A next-generation, serum-free, highly purified Vero cell rabies vaccine is safe and as immunogenic as the reference vaccine Verorab® when administered according to a post-exposure regimen in healthy children and adults in China

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ABSTRACT

Background: As an evolution of its currently licensed rabies vaccine Verorab®, Sanofi Pasteur has developed a next-generation, serum-free, highly purified Vero rabies vaccine (PVRV-NG). Through this Phase III clinical trial, we aimed to demonstrate the non-inferiority of PVRV-NG over Verorab when administered according to a post-exposure regimen and to assess its clinical safety.

Methods: A total of 816 healthy subjects aged ≥10 years were randomized according to a 2:1 ratio to receive PVRV-NG or Verorab. Half of the subjects were aged 10–17 years, the other half were aged ≥18 years. All subjects were to receive 5 injections on days 0, 3, 7, 14 and 28. Three blood samples were taken for rabies virus neutralizing antibodies (RVNA) assessment, at baseline, on day 14 and day 42. Solicited adverse reactions (between injections 1, 2 and 3, and within 7 days post-injections 4 and 5) and adverse events (up to 28 days after the last injection) were collected for clinical safety assessment; serious adverse events were reported up to 6-months after the last injection.

Results: The proportion of subjects with an RVNA titer ≥0.5IU/mL after the third injection of PVRV-NG was non-inferior to the proportion of those who received Verorab. PVRV-NG was shown to be as immunogenic as Verorab in each age range in the per-protocol and full analysis sets. PVRV-NG induced a strong immune response in both age ranges, with high RVNA levels and increased geometric mean titers compared to baseline after each measured time point. PVRV-NG had a satisfactory safety profile after each injection, similar to Verorab with regards to the nature, frequency, duration and severity of adverse events. Two serious adverse events were reported, none was related to vaccination.

Conclusions: This trial demonstrated the immunogenic non-inferiority of PVRV-NG over Verorab and showed that both vaccines have similar safety profiles. This trial is registered at ClinicalTrials.gov (NCT01339312). This manuscript is the first full report of the study. An abstract of the study results was previously presented at the Rabies in the Americas (RITA) conference in October 2012 in São Paulo, Brazil.

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1. Introduction

Rabies has been known for over 4000 years, yet the disease is still largely present worldwide with 150 countries and territories still affected. This viral, zoonotic disease remains a public health concern in developing countries and still kills an estimated 61,000 people every year in the world, especially in Asia and Africa [1]. People may become infected after exposure with infected animal saliva, through bites, licks and scratches, and rabies is almost always fatal if left untreated. If wild rabies vector species, such as raccoons, foxes, skunks, and bats, represent a high risk to the populations,
domestic animals may also carry and transmit the disease. Rabies in dogs accounts for the main cause of rabies-induced morbidity and mortality in humans and puts over 3.3 billion people at risk of being exposed to the disease [2].

There is no known treatment against rabies; human rabies prevention relies largely on vaccination. Cell-based rabies vaccines have a well-established safety and efficacy profile from their administration to millions of people worldwide over more than forty years. These vaccines may be used for both pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). PrEP is recommended for anyone who will be at continual, frequent, or increased risk of rabies exposure. PEP is recommended depending on the type of exposure and the vaccination status of the patient. Each year, over 15 million people worldwide receive PEP regimen, which prevents an estimated 327,000 annual deaths from rabies [2]. The World Health Organization (WHO) has defined three categories of contact from the least (Category I) to the most serious (Category III); depending on the category, PEP may include vaccination in conjunction with local wound cleansing and the simultaneous administration of rabies immunoglobulins (RIG) [1,3]. Several WHO-approved rabies vaccination schedules have shown to be immunogenic for PEP via the intramuscular (IM) route, such as the 5-dose Essen regimen and the 4-dose Zagreb regimen, or via the intradermal (ID) route, such as the Thai Red Cross (TRC) 2-site regimen [1,3]. Rabies vaccines are expected to meet the WHO recommended potency of ≥2.5 IU per single IM dose and to induce an antibody (Ab) response at a minimum titer of 0.5 IU/mL of serum, as measured by the rapid fluorescent focus inhibition test (RFFIT) or the fluorescent antibody virus neutralizing test (FAVN).

