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Safety and immunogenicity of an inactivated vero cell-based rabies vaccine (Rabivax-S) in pre-exposure prophylaxis schedule in Vietnam

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Purpose: We evaluated the immunogenicity and safety of Rabivax-S (Pitman-Moore 3218 strain) by intramuscular (IM) and intradermal (ID) routes in Vietnam.
Materials and Methods: We conducted an open-label, randomized, phase 4, single-center clinical trial in healthy individuals aged five to 60 years divided into two groups according to age (5-15 years old and 16–60 years old). They were randomized to receive 3 doses of Rabivax-S IM 1 mL) or Rabivax-S ID (0.1 mL) in 1:1 ratio on days 0, 7, and 21. Adverse events (AEs) were collected for 7 days after each dose and rabies-neutralizing antibody levels were measured were measured by RFFIT on days 0, 21 and 42.
Results: Totally 220 participants aged 5–15 years old (117 participants) and 16–60 years old (103 participants). The seroconversion rates of antibodies among the two groups (IM and ID doses) were all 100.0% on D21 and D42/42. On D21 and D42/42, the geometric mean concentration of the two groups was much higher than the immune protection level of 0.5 IU/mL. There were no AEs or serious AEs recorded in all four visits. Unsolicited AEs were reported by 3% of participants. The most common AEs during seven days after each dose were fever, pain, and erythema. Mostly mild local and systemic AEs were reported across the two groups and all resolved without sequelae.
Conclusion: The study results conclusively demonstrate that the complete regimen of both the IM and ID 3-dose series Rabivax-S was found to be clinically safe and immunogenic. After this study, Rabivax-S is now available in Vietnam and can be used for pre- and post-exposure prophylaxis.

Clinical Trials Registration: ClinicalTrials.gov Identifier: NCT05937113

Keywords: Rabies virus; Rabivax-S; Vaccine; Vietnam

INTRODUCTION

According to the World Health Organization (WHO) report, rabies is estimated to cause 59,000 human deaths annually in over 150 countries, with 95% of cases

occurring in Africa and Asia [1]. Due to widespread underreporting and uncertain estimates, this number is likely a gross underestimate of the true disease burden. 99% of rabies cases are dog-mediated, and the burden of disease is disproportionally borne by rural poor populations, with approximately half of cases attributable to children under 15 [2,3].

Rabies is a significant burden in Asia, with an estimated 35.172 human deaths per year. India accounts for 59.9% of rabies deaths in Asia and 35% of deaths globally [1]. The cost of Post Exposure Prophylaxis (PEP) is highest in Asia, with estimates up to US$ 1.7 billion per year [1].

In Vietnam, rabies is endemic and has been a notifiable disease for more than 40 years. The key factors contributing to the disease include low vaccination coverage in dogs, a lack of public awareness, and limited access to human rabies immune globulin and vaccine [3,4]. Fortunately, Vietnam has shown tremendous achievement in controlling rabies. The number of rabies deaths reported recently in Vietnam has been decreasing from 588 deaths in 1994 to 81 deaths in 2004 because of nationwide immunization against rabies [5]. According to a national report, over the last five years, more than 350,000 people per year have been bitten by dogs and cats, while more than 80 human deaths have been reported annually. According to the Department of Animal Health, only 29% (2.9 million) of dogs have been vaccinated, of an estimated population of 10 million. Currently, Vietnam is involved in the Association of South East Asian Nations (ASEAN) action plan for rabies elimination by 2020 [6]. The Ministry of Health and Ministry of Agriculture and Rural Development (MARD) organized a national five-year strategy for rabies elimination for 2017–2021 using the Stepwise Approach to Rabies Elimination (SARE), a key initiative to understand the complexities of rabies control and to develop a platform that makes rabies control programs more effective and manageable [7].

