Introduction

Rabies is an incurable and inevitably fatal zoonotic disease that kills approximately 59,000 people worldwide every year. Rabies virus, a genus of Lyssavirus from the Rhabdoviridae family, persists in nature largely in wildlife reservoirs with geographic specificity. Infection in humans begins at viral inoculation, most commonly from saliva transmitted through a bite sustained from an infected animal. Upon inoculation, the virus replicates locally within muscle tissue and then spreads to the neuromuscular junction, where it gains entry to neuronal axons through nicotinic acetylcholine receptor-dependent clathrin-mediated endocytosis; however, other cell-surface proteins such as neuronal adhesion molecule and p75 neurotrophin receptor may also play a role. Once entry into the nervous system takes place, the virus replicates in the dorsal root ganglia and ascends through the spinal cord and into the brain through retrograde fast axonal transport. Infection of the brain leads to an acute progressive encephalomyelitis and produces neurobehavioral symptoms through remodeling of neuronal signaling, including serotonergic and cholinergic transmission. Autopsy findings have shown that rabies deaths generally are not associated with markers of neuronal inflammation or apoptosis, suggesting that immunologic responses are evaded or suppressed.

Although nearly always fatal once clinical symptoms develop, rabies is preventable with adequate and timely administration of lifesaving post-exposure prophylaxis (PEP). In unvaccinated persons, this includes thorough wound washing, passive neutralization of the virus with local infiltration of rabies immunoglobulin (RIG), and induction of active immunity through vaccination. Passive immunization with RIG is crucial to neutralize the initial viral inoculum and prevent infection of the nervous system, particularly during the delay between vaccination and production of an adaptive immune response. PEP is indicated in all instances of potential exposure to rabies virus, and its efficacy for preventing death is nearly 100% when administered in a timely fashion. Nevertheless, fatal failures of PEP do occur and typically are associated with insufficient or delayed PEP treatment. Insufficient treatment may involve delayed or lacking RIG administration, as well as inadequate filtration of wounds (i.e., under-dosing). However, at high doses (above 20 IU/kg), human RIG interferes with the active immune response to the vaccine. This safety margin, in which weight-based dosing limits are respected while RIG volume is still sufficient for full wound infiltration, is further constrained in pediatric patients with low body weight. If the volume of the body-
weight–based RIG dose proves insufficient, volume expansion through dilution would be necessary to allow adequate infiltration of all wounds and to ensure full neutralization of the virus.\textsuperscript{14}

A large proportion of the global rabies disease burden affects pediatric patients. The World Health Organization (WHO) estimates that 40% of people bitten by suspected rabid animals are under 15 years of age, a group that represents only about 26% of the world’s population.\textsuperscript{15,16} Accordingly, children receive one-third to 60% of PEP procedures globally.\textsuperscript{17,18} Eight (24.2%) of 33 cases of rabies in the United States between 2003 and 2014 were in people under 18 years of age.\textsuperscript{19} Despite this, no clinical trial had been conducted in a pediatric population for any RIG formulation currently marketed in the United States, and only limited data exist for a discontinued formulation that was given to 10 children.\textsuperscript{17,20–22}

Pediatric research in rabies is particularly limited among neglected tropical diseases, when considering the high proportion of the global pediatric disease burden.\textsuperscript{23} Because rabies is universally fatal if untreated, the authoritative guidelines and data for treatment of adults have been extrapolated to apply to children.\textsuperscript{9} There are no reports of differences between adults and children in susceptibility to infection, pathophysiology, disease natural history, or clinical outcomes of rabies virus infections. However, children are at a higher risk for dog bites; they predominantly incur wounds in highly innervated regions (such as the head and neck); and their lower body weight limits the RIG dose that can be administered.\textsuperscript{9,14,24}

Given the higher susceptibility and burden of disease in the pediatric population, clinical research was warranted in order to determine the safety and tolerability profiles, and to establish the efficacy and immunogenicity of a RIG when used as part of PEP in pediatric patients suspected of exposure to rabies. To our knowledge, this is the first and only clinical trial of any currently available RIG.