Two rabies vaccines are currently manufactured by Sanofi Pasteur: a human diploid cell vaccine (HDCV), Imovax® Rabies, and a purified Vero cell rabies vaccine (PVRV), Verorab®. In an effort toward continuous improvement of its vaccine production process, Sanofi Pasteur has developed an improved serum-free, purified Vero cell rabies vaccine (PVRV Next Generation [PVRV-NG]) which will replace both Verorab® and Imovax® Rabies. This next-generation vaccine is prepared from the inactivated Pitman-Moore strain common to Verorab and Imovax Rabies. It is produced with the same potency of ≥2.5 IU/dose but without any component of human or animal origin and without antibiotics. The resulting virus is highly purified prior to its inactivation by beta propiolactone and thoroughly characterized, thus improving its overall robustness. In addition, as is widely acknowledged, the absence of components of animal or human origin eliminates the risk of contamination with non-conventional transmissible agents such as those associated with Bovine Spongiform Encephalopathy (BSE) and scrapie. PVRV-NG has a very low residual DNA content (100 pg/dose) while keeping the same key attributes as Verorab, as demonstrated by the pharmaceutical comparability study using the ICH Q5E standards [4]. The comparability of Verorab and PVRV-NG, with regards to safety and immunogenicity, was demonstrated in a recent Phase II clinical trial [5]. Further to this, and as PVRV-NG is an evolution of Verorab, the extensive clinical data and field experience with Verorab are considered to be supportive of the safety, immunogenicity and efficacy of PVRV-NG.

In China, where the present study was conducted, rabies remains a public health issue. The country reports the second highest number of human cases after India, with more than 117,500 deaths and three major epidemics since 1950. Over the last 15 years, more than 25,000 people have died of rabies in China in a context of high population density and low dog vaccination coverage [6]. Rabies vaccination in China is used mainly for PEP according to the 5-dose Essen regimen. This study aimed to generate data in humans on the immunogenicity and safety of PVRV-NG when administered in a post-exposure regimen and to show that PVRV-NG is at least as immunogenic as Verorab with regards to seroconversion rate after three injections.

2. Methods

This was a phase III, blind-observer, controlled, randomized, monocenter trial in China.

2.1. Participants

The 816 participants aged ≥10 years were randomized according to a 2:1 ratio to receive PVRV-NG (Group 1: 544 participants) or Verorab (Group 2: 272 participants). Half of the subjects were aged 10–17 years, the other half were ≥18 years. In each age range, there were 272 subjects in Group 1 and 136 in Group 2. Subjects were not included in the trial if they had been previously vaccinated against rabies for pre- or post-exposure; if they planned to receive other vaccinations during the trial period; if they had known or suspected congenital or acquired immunodeficiency or known systemic hypersensitivity to any of the vaccine components; if they had a chronic illness; if they were at high risk of rabies exposure during the trial or had current alcohol abuse or drug addiction. Pregnant women, or women likely to be pregnant, were not included. Subjects who were HIV or hepatitis C positive or who had received blood or blood-derived products in the 3 months prior to enrolment were excluded.

2.2. Ethics

The trial complied with the Declaration of Helsinki, ICH guidelines for good clinical practice (GCP) and all applicable local and national regulations and directives. We obtained written assent from all subjects aged 10–11 years and written informed consent from all subjects aged ≥12 years. The parents or legal guardians of subjects <18 years also provided written consent.

2.3. Interventions

Both study vaccines are freeze-dried purified inactivated rabies vaccines prepared on Vero cells and manufactured by Sanofi Pasteur. Each dose of vaccine contained ≥2.5 IU inactivated rabies virus (Wistar Rabies Pitman Moore/WI 38 1503-3M strain) to be diluted in 0.5 mL sodium chloride before use. Two needles were supplied (16 and 25 mm), one for product reconstitution and one for IM administration, at the vaccinator’s discretion. PVRV-NG and Verorab were released under batch numbers S4256 and E0589-1, respectively.