Considering the massive need for good quality, WHO prequalified rabies vaccines, Serum Institute of India Pvt. Ltd. (SII) started developing a rabies vaccine [8]. A new vaccine based on Vero cells (PVRV [Rabivax-S]) has been developed in India. Pitman–Moore strain of rabies virus was originally adapted to the human diploid cells (HDC) line, which was adapted well to the vero cell line for the first time. Vero cell line is a continuous cell line well characterized compared to primary cell cultures, that is important to avoid batch-to-batch variation. Traditionally, rabies vaccines are produced in roller bottles, whereas Rabivax-S is produced in a CellCube system, which, being a closed system with minimal human intervention, reduces the risk of any contamination. Quality control processes were stringently followed at every step of the production of vaccines. The stability profile of vaccine has been adequately characterized. Originally, modern tissue culture rabies vaccines were meant for intramuscular (IM) administrations. Though this was very effective in the prevention of rabies, the three-dose schedule was proving costly in many resource-limited settings, thus affecting the use of the vaccine. Subsequently, intradermal (ID) route was tested and was found comparable to IM regarding immune response. This resulted in dose sparing by up to 80% of the dose volumes, translating into significant financial savings [9].

Rabivax-S has been recently licensed in India. The data on Rabivax-S have been submitted to the WHO for prequalification of the vaccine. Once this vaccine is prequalified, it would be procured by UN agencies such as UNICEF and PAHO for use in PEP of rabies in humans in developing countries, mainly in Asia and Africa. It may be evaluated clinically with new recombinant human monoclonal antibody for PEP of rabies in patients with category III potential rabies exposure. Vaccine may be used in the evaluation of new shortened regimens for PEP by both IM and ID routes based on available evidence [9].

We conducted this clinical trial to provide data on the safety and immunogenicity of the RABIVAX-S vaccine to the regulatory authorities for the purpose of product registration in Vietnam.

MATERIAL AND METHODS

Clinical trial design and randomization of subjects

Study design

This was a cross-over, open-label, randomized, single-center clinical study conducted in 220 healthy Vietnamese individuals aged 5 to 60 years old. The study was conducted from May 13, 2020, to November 2, 2020 at Dong Hung district, Thai Binh province. Dong Hung district is a rural site located in North Vietnam, 90 km Southest of Hanoi capital. Hung Ha district covers an area of about 200 km^2, including delta, spread over 37 communes and a town. The population of Dong Hung in 2019 was around 257000. Most of the people here have low educational levels, and their work is mainly in agriculture all year round.

The trial was conducted in compliance with the protocol, good clinical practices, and ethical guidelines for biomedical research on human subjects (Viet Nam Council of Medical Research, 2012). A data safety monitoring board reviewed safety data periodically. The trial was registered with Clinical Trials (https://clinicaltrials.gov/) as Clinical Trials Registration (ClinicalTrials.gov Identifier: NCT05937113).

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The trial was approved by Institutional Ethics Committees in Vietnam.

Study participants

Healthy individuals of either sex above 5 years of age were included in this study. The exclusion criteria included the history of potential rabies exposure or receipt of rabies vaccination, history of hypersensitivity to any investigational vaccine component, receipt of any other vaccines or a serum or blood product within the previous 30 days, body temperature of ≥38.0°C, presence of any acute infection, history of any chronic illness, receipt of any immunomodulating agents within past six months, concomitant treatment with any antimalarial drugs, history of drug or alcohol abuse, those with deficient immunoglobulins (IgG, IgM, or IgA), and pregnant or lactating female.

Study vaccines

Rabivax-S is a lyophilized vaccine (Serum Institute of India Pvt Ltd. [SIIPL]) containing inactivated purified rabies antigen (Pitman Moore, PM3218 as virus strain) produced using Vero ATCC CCL 81 cells. The diluent (sterile water for injection) was provided in separate 1 mL ampoules. After reconstitution, a single dose of 1 mL contained an inactivated, purified rabies antigen (not less than 2.5 IU), glycine (40 mg), sucrose (40 mg) and human serum albumin (25% 10 mg). The potencies of the vaccine batches were 4.96 and 4.24 IU/mL, respectively. The vaccine potency was determined on the basis of the National Institute for Control of Vaccine and Biological (NICVB).

