HUMAN VACCINES & IMMUNOTHERAPEUTICS
2020, VOL. 16, NO. 2, 452–459
https://doi.org/10.1080/21645515.2019.1656967

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RESEARCH PAPER

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Safety and efficacy results of simulated post-exposure prophylaxis with human immune globulin (HRIG; KEDRAB) co-administered with active vaccine in healthy subjects: a comparative phase 2/3 trial

Mark A. Matson[a], Eran Schenker[b], Michal Stein[b], Vladislava Zamfirova[c], Huy-Binh Nguyen [c], and Garrett E. Bergman[c]

[a]Investigator. Prism Research, St. Paul, MN, USA; [b]Department of Medical Affairs, Kamada Ltd, Beit Kama, MP Negev, Israel; [c]Department of Medical Affairs, Kedrion Biopharma Inc, Fort Lee, NJ, USA

ABSTRACT

We conducted a clinical trial to assess the safety and putative efficacy of an additional human rabies immune globulin (HRIG; KEDRAB) versus an older product (Comparator, HyperRAB S/D® [Grifols]) and determine whether HRIG interferes with development of endogenous antibodies versus Comparator, when each is given with an active rabies vaccine. This was a prospective, double-blind, single-period, non-inferiority study in which subjects were randomized (1:1) to a single dose (20 IU/kg) of HRIG or Comparator on day 0 and rabies vaccine (RabAvert® [GlaxoSmithKline]; 1 mL of ≥2.5 IU/mL) on days 0, 3, 7, 14, and 28. Anti-rabies antibodies were measured by rapid fluorescent focus inhibition test on day 14, and subjects were followed until day 185. Rabies virus neutralizing antibody (RVNA) titers ≥0.5 IU/mL were considered seroconversion putatively indicative of protection. The non-inferiority criterion was the lower limit of the 90% confidence interval (CI) >−10%, for the between-group difference in the proportion of subjects achieving RVNA ≥0.5 IU/mL. On day 14, 98.3% of 59 subjects in the HRIG group and 100% of 59 in the Comparator group had RVNA ≥0.5 IU/mL (difference between proportions − 1.8%; 90% CI, − 8.2, 3.1; non-inferiority criterion met). One subject in the HRIG group did not meet the seroconversion criteria for anti-rabies antibody, and one subject in the Comparator group showed an anamnestic response, with much higher than expected anti-rabies antibody levels at both baseline and on day 14. Thus, HRIG allows for prophylactic anti-rabies antibody titers and is non-inferior to Comparator, when administered with rabies vaccine.

ARTICLE HISTORY
Received 29 May 2019
Revised 26 July 2019
Accepted 11 August 2019

KEYWORDS
Immunoglobulin; post-exposure prophylaxis; rabies; vaccine; zoonotic disease

Introduction

Rabies is a serious viral zoonosis that remains a significant public health problem in many regions of the world.[1–5] After entering the central nervous system, the rabies virus causes an acute, progressive encephalomyelitis that is almost always fatal if there is no intervention prior to the emergence of symptoms.[6,7] Globally, rabies is responsible for approximately 59,000 deaths annually, with infection from dogs accounting for over 99% of fatal cases.[8] In the United States, canine rabies has been largely controlled since the 1970s as a result of routine vaccination of domestic animals and wildlife, and animal control programs. Since then, the vast majority of rabies circulates among wildlife. In 2017, the major reservoir species in the United States were bats (32.2%), raccoons (21.1%), foxes (7%), cats (6.2%), dogs (1.2%), and cattle (0.8%).[9] As a result of aggressive control efforts, rabies in humans is extremely rare in the United States. During 2017, samples from 21 persons suspected clinically of having developed rabies were submitted to the U.S. Centers for Disease Control and Prevention (CDC) for diagnostic testing. Two persons (9.5%) were confirmed to have had rabies, and both died.[9]

Human infection occurs when an infected animal transmits the virus to man via saliva through a bite, a scratch, fluid (blood, saliva) contact with mucous membranes (such as the eyes, nose, or mouth), or licking of a wound.[12] Following viral inoculation *e.g.* at the bite site, viral entry into axonal terminals at the neuromuscular junction is mediated through nicotinic acetylcholine receptors, although neural cell adhesion molecule and p75 neurotrophin receptors may also play a role in neurotrophism and cell-to-cell spread.[6,13] From the peripheral nervous system, rabies virus spreads to the central nervous system (CNS) via retrograde fast axonal transport.[14] CNS neuropathophysiology includes altered serotonergic/cholinergic signaling, and altered immediate early gene activation patterns, although their role in the pathogenesis of clinical rabies is unclear.[15–17] Interestingly, at autopsy in rabies patients, inflammation is generally mild and neurodegeneration is minimal, suggesting that changes in neuronal function rather than neuronal loss or inflammatory effects drive rabies neuropathology.[6]