Participants received five deltoid injections on Days (D) 0, 3, 7, 14 and 28. The study was conducted in simulated post-exposure condition without administration of RIG. Blood samples were taken on D0 (before the first dose), D14 (before the fourth dose) and D42 (14 days after the last dose).

2.4. Objectives and outcomes

The primary objective was to demonstrate that PVRV-NG is at least as immunogenic as Verorab. The primary endpoint was the seroconversion status at D14 (rabies virus neutralizing antibody [RVNA] titer ≥0.5 International Unit [IU]/mL) measured by a RFFIT. The secondary objectives were to assess the safety of PVRV-NG after each injection, in each age range and overall, and to describe the immune response induced by PVRV-NG after 3 injections and 14 days after the last injection, in each age range and overall. Clinical safety was assessed based on the occurrence of solicited (pain, erythema, and swelling) and unsolicited injection site reactions in the 7 days after each injection; solicited systemic reactions (fever,
headache, malaise, and myalgia) between the first and the second injection, between the second and the third injections, and then within 7 days after each subsequent injection; unsolicited systemic adverse events (AEs) between injections and 28 days after the last injection; serious adverse events (SAEs) throughout the trial until 6 months after the last injection. Adverse events and reactions were measured as per the “Guideline for Rating Scales of Adverse Reaction of Clinical Trials of Preventive Vaccines” released by the Chinese FDA in October 2005. Unsolicited AEs and SAEs were referred to as adverse reactions (ARs) or serious adverse reactions (SARs) if the investigators considered that they were related to vaccination.

2.5. Sample size

In each age range, it was estimated that 230 participants in the PVRV-NG group and 115 in the Verorab group were necessary, using the Farrington and Manning method, with an alpha level of 2.5% (one-sided hypothesis), a minimum clinically relevant difference of 5% for the seroconversion rate at D14, a power of at least 95%, an assumed seroconversion rate of 99% for both vaccines, and 2:1 randomization. Assuming that 15% would not be evaluable, each age range had to include 272 (Group 1) and 136 (Group 2) participants for a total of 544 and 272 participants in each group, respectively.

2.6. Randomization and blinding

Participants were randomized via a scratchable randomization list created using the permuted block method with stratification by age range. The list mentioned the inclusion number of the participant and the corresponding vaccine to be administered.

The trial used an observer-blind design so that both vaccines were prepared in the absence of the subject and administered by someone not in charge of safety assessment. The subject was not aware which vaccine was injected.

2.7. Statistical methods

The immunogenicity of PVRV-NG was compared to that of Verorab using a non-inferiority test in each age range. The primary parameter was the proportion of subjects with an RVNA titer \( \geq 0.5 \) IU/mL after the third dose. The two-sided 95% confidence interval (CI) of the difference in the proportion of subjects with an RVNA titer \( \geq 0.5 \) IU/mL was used. The non-inferiority of PVRV-NG was demonstrated in each age range if the lower bound of the 95% CI of the difference between PVRV-NG and Verorab was \( > -5 \% \).

Three analysis sets were defined:

The Per-Protocol Analysis Set (PPAS) excluded participants who were seropositive on D0 (i.e., \( \geq \) lower limit of quantitation [LLOQ]), who did not provide a blood sample, who did not have a valid test result available at both D0 and D14, or who had not been vaccinated according to the protocol or did not fully comply with the protocol.

The Full Analysis Set (FAS) was defined for the descriptive analysis of immunogenicity. All randomized subjects who had received the first dose were included.

The Safety Analysis Set (SaFAS) was defined for each dose as the subset of subjects who received this dose. Participants were analyzed according to the vaccine received at this dose. For the analysis at any dose, participants were analyzed according to the vaccine received at the first dose.

2.8. Laboratory methods

Serum samples were assayed for RVNA determination at the National Institutes for Food and Drug Control (NIFDC, Beijing, China) using an RFFIT. The method is described in the Chinese Pharmacopoeia [7].

3. Results

3.1. Participant flow

A total of 816 subjects were enrolled in the study between April and August 2011. 544 were randomized to Group 1 (PVRV-NG) and 272 to Group 2 (Verorab). Each group included subjects aged 10–17 years or \( \geq 18 \) years; in each age range, there were 272 subjects in Group 1 and 136 in Group 2 (Figs. 1 and 2).