Clinical trial objectives/endpoints

Immunogenicity was assessed by two primary outcome measures: the rabies virus neutralizing antibody (RVNA) and change of RVNA at the time points of day 7, day 21 and day 42 compared to day 0 (pre-vaccination) was the first endpoint. The second endpoint was the seroconversion rate (RVNA titer of ≥0.5 IU/mL; rapid fluorescent focus inhibition test method) on day 0, day 7, day 21 and day 42.

Safety was assessed by three outcome measures: The safety of the vaccine was assessed by medical history and physical examinations on each visit. The proportion of any immediately adverse events (AEs) reported for 30 minutes post-vaccine administration. The proportion of solicited adverse reactions (local and systemic AEs), unsolicited AEs and serious adverse events (SAEs) were captured with structured diaries over 42 days. Participants were also monitored for compliance throughout the study.

Study procedures

Patients without exclusion criteria were enrolled and randomized by investigators to either the new purified Vero cell rabies vaccine Rabivax-S IM or Rabivax-S ID. Computer-generated block randomization was generated by the study statistician with block size of four. The block size was not provided to study sites. The randomization list was sequentially numbered. The treatment allocation was in the ratio of 1:1 for each IM rout and IM rout groups. Treatment assignments were concealed until the time of randomization using silver coating of treatment group. The IM doses were given as 1 mL injections on day 0, 7, 21 (or 28) while the ID doses were given as two 0.1 mL injections on days 0, 7 and 21 (or 28), with Day 0 being the day of presentation to the sites.

Sera samples were collected prior to vaccination on day 0 (pre-vaccination) and on day 7, 21 and 42 post vaccination. The samples were stored and transported at –20°C. The sera were tested for RVNA by rapid fluorescent focus inhibition test (RFFIT) at the National Institute of Hygiene and Epidemiology (NIHE), Hanoi, Vietnam as per the method described earlier. Seroresponse was defined as RFFIT titres ≥0.5 IU/mL. Clinical data management and analyses was contracted to Viet Star Biomedical Research.

Reactogenicity and safety

All participants were followed up for safety after each vaccination by documentation of AEs between the administration of the first dose and 42 days after the first dose of the vaccine. Participants were observed for 30 minutes post-vaccine administration for any immediate adverse reaction.

In addition, the subjects visited study clinics 4 times during their participation: D0, D7, D21 and D42. For each visit, a +1 week was allowed. At each visit, the subjects were physically examined and they or their parents (with participants aged under 18 years old) were asked for AEs and concomitant medication. Parents were asked to report any SAE immediately to the investigator. All AEs were graded as mild, moderate, severe, and life-threatening based on pre-specified definitions. All solicited local and systemic reactions were assumed to be caused by study vaccine. The causality assessment of all unsolicited AEs was done in the basis of clinical judgment of the investigators. The causality association was classified as Very likely/ Certain, Probable, Possible, Unlikely, Unrelated, and Unclassifiable.

Health staff were trained to document solicited adverse reactions, unsolicited AEs and SAEs, which were also provided with measuring scales in a structured diary. Detailed safety information for any AE, was collected via subject diary card, telephone contact by the study staff and reviewed at each visit.

SAEs were reported to the Institutional Ethics Committees and reviewed by an independent Data and Safety Monitoring Board within the stipulated timeline. Medical expenses and hospital visits were covered by the sponsor.

Statistical considerations

For the design used in this study, a sample size 220 gives approximately 90% power to document at least one of any AEs of RABIVAX-S. Thus, the study size of 220 would allow for almost 10% data loss due to dropout. An independent research organization, Viet Star Biomedical Research, conducted the analyses using SAS version 9.4.

Sex distribution was expressed in percentage (%). The percentage along with 95% confidence interval (CI) of solicited and unsolicited AEs and SAEs were calculated. Geometric mean titer (GMT) was calculated for days 0, day 7, day 21 and day 42 titers. Seroconversion and seroresponse was presented as counts and percentages with 95% CIs.

Ethics statement

The study was conducted as per the declaration of Helsinki, Good Clinical Practices guidelines and Vietnamese regulatory and ethical guidelines. The protocol of this study was approved by The Institutional Ethics Committees decision 107 dated 18/10/2019. Informed consent forms were used in local languages to obtain consent from the parents. The consent of illiterate parents was attested by an impartial witness. The study was independently monitored to assure the quality of data generated throughout the study site.