Rabies remains a fundamentally incurable disease. Although nearly universally fatal if left untreated, post-exposure prophylaxis (PEP) for individuals with suspected exposure to rabies is uniformly effective when appropriately administered.[18] Recommendations for PEP include 1) immediate washing of the wound with soap and water, and irrigation with a virucidal agent; 2) induction of active immunity with vaccine; and 3) providing passive immunity by administering rabies immunoglobulin.[19] Rabies immunoglobulin provides rapid passive rabies protection by reducing the local viral burden until a protective response from active immunization is mounted.[20–22] The utility of rabies immunoglobulin is supported by results

CONTACT Huy-Binh Nguyen hb.nguyen@kedrion.com Kedrion Biopharma Inc., 400 Kelby Street, 11th Floor, Fort Lee, NJ 07024, USA

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indicating that vaccination alone may not provide protection against rabies in all exposed individuals.[21,23,24] When administered according to guidelines, the efficacy of PEP with vaccination plus rabies immunoglobulin, for prevention of death, approaches 100%.[18]

Only two licensed rabies immunoglobulin products were available in the United States prior to 2017: Bayrab/HyperRAB S/D® (Comparator, Rabies Immune Globulin [Human], Grifols Therapeutics Inc., Research Triangle Park, NC, USA)[25] and Imogam® (Rabies Immune Globulin [Human], Sanofi Pasteur SA, Lyon, France),[26] until the approval of a third product, KEDRAB™ (HRIG, Rabies Immune Globulin [Human], Kedrion Biopharma Inc., Fort Lee, NJ, USA).[27] In 2016, HyperRAB S/D represented 96% of the rabies immunoglobulin market in the United States, with the remainder comprising of Imogam.[28] Such medicines whose supply are dependent on 3 or fewer manufacturers are particularly vulnerable to drug shortages.[29] Correspondingly, in the period from 2001 to 2015, among shortages of any vaccine or immune globulin in the United States, the longest shortage in duration was for rabies immunoglobulin.[30] In 2018, HyperRAB S/D was discontinued. As the consequences of untimely or inadequate (*e.g.* insufficient wound infiltration) administration of rabies immunoglobulin can lead to fatal PEP failure, such shortages are a critical concern in emergency medicine.[31,32] Thus, the clinical development of HRIG was undertaken in order to assess the non-inferiority of HRIG compared to the dominant market product and establish its suitability to diversify rabies immunoglobulin supply sources in the United States.

The pharmacokinetics (PK) and safety of this new HRIG had been investigated in 2 phase 1 studies, indicating that it was well tolerated and that recipients achieved an adequate level of rabies virus antibody titers reflective of seroconversion and indicative of protection (≥0.5 IU/mL),[33,34] when HRIG was administered in conjunction with active rabies vaccine.[27] Virus antibody titer of ≥0.5 IU/mL is used as a correlate of protection since a protective concentration cannot be established in humans. We report here the results of a phase 2/3, single-center, prospective, randomized, double-blind, parallel-group, non-inferiority study for licensure in healthy male and female volunteers ≥18 years old.

Materials and methods

Design

This study (NCT02040090; Figure 1) evaluated the safety of the new HRIG versus Comparator, an older marketed product, in a simulated PEP regimen. The objective was to determine whether either preparation interfered with development of endogenous antibodies, when co-administered with an active rabies vaccine (RabAvert®, GlaxoSmithKline, NDC#58160–964). Prior to any study activity, the protocol and Informed Consent Form were approved by RCRC Independent Review Board, Austin TX, USA. All subjects provided informed written consent prior to any study procedures.

Selection of study population

Subjects were healthy male and female volunteers 18 to 75 years of age who reported they had had no prior exposure to rabies epidemic, rabies vaccine, and/or rabies immunoglobulin. Subjects were identified and contacted based on eligibility criteria from an active database maintained by study site.

Treatment

Subjects were randomized (1:1) to receive a single dose (20 IU/kg) of HRIG or Comparator on day 0 and rabies vaccine (1 mL of ≥2.5 IU/mL) on days 0, 3, 7, 14, and 28. HRIG or Comparator was administered as a single dose via intramuscular injection as follows: the first 5 mL of the dose was administered to the left leg lateral muscle; the remainder (up to 5 mL) was administered to the right leg lateral muscle. Additional amounts up to 2.5 mL (for a subject >75 kg but ≤93.75 kg) were administered to the left deltoid muscle. The doses and timing of study treatments were based on the recommendations for rabies PEP at the time of study design.[35] The right deltoid muscle was utilized for the administration of the rabies vaccine. 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 subjects received.