The most frequent reason for discontinuation was voluntary withdrawal not due to an AE. Respectively in each group, 508 and 256 subjects received the full 5-dose schedule, and 507 and 255 were still present 28 days after Dose 5. Out of 66 subjects with protocol deviations (45 in Group 1 and 21 in Group 2) leading to exclusion from the per-protocol analysis, 49 were excluded because their post-dose 3 serology sample was not performed as a result, in most cases, of not receiving the required first three injections.

3.2. Baseline data

The study population had comparable baseline characteristics between Group 1 and Group 2 (Table 1); in each age range, the mean age of the subjects was similar between the groups, an unbalanced sex ratio in favor of female subjects was observed in each group (and was more marked in Group 2), and all subjects were of Asian origin. Baseline characteristics and demographic data were similar in the FAS and PPAS (Table 2).

3.3. Immunogenicity

As presented in Table 3, in each age range, all subjects included in the PPAS were naïve to rabies at baseline (RVNA titer \( < \) LLOQ of 0.141 IU/mL before vaccination). After the third injection, the seroconversion threshold was reached in all subjects in the younger age range and in all but 2 subjects, 1 from each group, in the older age range. The lower bound of the confidence interval of the difference between PVRV-NG and Verorab was \( > -5 \% \) in each age range, thus demonstrating the non-inferiority of PVRV-NG over Verorab. Similar results were observed in the FAS which included all randomized subjects who received the first vaccination, regardless of their baseline RVNA status.

The study also aimed to describe the immune response induced by PVRV-NG after 3 doses, and 14 days after the last injection in each age range and overall.

In the younger age range (10–17 years), five subjects in each group had detectable RVNA titers before the first dose but none had a titer \( \geq \) the WHO seroconversion threshold of 0.5 IU/mL. Pre-vaccination Geometric Mean Titers (GMTs) were close to 0.07 IU/mL in both groups. All subjects reached protective levels of RVNA titers after the third dose with an increase in GMTs to 7.26 (6.50; 8.11) IU/mL in Group 1 and 8.81 (7.60; 10.2) IU/mL in Group 2 and a further increase 14 days after the last dose to 9.61 (8.60; 10.7) IU/mL in Group 1 and 11.8 (10.2; 13.5) IU/mL in Group 2.

In the older age range (\( \geq 18 \) years), three subjects in each group had detectable RVNA titers before the first dose but none had a titer as high as 0.5 IU/mL. All subjects reached protective levels of RVNA titers after the third dose, except for two women aged 59 years who reached the 0.5 IU/mL threshold after the fifth dose of PVRV-NG (2.70 IU/mL) and Verorab (0.86 IU/mL). As was observed in the younger age range, GMTs were close to 0.07 IU/mL in both groups before vaccination, increased after the third dose (2.75 [2.40; 3.16] IU/mL in Group 1 and 3.76 [3.12; 4.55] IU/mL in Group 2), and
**PVRV-NG**
N Planned = 272
N randomized = 272

N at V01 = 272
N blood sample = 272
N vaccinated = 272

N discontinued = 17
14 voluntary withdrawal and
3 had an AE.

N at V02 = 256*
N vaccinated = 255

N at V03 = 251
N vaccinated = 251

N at V04 = 250
N blood sample = 250
N vaccinated = 250

N discontinued = 1
1 voluntary withdrawal

N at V05 = 249
N vaccinated = 249

N at V06 = 249
N blood sample = 249

N at V07 = 249

N 6-month follow-up = 253

**Verorab**
N Planned = 136
N randomized = 136

N at V01 = 136
N blood sample = 136
N vaccinated = 136

N discontinued = 7
5 voluntary withdrawal and
2 had an AE.

N at V02 = 130*
N vaccinated = 129

N at V03 = 129
N vaccinated = 129

N at V04 = 129
N blood sample = 129
N vaccinated = 129

N at V05 = 127
N vaccinated = 127

N at V06 = 127
N blood sample = 127

N at V07 = 127

N 6-month follow-up = 129

Fig. 1. Flow diagram – Participants aged 10–17 years – Full Analysis Set.
*1 participant present at V02 but not vaccinated and therefore discontinued.
Fig. 2. Flow diagram – Participants aged ≥18 years – Full Analysis Set.