RESULTS

Demographics

Overall, a total of 247 participants were screened, and 220 eligible participants were randomized in 1:1 ratio (111 participants in the ID group and 109 participants in the IM group). The common reasons for exclusion are shown in **Fig. 1**. The demographic baseline characteristics of the participants in both age groups were comparable (**Table 1**).

Table 1. Summary of demographic characteristics of subjects enrolled in the study (n=220)

Characteristics	5–15-year-old group	16–60-year-old group
Age (yr)	9.9±3.1	35.1±12.7
Sex		
Female	60 (51.3)	62 (60.2)
Male	57 (48.7)	41 (39.8)
Weight (kg)	34.7±12.9	53.6±8.5
Height (cm)	138.5±16.8	158.1±7.2

Values are presented as mean ± standard deviation or number (%).

There were no significant differences in demographic characteristics in the two groups. Increasing height and weight was in line with the development progress. By the end of the study, 6/220 (2.73%) participants had not completed the study. At enrollment, the investigator examined all participants and detected no significant abnormal clinical presentations.

Safety

AEs immediately during 30 minutes after taking the vaccine.

There were no unexpected AEs or SAEs recorded in the period 30 minutes after taking the vaccine in all three-time visits (**Tables 2** and **3**). The most common local AEs during 7 days after each time visit were induration, pain, and erythema. And the most common systemic AEs during 7 days after each time visit were fever. Other AEs were at a low rate, and there was no case of intussusception. AEs from day 8 onwards after each time taking the vaccine. No AEs recorded from day 8 onwards after each time taking vaccine in all three visits.

A total of 7 unsolicited AEs distributed by treatment arm groups were reported. These were blood and lymphatic system disorders (axillary lymphadenitis); gastrointestinal disorders (stomach pain); infections and infestations (acute amyitis); musculoskeletal and connective tissue disorders (left-hand fracture) and respiratory, thoracic and mediastinal disorders (running nose and sore throat). Most AEs were of mild and moderate intensity; 5 of 7 unsolicited AEs were unrelated and others were un likely related to study vaccines and resoled with-out any sequelae. No SAE was reported in the study.

Immunogenicity

The immunogenicity of RABIVAX-S was assessed by analyzing two measures of the immune response in terms of RVNA titres and GMTs at pre-vaccination and post-vaccination (**Table 4**).

It can be seen that an immune response to intradermal and intramuscular administration in subjects aged 5–15 years old did not appear after 7 days of the first dose. At 21 days after the first injection (D21) and 42 days after the first injection (D42), an immune response was formed with a mean RVNA at D21 and D42 in the intradermal subgroup of 8.6±5.4 IU/mL and 9.4±3.4 IU/mL. In the intramuscular subgroup, the mean RVNA values at D21 and D42 were 18.5±9.2 IU/mL and 23.7±9.8 IU/mL, respectively (**Fig. 2**, **Tables 5** and **6**).

In all the study participants, positive seroresponse was developed by day 7 and titres remained ≥0.5 IU/mL at all time points through days 21 and 42.