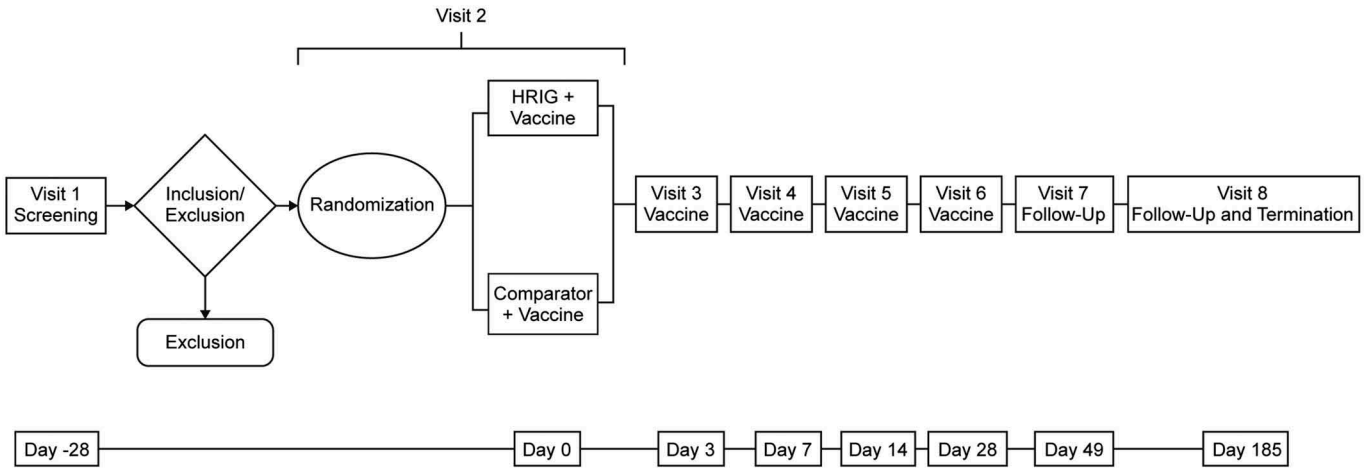

Figure 1. Study design. HRIG = human rabies immune globulin.

Assessments

Blood and urine collection

Serum samples for determination of rabies virus neutralizing antibody (RVNA) titers were collected on days 0, 3, 7, 14, 28, 49, 185, and/or early discontinuation. Serum samples for immunogenicity markers (complement activation markers C3, C4, and CH50) were collected on days 0 (prior to drug administration), 14, 49, 185, and/or early discontinuation. Samples for hematology, clinical biochemistry, and urinalysis tests were collected at screening, days 7, 28, 49, 185, and/or early discontinuation. Additional samples for hemolysis assessment were collected on days 0, 3, 7, and 14 (and day 28 if results from day 14 were abnormal).

Diary cards

Diary cards were completed by subjects at home to record adverse events (AEs), concomitant medications, and any additional information deemed relevant by the subjects, for 14 days from the start of treatment (day 0) until day 14 or early discontinuation.

Vital signs, electrocardiograms, and physical examinations

Vital signs were recorded at screening, days 28, 49, 185, and/or early discontinuation. Electrocardiograms (ECGs) were performed at screening, day 185, and/or upon early discontinuation, if applicable. Physical exams were performed at screening, days 49 and 185, and/or upon early discontinuation. Body temperature was recorded before administration of study treatment and at all visits through day 28.

Adverse events

Adverse events were solicited and recorded throughout the study.

Assays

The rapid fluorescent focus inhibition test (RFFIT) was used to determine the total RVNA titer. RFFIT does not distinguish between IgG and IgM, but measures the combined activity of passive (IgG) and active immunity, and is considered the appropriate test to ascertain the effectiveness of rabies vaccination.[36,37]

Endpoints

Efficacy

The primary endpoint was achievement of an RVNA titer ≥0.5 IU/mL on day 14, as determined by RFFIT. This threshold was chosen based on the World Health Organization recommended minimum anti-rabies antibody titer threshold value (≥0.5 IU/mL), which is considered an adequate measure of seroconversion after vaccination and uniformly thought to provide protection during rabies exposure.[33,34] In this non-inferiority trial, the null hypothesis was that the proportion of HRIG + vaccine subjects with anti-rabies concentration ≥0.5 IU/mL on day 14 would not be less than the corresponding proportion of Comparator + vaccine subjects by ≥0.1.

Pharmacokinetics

Secondary endpoints included selected PK parameters: maximum concentration in plasma (C_{max}), time to maximum concentration in plasma (t_{max}), area under the concentration-time curve from 0 to the last observation ($AUC_{0\text{-last}}$), area under the concentration-time curve from 0 to infinity ($AUC_{0\text{-}\infty}$), and the plasma half-life ($t_{1/2}$) of anti-rabies antibody titers, as measured by RFFIT.