2 participants who were randomized to receive PVRV-NG received Verorab by mistake at D0.

*The subject with the SAE attended V03 but was not vaccinated as she was discontinued from the study at that visit.
Table 1
Baseline characteristics and demography according to randomized vaccine group – Full Analysis Set.

<table>
<thead>
<tr>
<th>Age at D0 (years)</th>
<th>10–17 years</th>
<th>18 years and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVRV-NG (N = 272)</td>
<td>Verorab (N = 136)</td>
<td>PVRV-NG (N = 272)</td>
</tr>
<tr>
<td>M (available data)</td>
<td>272</td>
<td>136</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.8 (1.9)</td>
<td>12.5 (1.8)</td>
</tr>
<tr>
<td>Minimum: Maximum</td>
<td>10.0: 17.4</td>
<td>10.0: 17.7</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: n (%)</td>
<td>121 (44.5)</td>
<td>51 (37.5)</td>
</tr>
<tr>
<td>Female: n (%)</td>
<td>151 (55.5)</td>
<td>85 (62.5)</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>0.80</td>
<td>0.60</td>
</tr>
<tr>
<td>Ethnic origin: n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>272 (100.0)</td>
<td>136 (100.0)</td>
</tr>
</tbody>
</table>

Fig. 3. RVNA Geometric Mean Titer (GMTs) – RFFIT method – Full Analysis Set.

Further increased after the fifth dose (5.09 [4.52; 5.74] IU/mL in Group 1 and 5.72 [4.86; 6.73] IU/mL in Group 2). See Fig. 3.

In all subjects overall and in each age range separately, GMTs tended to be slightly higher with Verorab than with PVRV-NG after the third and after the fifth injections. This was considered to be of limited clinical significance since RVNA titers reached levels far above 0.5 IU/mL in both groups.

Based on the homogeneity test performed after the third injection, gender and age were shown to have no impact on the response to vaccination.

3.4. Safety

An overview of safety data after any injection is presented in Table 4.

There were no related SAEs during the trial. Two unrelated SAEs were reported (two adult subjects randomized to Group 1 reported dog bites). No immediate (i.e. occurring within 30 min post-vaccination) unsolicited AEs were reported in any of the groups. Group 1 and Group 2 reported similar proportions of solicited reactions, unsolicited AEs and unsolicited ARs.

Solicited reactions tended to be more frequently systemic than injection site reactions and they occurred in higher proportions in the younger age range (see Figs. 4 and 5). Unsolicited AEs occurred in low proportions in Group 1 and Group 2, none of them was reported at the site of injection and the majority was assessed as not related. In younger subjects, unsolicited AEs were mostly Grade 1 or Grade 2 in severity, occurred within 3 days and resolved in a maximum of 14 days. In older subjects, unsolicited AEs were mostly Grade 1 in severity, occurred within 3 days and resolved in a

Table 2
Subject disposition in each analysis set.