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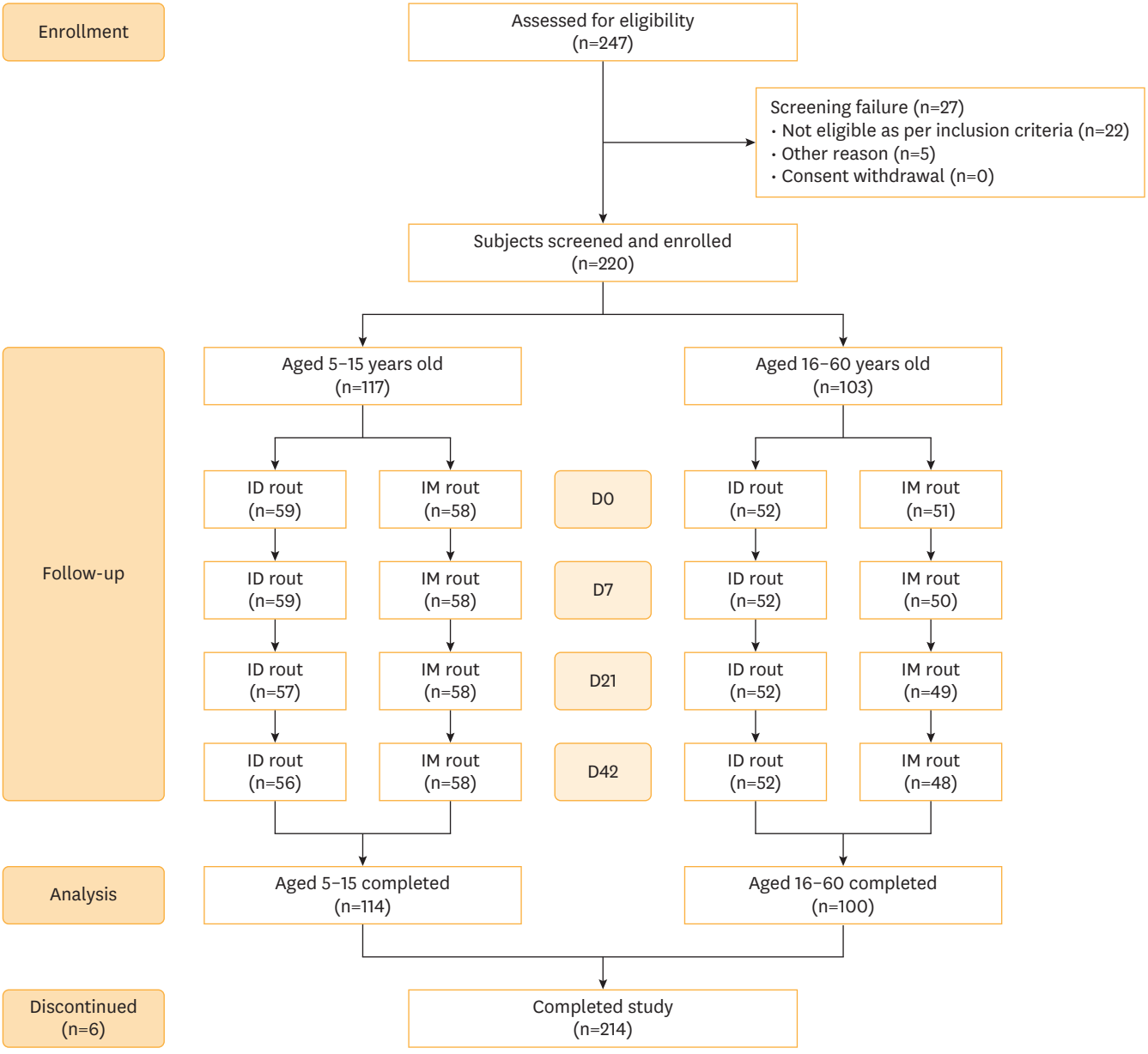

Fig. 1. Enrollment flow chart.
ID, intradermal; IM, intramuscular.

Table 2. Adverse events recorded in the period 30 minutes after taking the vaccine in all three time visits

Expected adverse event	Aged 5–15 years old (n=117)			Aged 16–60 years old (n=103)		
	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 1st dose	Post 2nd dose	Post 3rd dose
Local pain	1 (0.85)	1 (0.85)	0 (0.00)	1 (0.97)	0 (0.00)	0 (0.00)
Itching	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Induration	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Fever	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Headache	1 (0.85)	2 (1.71)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.97)
Total	2 (1.71)	3 (2.56)	0 (0.00)	1 (0.97)	0 (0.00)	1 (0.97)

Values are presented as number (%).
Adverse events during 7 days period after each of the three-time visit.