Safety

The safety and tolerability of the study treatments were assessed based on vital signs and physical examination findings, ECGs, laboratory findings, and the occurrence of AEs after drug administration. A treatment-emergent adverse event (TEAE) was defined as any AE that occurred on or after the date and time of the first dose of study treatment. Related AEs were considered by the principal investigator to have a relationship ("Related", "Probable", "Definite") to study drug.

Data analysis

Study populations

The as-treated population was defined as all randomized subjects who received at least three vaccine doses and one dose of the HRIG or Comparator on day 0. The safety population included all subjects who were randomized and who received at least one dose of study medication.

Statistical methods

The proportions of subjects in the HRIG and Comparator groups with RVNA titers ≥0.5 IU/mL on day 14 were determined using assessment of proportions and confidence intervals (CIs). The null hypothesis, that the difference between the proportions of subjects in the HRIG versus Comparator groups was ≤ − 0.1, was rejected if the lower bound of an exact 90% binomial CI exceeded 0.1.[38] A sample size of 53 in each group provided 80% power to reject the null hypothesis.

Safety and tolerability were assessed descriptively and displayed by arithmetic means and standard deviation (S.D.) for quantitative outcomes and by comparing the differences between day 0 (baseline) and post-dosing days. PK analysis was done by log transformation of the plasma HRIG concentrations, and an asymptotic 90% CI for these values was calculated.

This trial is registered under Clinicaltrials.gov identifier NCT02040090.

Results

Subjects

A total of 118 subjects were randomized and treated with HRIG (59 subjects) or Comparator (59 subjects). Overall, 113 subjects (95.8%) completed the study and 5 subjects (4.2%) terminated early (Figure 2), most often for an adverse event (2 subjects, both in the HRIG group). All but 5 subjects (4 in the HRIG group and 1 in the Comparator group) received all 5 doses of rabies vaccine. Demographic characteristics were comparable between treatment groups, with the majority of subjects being female (63.6%), white (93.2%), not of Hispanic or Latino ethnicity (97.5%), and with a median age of 47.5 years (Table 1).