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>PVRV-NG</th>
<th>Verorab</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Full Analysis Set</td>
<td>544</td>
<td>272</td>
<td>816</td>
</tr>
<tr>
<td>10–17 years (n)</td>
<td>272</td>
<td>136</td>
<td>408</td>
</tr>
<tr>
<td>≥ 18 years (n)</td>
<td>272</td>
<td>136</td>
<td>408</td>
</tr>
<tr>
<td>N Per-Protocol Analysis Set</td>
<td>499</td>
<td>251</td>
<td>750</td>
</tr>
<tr>
<td>10–17 years (n)</td>
<td>245</td>
<td>126</td>
<td>371</td>
</tr>
<tr>
<td>≥ 18 years (n)</td>
<td>254</td>
<td>125</td>
<td>379</td>
</tr>
<tr>
<td>N Safety Analysis Set*</td>
<td>542</td>
<td>274</td>
<td>816</td>
</tr>
<tr>
<td>10–17 years (n)</td>
<td>272</td>
<td>136</td>
<td>408</td>
</tr>
<tr>
<td>≥ 18 years (n)</td>
<td>270</td>
<td>138</td>
<td>408</td>
</tr>
<tr>
<td>Dose 1</td>
<td>521</td>
<td>259</td>
<td>780</td>
</tr>
<tr>
<td>10–17 years (n)</td>
<td>255</td>
<td>129</td>
<td>384</td>
</tr>
<tr>
<td>≥ 18 years (n)</td>
<td>266</td>
<td>130</td>
<td>396</td>
</tr>
<tr>
<td>Dose 2</td>
<td>511</td>
<td>259</td>
<td>770</td>
</tr>
<tr>
<td>10–17 years (n)</td>
<td>251</td>
<td>129</td>
<td>380</td>
</tr>
<tr>
<td>≥ 18 years (n)</td>
<td>260</td>
<td>130</td>
<td>390</td>
</tr>
<tr>
<td>Dose 4</td>
<td>508</td>
<td>259</td>
<td>767</td>
</tr>
<tr>
<td>10–17 years (n)</td>
<td>250</td>
<td>129</td>
<td>379</td>
</tr>
<tr>
<td>≥ 18 years (n)</td>
<td>258</td>
<td>130</td>
<td>388</td>
</tr>
<tr>
<td>Dose 5</td>
<td>507</td>
<td>257</td>
<td>764</td>
</tr>
<tr>
<td>10–17 years (n)</td>
<td>240</td>
<td>127</td>
<td>376</td>
</tr>
<tr>
<td>≥ 18 years (n)</td>
<td>258</td>
<td>130</td>
<td>388</td>
</tr>
</tbody>
</table>

* Based on the vaccine received at each dose.

Table 3
Non-inferiority of PVRV-NG versus Verorab – Proportions of subjects with RVNA titer ≥0.5 IU/mL at D14 by group – RFFIT method – Per-Protocol Analysis Set.

<table>
<thead>
<tr>
<th></th>
<th>PVRV-NG (N = 499)</th>
<th>Verorab (N = 251)</th>
<th>PVRV-NG-Verorab</th>
<th>Non-inferiority*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–17 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with RVNA titer ≥0.5 IU/mL at D0</td>
<td>0/245</td>
<td>0.0</td>
<td>(0.0; 1.49)</td>
<td>0/126</td>
</tr>
<tr>
<td>Subjects with RVNA titer ≥0.5 IU/mL at D14</td>
<td>245/245</td>
<td>100.0</td>
<td>(98.5; 100)</td>
<td>126/126</td>
</tr>
<tr>
<td>18 years and over</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with RVNA titer ≥0.5 IU/mL at D0</td>
<td>0/254</td>
<td>0.0</td>
<td>(0.0; 1.44)</td>
<td>0/125</td>
</tr>
<tr>
<td>Subjects with RVNA titer ≥0.5 IU/mL at D14</td>
<td>253/254</td>
<td>99.6</td>
<td>(97.8; 100)</td>
<td>124/125</td>
</tr>
</tbody>
</table>

* Non-inferiority concluded if the lower limit of the two-sided 95% CI of the difference PVRV-NG – Verorab for proportion of subjects with RVNA titer ≥0.5 IU/mL is > −.5.0%.

n: number of subjects experiencing the endpoint.
M: number of subjects with available data for the relevant endpoint.
maximum of 7 days. There was no increase in the occurrence of AEs and ARs after each successive injection.

Overall, 10 subjects experienced AEs that led to study discontinuation. One subject was withdrawn by the Investigator after Level II dog bite (unrelated SAE) 3 days after the second dose of PVRV-NG. This 38-year-old woman received 5 doses of a commercial rabies vaccine as PEP. In the younger age range, two subjects, one from each group, were discontinued by the Investigator due to Grade II urticaria after the first vaccination. Both cases resolved within 8 days after healthcare contact. Additionally, seven subjects (six in the PVRV-NG group and one in the Verorab group) discontinued the study after they experienced AEs such as urticaria, common cold, malaise, headache, and pharyngalgia. These were all Grade I events of short duration that resolved spontaneously.