Herein we report the safety, tolerability, efficacy, and immunogenicity results of a post-marketing clinical trial in which KEDRAB™ 150 IU/mL (HRIG150, rabies immune globulin [human], Kedrion Biopharma Inc. NDC#76125-150) was evaluated as part of PEP in pediatric participants under 17 years of age with suspected rabies exposure. The pharmacokinetics and efficacy of this product were previously investigated in two phase 1 trials and a phase 2/3 trial in adults, which supported its licensure by the Food and Drug Administration (FDA) in 2017.

**Methods**

**Study design and objective**

This study (NCT02912845) was a phase 4, prospective, open-label, 2-center, single-arm study of the safety, immunogenicity, and efficacy of a PEP protocol including HRIG150 to prevent rabies disease in pediatric patients suspected of being exposed to the rabies virus. The primary objective was to confirm the safety of HRIG150 in pediatric patients under 17 years of age, when administered with a rabies vaccine (Rabavert, GlaxoSmithKline NDC#58160–964), as part of PEP. The two participating study sites were hospitals in the United States with experience administering rabies PEP to pediatric patients. Before any study activity began, the protocol and informed consent form were approved by the institutional review boards of the participating sites. Prior to any study procedures, parental consent was obtained for all participants; for participants mature enough to provide personal assent, assent was documented in accordance with institutional regulations.

**Study population**

Participants were healthy male and female children, aged 0 to <17 years, with exposure or possible exposure to rabies, such as to a potentially rabid animal, for whom PEP against rabies infection was indicated based on local health department guidance and aligned with Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations.\textsuperscript{9} Potential participants with a history of prior rabies vaccine or RIG, suspected rabies exposure with unknown timing or longer than 7 days prior to PEP, live virus vaccination within the preceding 3 months, or with any other clinically relevant health issue, were excluded. The safety population included all participants who received any amount of HRIG150, and was used for safety data analysis and baseline characteristics summaries. The as-treated population was defined as all participants who received at least three vaccine doses (until day 14) as well as 1 dose of HRIG150. Once enrolled, patients participated in the study for 85 days.

**Treatment**

Participants received treatment in accordance with recommendations of the CDC ACIP for PEP, which includes the standard of care wound washing, passive immunization with HRIG, and induction of active immunity through initiation of the rabies vaccine series.\textsuperscript{25} On day 0, the wound site (if identifiable) was infiltrated with HRIG150 (20 IU/kg), and any remaining HRIG150 was administered by intramuscular (IM) injection at a different site, distant from the vaccine site. Per WHO recommendations, if the weight-based dose of RIG was considered too small to infiltrate all wounds (e.g., cases with multiple bites), dilution in physiologic-buffered saline to ensure full wound coverage was permitted.\textsuperscript{26} If the volume for IM injection exceeded the recommended maximum single IM injection volume for the size/age of the child, IM HRIG150 administration was permitted at multiple sites. A 1-mL dose of licensed rabies vaccine was administered on days 0, 3, 7, and 14.

**Assessments**

Screening/treatment was performed on day 0. Follow-up visits occurred on days 3, 7, and 14, and follow-up telephone calls on days 1, 28, 56, and 84.

**Diary cards**

Following baseline evaluations and treatment on day 0, a diary card was issued to participants’ parents/guardians, who were instructed to record information on any adverse events (AEs) experienced by the child. Diaries were reviewed by the
investigator on day 1 (telephone follow-up) and during the visits on days 3, 7, and 14.

Safety and tolerability
Safety and tolerability were assessed by monitoring local and systemic AEs and physical examination findings for the 14 days following HRIG150 administration. Monitoring for serious adverse events (SAEs) continued throughout the entire study. AEs were defined as any untoward medical occurrences in a participant receiving a pharmaceutical product, with or without potential causal relationship to the study treatment. AE relatedness to the study treatment was assessed by the investigator as "probable," "possible," "unlikely," or "unrelated," and assessed separately for HRIG150 and the vaccine. Treatment-emergent adverse events (TEAE) were defined as AEs meeting any of these criteria: assessed as related to study treatment (possibly, probably, or definitely) by the investigator, missing or undetermined relationship to the study drug, or AE onset within 24 h of HRIG150 administration. SAEs were any untoward medical occurrence at any dose, that resulted in death, were lifethreatening at the time of the event, required inpatient hospitalization or prolongation of existing hospitalization (unless <12 hours, preplanned, or not associated with an AE), resulted in persistent or significant disability or incapacity, or were a congenital or birth defect or an important medical event.

