketing Activities

PREA PMR

1. Kamada committed to a deferred pediatric study under PREA for passive, transient post-exposure prophylaxis of rabies infection in pediatric patients ages 0 months to <17 years. The timelines for the study are:

Final Protocol Submission: December 14, 2016
Study Initiation Date: March 31, 2017
Study Completion Date: June 15, 2020
Final Report Submission: January 15, 2021
In addition, the sponsor will conduct routine pharmacovigilance studies as described above, in Section 7.

PMC

As discussed above, the following post-marketing commitments not subject to the reporting requirements under Section 506B are recommended:

2. Kamada commits to perform full scale validation on (b) (4) full scale lots, (b) (4) of the critical operating parameter ranges and times, including the (b) (4) for the (b) (4) step, with in-process testing for (b) (4) at each manufacturing step.

   Kamada will submit a validation protocol outlining the operating parameters for each lot, and (b) (4) tests along with the acceptance criteria, as a Postmarketing Commitment – Product Correspondence prior to manufacture of these lots. The final report will be submitted as a Postmarketing Commitment – Final Study Report by August 31, 2018. These lots will be placed on stability and a final stability report will be submitted as a Postmarketing Commitment – Final Study Report by February 28, 2022.

   Final Protocol Submission: October 31, 2017
   Study Completion Date: June 29, 2018
   Final Report Submission: August 31, 2018
   Final Stability Report Submission: February 28, 2022

3. Kamada commits to perform validation of an improved (b) (4) method and determine the (b) (4) specifications accordingly.

   A final validation report as well as the method SOP and specifications will be submitted to FDA by October 31, 2017 as a CBE-30 Supplement. In case a different (b) (4) than the (b) (4) will be chosen for the validation, a full characterization of the (b) (4) will be performed.

The final method specification will include (b) (4) .

The submission will include the acceptance criteria for (b) (4) .

Study Completion Date: September 29, 2017
Final Report Submission: October 31, 2017

4. Kamada commits to perform validation of the container closure integrity test for each stopper and vial combinations (2 ml product fill (in 4 ml vial size) and 10 ml product fill (in 13.5 ml vial)size vials and stoppers, from each of two vendors) with the inclusion of (b) (4) . Kamada will submit a final validation report.

   Final Report Submission: December 29, 2017