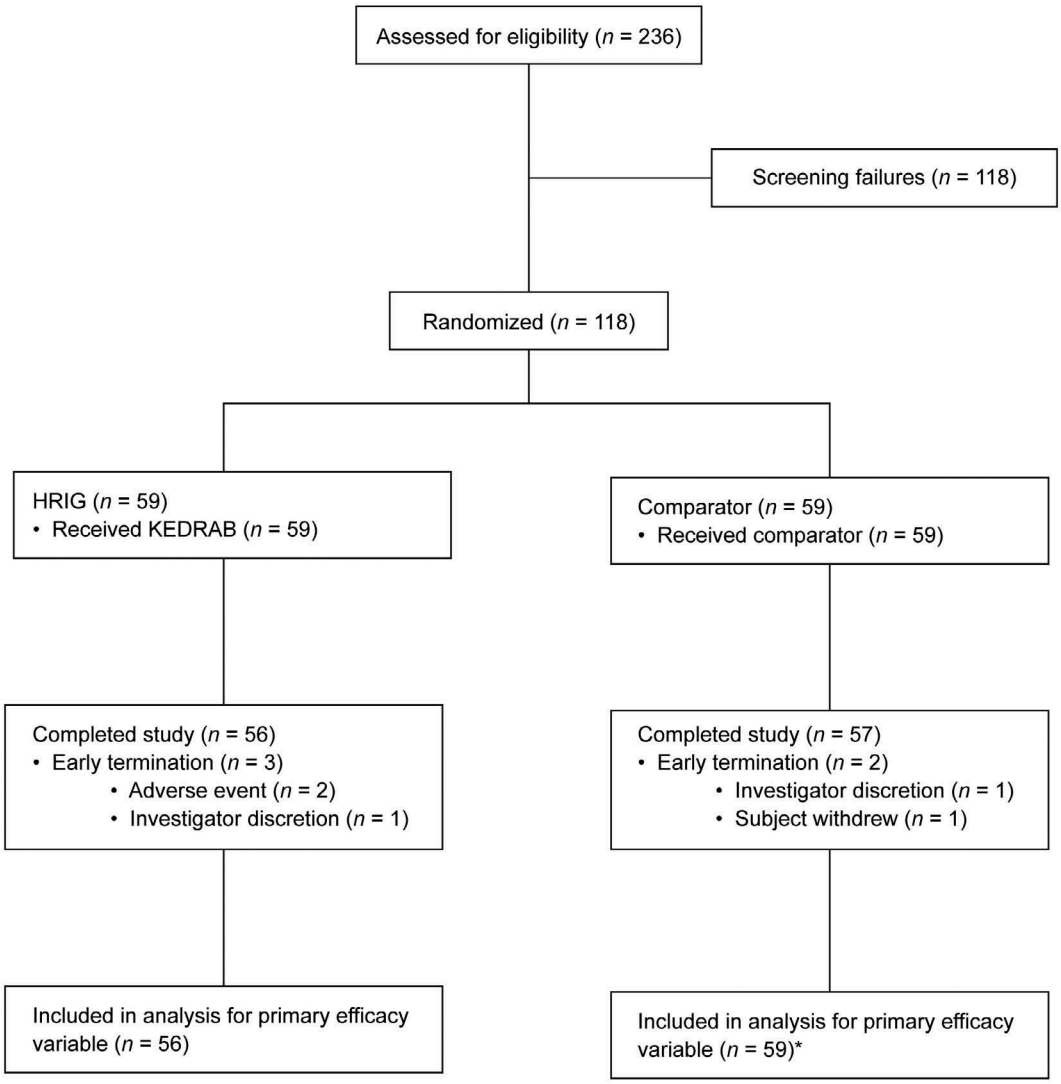

Figure 2. Subject disposition. HRIG = human rabies immune globulin. *Early termination subjects in Comparator group met the criteria for inclusion in the as-treated population and therefore were not excluded from the analysis.

Efficacy

Overall, 98.2% of subjects in the HRIG group and 100% of those in the Comparator group had an RVNA titer ≥0.5 IU/mL on day 14. The difference between the proportions of subjects achieving this endpoint was – 1.8% (90% CI, – 8.2, 3.0; Table 2). The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of – 10%, thus demonstrating that the primary endpoint of non-inferiority was achieved.

A post-hoc sensitivity analysis, including available data for day 14 for one of the study subjects who discontinued due to an AE, provided results consistent with those from the primary analysis (between-group difference in proportions achieving RVNA ≥0.5 IU/mL = – 1.8%; 90% CI, – 8.1, 3.2).

Pharmacokinetics

The plasma concentration-time profiles following intramuscular injection of HRIG and Comparator appeared similar (Figure 3), and demonstrated that plasma RVNA concentrations declined in a biphasic manner after the absorption phase was complete. All subjects in both treatment groups had detectable RVNA at day 3, and there were no statistically significant between-group differences in plasma neutralizing antibody PK parameters (Table 3). Only the RVNA titers at visit 3 (day 3) were statistically different between the HRIG and Comparator groups. The geometric mean (S.D.) values were 0.18 (0.05) IU/mL and 0.22 (0.05) IU/mL, respectively (p = .0003). Although RVNA titers were still quantifiable on day 185 in all subjects who completed the study, it was not possible to calculate a terminal-phase $t_{1/2}$ in all subjects because it requires at least 3 quantifiable RVNA titers to be determined from samples collected after the observed t_{max}. The geometric mean (S.D.) for the terminal-phase $t_{1/2}$ was 45.9 (1.39) days for HRIG (n = 43) and 50.9 (1.30) days for Comparator (n = 44).

Safety

Overall, HRIG was well tolerated with a safety profile similar to that for Comparator (Table 4). The most frequently reported TEAEs in the HRIG and Comparator groups, respectively, were

Table 1. Subject characteristics[a].

	HRIG	Comparator	Total
	(*n* = 59)	(*n* = 59)	(*N* = 118)
Age, yr (mean [S.D.)	43.3 (16.1)	46.3 (14.5)	44.8 (15.3)
median	43.0	49.0	47.5
Sex, no. (%)			
Male	22 (37.3)	21 (35.6)	43 (36.4)
Female	37 (62.7)	38 (64.4)	75 (63.6)
Race, no. (%)			
Asian	1 (1.7)	0	1 (1.8)
White	57 (96.6)	53 (89.8)	110 (93.2)
Black/African-American	0	4 (6.8)	4 (3.4)
Other	1 (1.7)	2 (3.4)	3 (2.5)
Ethnicity, no. (%)			
Hispanic/Latino	2 (3.4)	1 (1.7)	3 (2.5)
Not Hispanic/Latino	57 (96.6)	58 (98.3)	115 (97.5)
BMI, kg/m^2 (mean [S.D.])	26.4 (3.7)	26.3 (3.8)	26.3 (3.7)
median	26.1	26.8	26.3
Weight, kg (mean [S.D.])	75.3 (10.1)	76.6 (11.4)	75.9 (10.8)
median	75.0	78.2	77.0
Height, cm (mean [S.D.])	169.0 (8.3)	170.5 (8.4)	169.8 (8.4)
median	168.3	170.3	168.9

[a]S.D. = standard deviation, BMI = body mass index.

Table 2. Subjects with geometric mean RVNA ≥0.5 IU/mL on day 14[a].