Assays
On day 14, blood samples were collected from participants for assessment of RVNA levels by rapid fluorescent focus inhibition testing.

Endpoints
Safety
The primary safety endpoint was the frequency and severity of local and systemic AEs occurring within 14 days of HRIG150 treatment, and of SAEs occurring within 84 days of treatment.

Efficacy and immunogenicity
Key secondary endpoints were RVNA titer and the incidence of active rabies disease on day 14 following administration of HRIG150. At all time points during the study, participants were assessed by the investigators for any sign or symptom of active rabies disease.

Data analysis
Sample size was determined based on the feasibility of enrolling pediatric participants with possible rabies exposure at the participating study sites and in agreement with FDA. With regards to the primary endpoint, this sample size provides 80% probability of detecting AEs with a true incidence of ≥5.3% and 90% probability of detecting AEs with a true incidence of ≥7.4%, and exceeded the FDA minimum of 25 participants for meaningful evaluation for the secondary pharmacokinetic endpoint. Continuous variables were summarized using descriptive statistics. Analyses were performed using SAS version 9.3 or higher (SAS Institute Inc., Cary, NC).

Results
Participants
Thirty-three participants were screened, 30 of whom were enrolled (3 participants did not meet enrollment criteria). All 30 participants (100%) remained enrolled on day 14, and 28 (93.3%) completed the study through day 84. Two participants were lost to follow-up, although both subjects received HRIG150 and were available for evaluation at day 14, and thus met criteria for inclusion in analyses. All 30 participants were therefore included in both the safety and as-treated populations. The majority of participants were white (21; 70%), 7 (23.3%) were Black or African American, and 2 (6.7%) were Asian. The mean age (± standard deviation [SD]) was 7.45 ± 4.3 years, and ranged from 0.5 to 14.9 years. Fourteen participants (46.7%) were female, and 16 (53.3%) were male (Table 1).

Safety
Throughout the study, no participants reported experiencing a SAE, nor an AE leading to study discontinuation, and there were no deaths. During the 14 days following treatment with HRIG150, 21 (70.0%) out of the 30 participants experienced 57 TEAEs overall. All TEAEs that occurred within 14 days of treatment were mild in severity. The most common treatment-related AE was injection-site pain (five events; Table 2). The most common TEAE also was injection-site pain (nine events; Table 2). Twelve (40%) of the 30 patients experienced 13 TEAEs within 14 days that were deemed related to the study treatment, all of which were mild in severity.

Efficacy
Among the 30 suspected exposures to rabies, 3 (10.0%) were from animals that were subsequently confirmed rabid; the others were associated with uncaptured/untested or confirmed-negative animals. All 30 participants (100%) were free of rabies infection on day 14 according to investigator assessment, and active rabies infection did not develop in any participant at any

Table 1. Demographics of the Study Population.

| Characteristic          | Mean ± SD        | Median | Range (min – max) |
|-------------------------|------------------|--------|-------------------|
| Age, y                  | 7.45 ± 4.3       | 7.15   | 0.5–14.9          |
| Sex, no. (%)            |                  |        |                   |
| Female                  | 14 (46.7%)       |        |                   |
| Male                    | 16 (53.3%)       |        |                   |
| Race, no. (%)           |                  |        |                   |
| White                   | 21 (70)          |        |                   |
| Black/African American  | 7 (23.3%)        |        |                   |
| Asian                   | 2 (6.7)          |        |                   |
| Ethnicity, no. (%)      |                  |        |                   |
| Hispanic or Latino      | 3 (10.0%)        |        |                   |
| Not Hispanic or Latino  | 27 (90.0%)       |        |                   |
| Weight, kg              | 32.61 ± 21.83    | 22.25  | 6.6–85.7          |
| Height, cm              | 122.68 ± 31.03   |        |                   |
| BMI, kg/m²              | 19.19 ± 4.48     |        |                   |