Table 3. AEs assessed to be probably possibly, or remotely related to testing article administration during 7 days period after each of the three-time visit in participants both groups

AE	Aged 5–15 years old (n=117)			Aged 16–60 years old (n=103)		
	Post 1st dose	Post 2nd dose	Post 3rd dose	Post 1st dose	Post 2nd dose	Post 3rd dose
Local AEs	14 (12.0)	23 (19.8)	18 (15.7)	11 (10.6)	14 (13.8)	28 (28.2)
Induration	5 (4.3)	3 (2.6)	2 (1.7)	5 (4.8)	2 (2.0)	4 (4.0)
Pain	7 (6.0)	6 (5.1)	8 (7.0)	4 (3.9)	5 (4.9)	10 (10.1)
Erythema	2 (1.7)	10 (8.6)	6 (5.2)	2 (1.9)	6 (5.9)	12 (12.1)
Pruritus	0 (0.0)	4 (3.5)	1 (0.9)	0 (0.0)	1 (1.0)	1 (1.0)
Oedema	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (1.0)
Systemics AEs	3 (2.6)	3 (2.6)	3 (2.6)	4 (4.0)	3 (3.0)	0 (0.0)
Fever	3 (2.6)	0 (0.0)	2 (1.7)	1 (1.0)	1 (1.0)	0 (0.0)
Shivering	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Faintness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)
Myalgia	0 (0.0)	1 (0.9)	1 (0.9)	1 (1.0)	1 (1.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are presented as number (%).
AE, adverse event.

Table 4. The rabies virus neutralizing antibody response observed at different time points in aged 5–15 years old groups

Variables	Aged 5–15 years old							
	Intradermal				Intramuscular			
	Visit – Day				Visit – Day			
	D0	D7	D21	D42	D0	D7	D21	D42
Total	16	16	15	14	19	19	19	19
Mean ± SD	0.0±0.0	0.0±0.0	8.6±5.4	9.4±3.4	0.0±0.0	0±0.1	18.5±9.2	23.7±9.8
Median	0	0	7.3	10.4	0	0	19.7	21.4
Min–Max	0–0	0–0	1–19	3–15	0–0	0–0	2–41	6–44

SD, standard deviation.

Table 5. The rabies virus neutralizing antibody response observed at different time points in aged 16–60 years old groups

Variables	Aged 16–60 years old							
	Intradermal				Intramuscular			
	Visit – Day				Visit – Day			
	D0	D7	D21	D42	D0	D7	D21	D42
Total	19	19	19	19	16	15	15	14
Mean ± SD	0.0±0.0	0.0±0.0	9.2±8.5	13.6±10.3	0.0±0.0	0.0±0.0	13.5±7.7	16.2±4.5
Median	0	0	6.6	12.5	0	0	15.2	15.9
Min–Max	0–0	0–0	1–37	3–42	0–0	0–0	3–33	9–26

Similar results were also observed in the study subjects aged 16–60 years old.
SD, standard deviation.

Table 6. Number and percentage of subjects achieving positive conversion at different time points of study

Variables	D0	D7	D21	D42
Seronegative	70 (100.0)	69 (100.0)	0 (0.0)	0 (0.0)
Seropositive	0 (0.0)	0 (0.0)	68 (100.0)	66 (100.0)

Values are presented as number (%).

DISCUSSION

Vaccination is an efficacious way of preventing rabies. In the current world, many approved rabies vaccines of different components (such as PVRV, PCECV, and HDCV [10]) and different vaccination programs (Zagreb, Essen [11]) are being widely used. This study evaluated the immunogenicity and safe of RABIVAX-S with regimens of 0, 7, and 21 days. We selected the expected number of research subjects, and the follow-up of the subjects in the study has also achieved the set goal with a low rate of loss of track in the study. At the end of the study, 97.3% of the subjects completed all 3 injections and followed up for 42 days after the first vaccination. Attempts to contact those who lost follow-up have