	HRIG With Rabies Vaccine	Comparator With Rabies Vaccine
	(*n* = 57)	(*n* = 59)
RVNA titer ≥0.5 IU/mL, no. (%)	56 (98.2)	59 (100)
Exact 95% CI for proportion, %	90.6, 100	93.9, 100
Difference HRIG – Comparator, %	−1.8	
Exact 90% CI for difference, %	−8.1, 3.0	

[a]RVNA = rabies virus neutralizing antibody, HRIG = human rabies immune globulin, CI = confidence interval.

injection site pain (49.2% vs. 39.0%), headache (13.6% vs. 15.3%), upper respiratory tract infection (13.6% vs. 13.6%), and myalgia (13.6% vs. 10.2%). The most common drug-related TEAEs in the HRIG and Comparator groups, respectively, were injection site pain (42.4% vs. 28.8%), headache (3.4% vs. 5.1%), and myalgia (1.7% vs. 5.1%; Table 4). While the incidence of injection site pain considered to be related to treatment was numerically higher with HRIG versus Comparator, a post hoc statistical analysis indicated that this difference was not significant (Fisher exact test, $p = .178$). No deaths occurred during the study. One subject in the HRIG group had a serious TEAE, an intraductal proliferative breast lesion that resulted in discontinuation of study treatment. One additional subject in the HRIG group had a non-serious TEAE of nipple pain that resulted in discontinuation of study treatment. Neither of these TEAEs were considered related to study drug.

There were no clinically meaningful differences between the HRIG and Comparator groups for changes from baseline in hematology, clinical chemistry, urinalysis, vital signs, ECGs, serology, or immunogenicity during the study. There were no clinically meaningful differences between treatment groups in medical/surgical history or concomitant medication usage. No AEs related to hemolysis or thrombogenicity were observed.

Discussion

The results from this study showed that HRIG was non-inferior to an established product, Comparator, for achieving RVNA ≥0.5 IU/mL on day 14, when each was administered concomitantly with rabies vaccine. The design for this study was based on the Advisory Committee on Immunization Practices guidelines[35,39] for rabies PEP, which recommend that treatment in individuals without prior vaccination consist of both rabies immunoglobulin and vaccine. This protocol provides passive immunity protection in the initial stage of exposure, while the active immune response is just developing and the patient is at risk. Although an endogenous anti-rabies antibody response elicited by active immunization is crucial for effective protection, passive immunization with rabies immunoglobulins may interfere with this active immune response.[39] Thus, a key objective of this study was to establish the non-inferiority of the RVNA response after simulated PEP using HRIG + vaccine, as compared to with Comparator + vaccine. The threshold for non-inferiority was achieved by HRIG despite the fact that one subject in the HRIG group demonstrated outlying results in not achieving anti-rabies neutralizing antibody titer ≥0.5 IU/mL on day 14 after administration (but did by day 28). A personal communication with Susan M. Moore, Ph.D., from the reference laboratory (Kansas State University Veterinary Diagnostic Laboratory), revealed that " … though not common, there are some subjects who fail to reach 0.5 IU/mL by day 14 (1.4%-13%)." Failures to achieve neutralizing antibody titers ≥0.5 IU/mL on day 14 have also been reported in prior studies of rabies vaccines.[40–42] One subject who received Comparator had an elevated RVNA level at baseline and RVNA level of 724.1 IU/mL on day 14, which was considerably higher than other subjects and was suggestive of an anamnestic immune response resulting from prior exposure to rabies antigen.[43] One subject in the Comparator group withdrew from the study after missing a dose of vaccine on day 28. These subjects met the criteria for inclusion in the as-treated population and therefore were not excluded from the analysis.

Two subjects in the HRIG group withdrew due to adverse events that were not considered related to the study by principal investigator. One subject had a positive mammogram test and ultrasound-guided biopsy of breast mass diagnosed as positive for Grade II ductal carcinoma, after screening but

Table 3. RVNA pharmacokinetic parameters for HRIG and comparator[a].

	Geometric LS Mean Values			
Parameter	HRIG	Comparator	HRIG/Comparator, %	90% CI, %
C_{max} (IU/mL)	44.9	36.0	124.6	90.6–171.3
$AUC_{0\text{-last}}$ (day • IU/mL)	1741.4	1686.0	103.9	75.0–135.0
$AUC_{0\text{-}\infty}$ (day • IU/mL)	2045.9	1916.9	106.7	80.5–141.5

[a]RVNA = rabies virus neutralizing antibody, HRIG = human rabies immune globulin, LS = least squares, CI = confidence interval, C_{max} = maximum plasma concentration, AUC = area under the curve.