SD, standard deviation; min – max, minimum to maximum; BMI, body mass index.
Table 2. Incidence of adverse events within 14 days of treatment of 30 patients with KEDRAB.

| A. | Serious AE | Number of subjects (%) |
|----|------------|------------------------|
| Serious AE | 0 (0.0) | |
| Deaths | 0 (0.0) | |
| TEAE: any cause | 21 (70.0) | |
| TEAE: by severity | | |
| Mild | 21 (70.0) | |
| Moderate | 0 (0.0) | |
| Severe | 0 (0.0) | |
| TEAE: treatment related | 12 (40.0) | |
| TEAEs leading to discontinuation | 0 (0.0) | |

| B. | Number of TEAEs (% of subjects with TEAEs) |
|----|------------------------------------------|
| [N = 30] | Any cause<sup>a</sup> | Treatment related<sup>b</sup> |
| Individual TEAEs | | |
| Injection-site pain | 9 (26.7) | 5 (16.6) |
| Injection-site erythema | 2 (3.3) | 1 (3.3) |
| Fatigue | 2 (6.7) | 2 (6.7) |
| Vomiting | 2 (6.7) | 1 (3.3) |
| Pyrexia | 2 (6.7) | 1 (3.3) |
| Body temperature increased | 3 (6.7) | 1 (3.3) |
| Headache | 4 (13.3) | 1 (3.3) |
| Ecchymosis | 2 (6.7) | 1 (3.3) |
| Arthropod bite | 4 (10.0) | 0 (0.0) |
| Contusion | 2 (6.7) | 0 (0.0) |
| Pain in extremity | 3 (10.0) | 0 (0.0) |
| Anxiety | 2 (6.7) | 0 (0.0) |

A. Incidence of adverse events within 14 days of treatment. B. Local and systemic TEAEs with incidence >1 recorded during the 14 days following administration of HRIG150; data are based on the safety population.

<sup>a</sup>Any-cause AE include events assessed as having “probable,” “possible,” “unlikely,” or “unrelated” relation to the study treatment. These AEs occurred on or after HRIG150 administration, or were a pre-treatment event or preexisting medical condition that worsened in intensity after HRIG150 administration. <sup>b</sup>Related AEs are those assessed as having “probable” or “possible” relation to the study treatment.

AE, adverse event; TEAE, treatment-emergent adverse event.

time during the study. On day 14, 28 patients (93.3%) had RVNA titers ≥0.5 IU/mL (mean ± SD of all participants: 18.89 ± 31.61; range: 0.21–153.62; Table 3). Two participants had RVNA titers <0.5 IU/mL (0.4 IU/mL and 0.21 IU/mL).

Table 3. Efficacy.

| Participants free of active rabies infection, no. (%) | | |
|---------------------------------------------------|--|--|
| At day 14 | 30 (100) | |
| At day 84 | 30 (100) | |
| RVNA titer | | |
| No. of participants with RVNA titer ≥0.5 IU/mL at day 14 | 28 (93.3) | |
| Mean ± SD | 18.89 ± 31.61 | |
| Median | 8.81 | |
| Range (min – max) | 0.21–153.62 | |

Percentages are based on the number of participants in the as-treated population. RVNA titers denote the geometric mean of the results per participant per visit. min – max, minimum to maximum; RVNA, rabies virus neutralizing antibody; SD, standard deviation.