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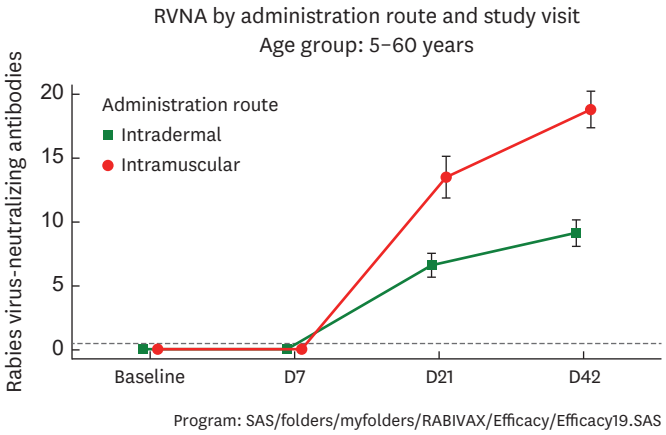

Fig. 2. RVNA geometric mean titer by administration routes and study visit.
RVNA, rabies virus neutralizing antibody.

determined that opt-out is unrelated to the study vaccine's safety.

The total incidence of AEs was not significantly different among 2 treatment groups. However, from the incidence of solicited AEs, the age group 5–15 years was higher than that of the age group 16–60 years. Adverse reactions in each group occurred equally after each injection and occurred mainly within 3 days after vaccination. The incidence of local and systemic reactions was not different between the two groups. The main symptoms of local reaction were pain and erythema, and fever was the main symptom of systemic reaction. For safety analysis, pain of injection site, erythema and fever were the most general symptoms, respectively, in local and systemic reactions, which agreed with Hu et al. [11]. Adverse reactions did not increase with the number of injections.

The major local expected AEs were pain at the injection site and mild or moderate rash with an incidence of <10%. The expected systemic AEs were mainly mild fever with low frequency (2%). The incidence of local and systemic expected AEs was much lower in other studies with the same vaccine [9,12-15]. A small proportion of study subjects experienced an unexpected AE, although no AEs were identified as related to the study vaccine. The occurrence of unexpected AEs in clinical trials is generally common. The evaluation of the causal relationship of AEs with the research product is carried out according to the general principles of assessment, performed by trained and tasked researchers, which makes more accurate and objective assessment.

The regimen of 3 doses of pre-exposure prophylaxis on days 0, 7, and 21 and the immunogenicity assessment (RVNA) scores in this study were consistent with the approved vaccination schedule worldwide. As shown in the results of this study, in the subjects who were seronegative before vaccination, an immune response did not been formed after 7 days of the first injection for both intramuscular and intradermal routes, while the seroconversion rates of antibodies of each group achieved 100% on day 21 and day 42 and at the same time attained RVNA concentrations ≥0.5 IU/mL, exceeding sufficient titers as specified by the WHO [2]. Similar to the results of this vaccine's phase I and II/III study, seroresponse was reached after two doses [16,17]. The observations and comparisons of RVNA between the intradermal route and the intramuscular route showed a stronger immune response in the intramuscular route. This could be explained by the faster absorption and higher dose administered by the intramuscular route (1 mL) compared with the intradermal route (0.1 mL). In any case, the study was not designed to compare two administration routes, and more importantly, neither route met the expected level of efficacy response.

A recent study by Beran et al. [18] showed that there is a correlation between the antigenicity and immune response. In the present study, the vaccine produced good serum antibody titers by Day 21 (antibody titre's were ≥0.5 IU/mL) and significant rise in the neutralizing antibody titre was observed for all treatment groups during the study period of 42 days. On day 21 and day 42, the GMC was lower in ID route than in IM route, while it was not significantly different between two age groups on day 7 regarding seroconversion rates of antibodies. All the two age groups showed that the 42 day after the first vaccination reached the highest GMCs.

This cross-over clinical trial confirms that the RABIVAX-S vaccine offers a new alternative for the pre and PEP of rabies. RABIVAX-S complies with the specifications defined by Indian pharmacopoeia and WHO for rabies vaccines released in the international market.

In conclusion, the study has provided sufficient evidence for the safety and protective efficacy of the RABIVAX-S vaccine, a 3-dose regimen on days D0, D7 and D21, administered intradermally or intramuscularly. The data in this study are the basis for the vaccine regulatory agency to evaluate, approve and grant the marketing authorization for the vaccine in Vietnam.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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