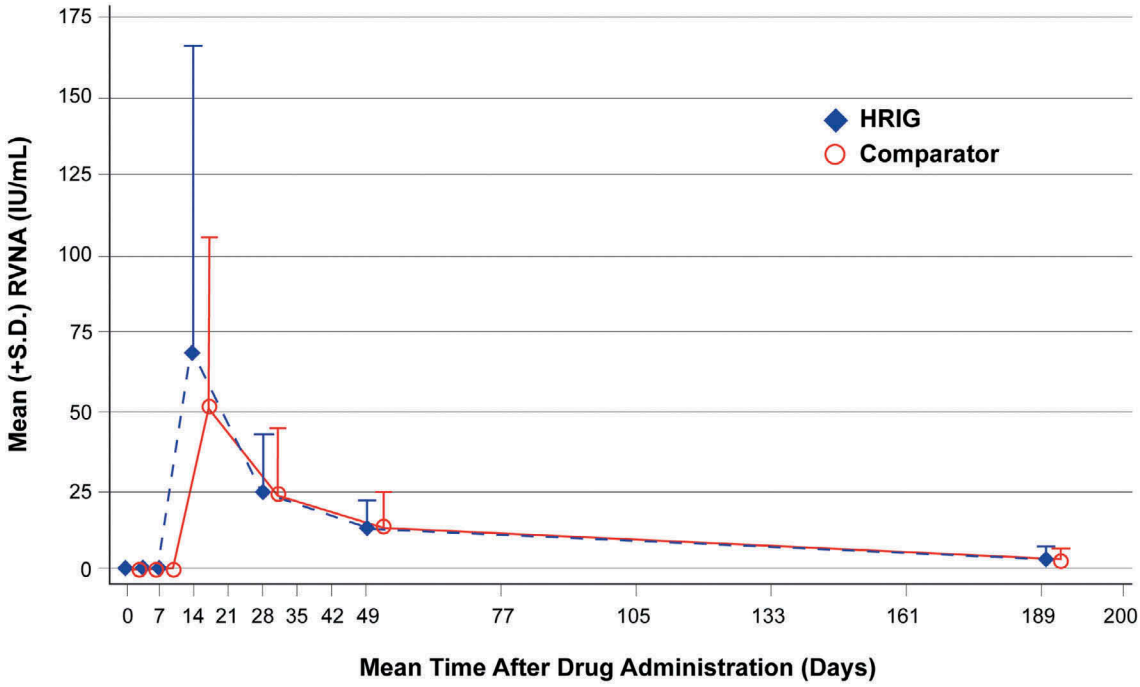

Figure 3. Mean (+S.D.) plasma RVNA concentrations for HRIG and Comparator (each administered with vaccine). S.D. = standard deviation, RVNA = rabies virus neutralizing antibody, HRIG = human rabies immune globulin.

Table 4. Adverse events[a]

	HRIG + Vaccine	Comparator + Vaccine	Overall
	(*n* = 59)	(*n* = 59)	(*N* = 118)
	no. (%)	no. (%)	no. (%)
Any TEAEs	48 (81.4)	51 (86.4)	99 (83.9)
Related TEAEs	32 (54.2)	27 (45.8)	59 (50.0)
Serious TEAEs	1 (1.7)	0	0
TEAEs leading to discontinuation of study treatment	2 (3.4)	0	2 (1.7)
TEAEs leading to death	0	0	0
Individual TEAEs (all causality)			
Injection site pain	29 (49.2)	23 (39.0)	52 (44.1)
Headache	8 (13.6)	9 (15.3)	17 (14.4)
Upper respiratory tract infection	8 (13.6)	8 (13.6)	16 (13.6)
Myalgia	8 (13.6)	6 (10.2)	14 (11.9)
Nausea	4 (6.8)	2 (3.4)	6 (5.1)
Dizziness	3 (5.1)	2 (3.4)	5 (4.2)
Presyncope	4 (6.8)	1 (1.7)	5 (4.2)
Pain in extremity	2 (3.4)	3 (5.1)	5 (4.2)
Arthralgia	4 (6.8)	0	4 (3.4)
Back pain	2 (3.4)	2 (3.4)	4 (3.4)
Fatigue	3 (5.1)	1 (1.7)	4 (3.4)
Diarrhea	2 (3.4)	2 (3.4)	4 (3.4)
Ecchymosis	3 (5.1)	1 (1.7)	4 (3.4)
Laceration	2 (3.4)	2 (3.4)	4 (3.4)
Individual TEAEs (drug-related)			
Injection site pain	25 (42.4)	17 (28.8)	42 (35.6)
Headache	2 (3.4)	3 (5.1)	5 (4.2)
Myalgia	1 (1.7)	3 (5.1)	4 (3.4)

[a]HRIG = human rabies immune globulin, TEAE = treatment-emergent adverse event.

before receiving HRIG on day 0. This subject underwent a breast mass lumpectomy during the study, at which time it was determined to end her participation in the study. Another subject discontinued due to a TEAE of non-serious nipple pain of "moderate" intensity, which was considered "unlikely related" to the study treatment by the principal investigator and which resolved by the end of the study. One subject in the HRIG group prematurely stopped receiving vaccine at the investigator's discretion due to medication use (prednisone, naproxen, hydrocodone) associated with shoulder pain that was part of the subject's medication history; no AE was reported in association with this medication use.