Discussion

These results demonstrate the safety, efficacy, and immunogenicity of HRIG150 used as part of PEP in pediatric patients with suspected or confirmed rabies exposure. No SAE occurred during the 3 months of follow-up. HRIG150 injections were largely well tolerated, and all TEAEs possibly related to the study treatment were mild in severity. Registration trials for HRIG products have, to date, enrolled no pediatric subjects (HyperRAB – 12 adults, KEDRAB – 59 adults, Imogam-HT – 32 adults).<sup>21,22,27</sup> The present study evaluated a cohort of 30 pediatric participants based on feasibility of enrolling subjects indicated for post-exposure prophylaxis, and is comparable in size to other HRIG registrational studies supporting FDA approvals. To our knowledge, this is the first study in pediatric patients for any RIG currently available in the United States.<sup>20–22</sup> This sample size provides power for the primary safety endpoint, enabling 80% probability of detecting AEs with true incidence of ≥5.3%, and 90% for AEs with true incidence of ≥7.4%. Twenty-one of 30 participants experienced a TEAE, with 12 (40%) participants experiencing TEAE deemed related to HRIG150. We note that all TEAEs were mild in severity, whether related to HRIG150 administration or not, the most common of which was pain at injection site. This safety and tolerability profile is comparable to that observed previously in adults.<sup>23</sup> As PEP is life-saving, its omission can be associated with fatal outcomes; thus, the potential benefit of averting death through appropriate PEP that includes HRIG likely outweighs the risk for mild tolerability events. As is mandatory for any human RIG formulation used as part of lifesaving PEP, the efficacy of this protocol in preventing death was 100%. No case of active rabies infection was found at any point during the study, which included 3 months of follow-up. Rabies incubation times range from 2 to 12 weeks, but longer times have been reported occasionally.<sup>25</sup> The efficacy results of the present study are consistent with more than 10 years of global experience with this product, including nearly a half million recipients to date, during which there have been no reported cases of PEP failure leading
to rabies when appropriate PEP included HRIG150. The majority of participants had circulating RVNA titers ≥0.5 IU/mL on day 14 following treatment. Although two participants did not achieve this titer level, neither exhibited active rabies infection at any time during the study. One of these participants was an 11-year-old girl whose RVNA titer was 0.4 IU/mL on day 14. The other was a 4-year-old boy with an RVNA titer of 0.21 IU/mL on day 14 who received PEP in response to possible rabies exposure from an animal subsequently confirmed positive for rabies. Correspondence with the reference laboratory (Kansas State University [KSU] Veterinary Diagnostic Laboratory) confirmed that individual immunogenic responses are heterogeneous within a population. A retrospective review of serum samples processed at KSU in the context of rabies clinical trials, conducted from 2010 to 2014, suggests that up to 13% of tested participants fail to reach RVNA titers of 0.5 IU/mL by day 14 (unpublished data). Although most individuals display early high-titer immunogenic responses, a small percentage may have lower later immunogenic responses to PEP that do not achieve the 0.5 IU/mL by day 14, but achieve seroconversion by day 30.28,29 In our study, blood draw for RVNA titer was performed at day 14 and not repeated subsequently; thus, it remains possible that the two subjects that did not attain the cutoff by day 14 seroconverted by day 30.

The present study was designed as a single-arm open-label trial without placebo control to evaluate PEP in patients with actual indication for prophylaxis based on suspected exposure to virus, in order to evaluate clinical efficacy particularly in subjects with confirmed rabies exposures. Without a placebo control group, we are unable to determine whether placebo-treated children would have developed rabies, nor whether they would have survived the disease if they had. Due to the high fatality rate of rabies, it is ethically unacceptable to treat exposed patients with placebo; thus, most prospective placebo-controlled clinical studies are necessarily limited to studying RVNA pharmacokinetics following simulated regimens in unexposed, healthy volunteers.21,22,27 While appropriate PEP is expected to be protective in preventing rabies disease and death, rare instances of PEP failure have been reported, particularly when delayed or incomplete.14 The possibility remains that, when administered to large numbers of patients, very rare occurrences of PEP failure may occur; however, our experience between 2006 and 2015 involving over 380 million IU of HRIG150 sold worldwide (sufficient to treat approximately 270,000 70-kg adults) has detected no instance of PEP failure when HRIG150 is given as part of appropriate PEP.