Overall, HRIG was well tolerated and had a comparable safety profile to Comparator. Treatment-related local injection site pain was reported more often in the HRIG group (42.4%) compared with the Comparator group (28.8%), but this difference was not statistically significant. There are slight differences in the HRIG and Comparator formulations that may have contributed to the trend toward a higher incidence of injection site pain with HRIG.

The efficacy of HRIG in the present controlled trial is consistent with real-world results for this product. Between January 2006 and December 2015, a total of 1,165,279 vials of 2 mL (each equivalent to 300 IU) and 22,551 vials of 10 mL (each equivalent to 1500 IU) of the product have been sold worldwide. This is sufficient to treat approximately 270,000 individuals, assuming a 70-kg average body weight and the recommended dose of 20 IU/kg. No reports of failure of this product to protect recipients, all of whom were also administered rabies vaccine as recommended, have been received by the manufacturer.

The study efficacy assessment was limited to a surrogate immunogenicity measure since studying clinical efficacy in a placebo-controlled design is ethically unacceptable. That an RVNA level of ≥ 0.5 IU/mL indicates adequate seroconversion, and would putatively prevent rabies infection, is a widely used reference recommended by the World Health Organization.[33,34] A small study such as this could not establish or verify a "protective level" of RVNA, as subjects were normal healthy volunteers, not patients who were actually or potentially exposed to rabies virus. Because it would be unacceptable to

risk exposing volunteers to a potentially lethal virus, a non-inferiority comparison study in unexposed heathy volunteers with an existing effective product was undertaken. When used in much larger numbers of actual rabies virus exposed patients, it is possible that not all would be protected, although both the study and Comparator products are hyperimmune rabies immunoglobulins standardized to 150 IU/ml potency.[39]

Prompt appropriate medical care can prevent nearly all cases of rabies.[18] The number of PEP treatments given in the United States each year is estimated to be about 40,000 to 50,000.[44] During 2017, 4,454 cases of rabies in animals and 2 human rabies cases were reported to the CDC. Neither of the human cases received PEP, and both died.[9,45] Because shortages of HRIG have been reported and may limit access to appropriate medical treatment in the acute setting of suspected rabies exposure,[22,44–46] the availability of another safe and effective HRIG option has the potential to facilitate PEP, potentially assisting in saving lives.

The two existing 150 IU/mL HRIG products available prior to 2017 were licensed in 1974 and 1984; such formulations have been viewed as standard, interchangeable, and established as an essential component of effective rabies PEP.[39] In 2016, the Comparator product studied in this trial accounted for 96% of rabies immune globulin in the United States.[28] However, poorly diversified biologic markets are vulnerable to supply disruptions due to manufacturing problems, supply-and-demand pressures, or product discontinuation. Unlike vaccines, shortages of emergency products such as HRIG may require institutional responses up to and including importation of commercial alternatives from abroad, potentially increasing healthcare costs.[30] In 2018, the market-leading Comparator product was discontinued. Thus, the establishment of HRIG with demonstrated non-inferiority relative to Comparator, meeting FDA bioequivalence criteria, provides an option for supply continuity for use in life-saving PEP.[38]

In conclusion, results from this controlled trial indicated that HRIG was non-inferior to Comparator for achievement of RVNA titer ≥0.5 IU/mL on day 14, when each product was administered concomitantly with rabies vaccine. HRIG was well tolerated and had a comparable safety profile to Comparator with no clinically meaningful between-treatment differences in TEAEs, laboratory values, vital signs, and ECGs. HRIG provides an important additional treatment option for PEP in individuals exposed to rabies.

Disclosure of potential conflicts of interest

Mark A. Matson, MD – no conflicts of interest; Eran Schenker, MD – former employee of Kamada Ltd, manufacturer of product investigated; Michal Stein, MD – Employee of Kamada Ltd, manufacturer of product investigated; Vladislava Zamfirova, MD former employee of Kedrion Biopharma Inc., US distributor of product investigated; Huy-Binh Nguyen, PhD - employee of Kedrion Biopharma Inc., US distributor of product investigated. Garrett E. Bergman, MD – former employee of Kedrion Biopharma Inc., US distributor of product investigated.

Funding

Research funding provided by Kamada Ltd. and Kedrion Biopharma Inc; Kamada Ltd.[N/A]; Kedrion Biopharma Inc [N/A].

ORCID

Huy-Binh Nguyen http://orcid.org/0000-0002-0842-1796

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