Pre-specified inclusion criteria in the present study allowed for enrollment of participants under 17 years of age, with the oldest participant enrolled being 14.9 years of age. The WHO estimates that 40% of the global rabies disease burden occurs in children under 15 years of age.15 Globally, most of the human rabies burden is associated with dog bites. Widespread vaccination of domestic pets in the United States has significantly reduced the endemicity of the canine-variant rabies virus. However, if infected from other reservoir species, dogs may still represent an important transmission vector due to their close proximity to humans. Accordingly, a significant proportion of PEP in the United States is administered in response to dog encounters: estimates range from 48% to 81%.30–32 Children are at an increased risk for dog bites, and incur wounds predominantly in the head and neck, rather than the limbs as is seen in adults.24,33,34 Rabies virus inoculation in highly innervated regions is associated with shorter incubation times, potentially as short as 10 days, due to greater risk for deposition of the initial inoculum in proximity to the central nervous system.26 Moreover, wound morphology commonly seen in pediatric patients associates with infection risk and must inform treatment. Puncture wounds and lacerations of more than 3 cm are associated with a threefold greater risk for infection, and the size and depth of wounds dictate the volume of RIG required to adequately infiltrate and neutralize all virus likely to be present.35,36

Dosing and administration of RIG are governed by two countervailing principles: (1) the RIG volume must be sufficient to infiltrate all wounds and neutralize all of the viral inoculum and, simultaneously, (2) the RIG dose must be constrained by body weight and must not exceed 20 IU/kg to avoid vaccine interference.9,25,37,38 Before 1999, the CDC ACIP guidelines recommended administering 50% of the body-weight–based RIG dose into wounds and the remaining 50% by IM injection. Following reports of death among pediatric patients despite PEP administration, in whom RIG was insufficiently infiltrated into wounds or who received IM injection only (without wound infiltration), these recommendations were revised to emphasize infiltration of as much of the dose as anatomically feasible into the wounds, with IM injection of any remainder.14,39 Recent evidence from a study of 7506 patients demonstrates that infiltration of RIG alone, without IM injection, also is protective, with no adverse outcomes after 1 year of follow-up for 80% of the cohort.36 Accordingly, 2018 revisions to the WHO rabies treatment guidelines specify only infiltration with RIG (i.e., no IM injection).25,38 At the time of this study, CDC ACIP guidelines have not yet been revised to adopt this new regimen, and so 2010 guidelines on body-weight-based dosing remain in effect.25 For cases in which the RIG dose calculated by body weight would be insufficient to adequately infiltrate all wounds, it is recommended to expand the RIG volume through dilution.14 150 IU/mL-concentration of human RIG preparation can be expanded two to three times with normal saline, whereas high-concentration, low-volume, 300 IU/mL preparations can be expanded only by equal-part dilution with 5% dextrose.14,21 Conversely, when no wounds or animal contact sites are documented, as is characteristic of many bat exposures, these wound-based directives may not apply; thus, a subset of cases may not be adequately addressed by the revised guidelines.

Rabies remains fatal yet is one of the most preventable infectious diseases. Physicians and nurses working in emergency departments often are the first healthcare providers to interface with patients suspected of rabies exposure. Despite the crucial importance of appropriate PEP for preventing death, baseline knowledge of rabies disease and its clinical management guidelines remains lacking or inadequate.40,41 Appropriate initiation of PEP and correct administration of RIG are areas of deficiency for many healthcare providers.40 Retrospective studies show low rates of adherence to treatment guidelines in the United States, with particularly high rates of incorrect omission of wound infiltration with RIG when indicated (i.e., when wound sites are present). Incorrect
treatment in the form of insufficient or non-administration of RIG has been reported in 42% to 48% of cases. These gaps in knowledge and practice create unnecessary risks of preventable death from treatment failure, as documented in literature, and emphasize the need for improved education and awareness.

Results of this study confirm the safety profile and efficacy of HRIG150 in preventing rabies in pediatric patients when used as part of a PEP regimen. HRIG150 was well tolerated with all AEs being mild in severity, and that included no SAEs. Therefore, we conclude that HRIG150 is appropriate for use as a lifesaving component of PEP in pediatric patients.

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Abbreviations
ACIP  Advisory Committee on Immunization Practice
AE  Adverse event
BMI  Body mass index
CDC  Centers for Disease Control and Prevention
HRIG150  KEDRA® human rabies immunoglobulin 150 IU/mL
IU  Intramuscular
KSU  Kansas State University
PEP  Post-exposure prophylaxis
RIG  Rabies immunoglobulin
IU  International unit
RVNA  Rabies virus neutralizing antibody
SAE  Serious adverse event
SD  Standard deviation
TEAE  Treatment-emergent adverse event
WHO  World Health Organization

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