4. Discussion

PVRV-NG is a next-generation, highly purified rabies vaccine developed with innovative technology in human- and animal-free medium as an evolution of the reference vaccine Verorab. The vaccine benefits from decades of experience gathered from the administration of Verorab to millions of people in over 100

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**Table 4**

Safety overview during the trial – Safety Analysis Set – All subjects.

<table>
<thead>
<tr>
<th>Event</th>
<th>PVRV-NG (N=542)</th>
<th>Verorab (N=274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate unsolicited AE</td>
<td>n/M</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Solicited reaction</td>
<td>0/542</td>
<td>0.0 (0.0; 0.7)</td>
</tr>
<tr>
<td>Solicited injection site reaction</td>
<td>60/540</td>
<td>11.1 (8.6; 14.1)</td>
</tr>
<tr>
<td>Solicited systemic reaction</td>
<td>86/540</td>
<td>15.9 (12.9; 19.3)</td>
</tr>
<tr>
<td>Unsolicited AE</td>
<td>20/542</td>
<td>3.7 (2.3; 5.6)</td>
</tr>
<tr>
<td>Unsolicited AR</td>
<td>6/542</td>
<td>1.1 (0.4; 2.4)</td>
</tr>
<tr>
<td>Unsolicited non-serious AE</td>
<td>19/542</td>
<td>3.5 (2.1; 5.4)</td>
</tr>
<tr>
<td>Unsolicited non-serious AR</td>
<td>6/542</td>
<td>1.1 (0.4; 2.4)</td>
</tr>
<tr>
<td>Unsolicited non-serious injection site AR</td>
<td>0/542</td>
<td>0.0 (0.0; 0.7)</td>
</tr>
<tr>
<td>Unsolicited non-serious systemic AE</td>
<td>19/542</td>
<td>3.5 (2.1; 5.4)</td>
</tr>
<tr>
<td>AE leading to study discontinuation</td>
<td>8/542</td>
<td>1.5 (0.6; 2.9)</td>
</tr>
<tr>
<td>SAE collected up to 28 days after last vaccination</td>
<td>2/542</td>
<td>0.4 (0.0; 1.3)</td>
</tr>
<tr>
<td>SAE collected during 6-month follow-up</td>
<td>0/542</td>
<td>0.0 (0.0; 0.7)</td>
</tr>
<tr>
<td>SAE collected up to the end of 6-month follow-up</td>
<td>2/542</td>
<td>0.4 (0.0; 1.3)</td>
</tr>
</tbody>
</table>

\( n \): number of subjects experiencing the endpoint.

M: number of subjects with available data for the relevant endpoint.

AE = adverse event; AR = adverse reaction.

Identified in the termination form as SAE or other AE up to 28 days after the last vaccination.

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![Fig. 4. Solicited injection site reactions within 7 days after any dose – Safety Analysis Set.](image1)

![Fig. 5. Solicited systemic reactions within 7 days after any dose – Safety Analysis Set.](image2)
countries for the pre- and post-exposure prophylaxis of rabies. Moreover, PVRV-NG complies with the European Union pharmacopeia and the specifications defined by the WHO and the US Food and Drug Administration (FDA).

As was already shown for pre-exposure in a Phase II trial [5], this Phase III trial demonstrated the immunogenic non-inferiority of PVRV-NG compared with Verorab after three doses of a post-exposure regimen, with regards to RVNA titers in healthy subjects aged 10 years and over, regardless of gender, pre-vaccination titer and age. All subjects reached the 0.5 IU/mL seroconversion titer threshold after three doses, apart from one subject in the PVRV-NG group and one in the Verorab group who reached the threshold after completion of the full schedule. No further information could be collected to explain why their immune response was delayed, except for the concomitant intake of cephalosporin by one of these subjects for the treatment of chronic faucitis. Such delayed immune response is rare and was reported in a recent rabies study in China [8]. The GMTs were similar between the groups and in both the PPAS and the FAS. A marked increase in GMTs after three injections and a further increase 14 days after completion of the 5-dose schedule were observed with both vaccines.

PVRV-NG was safe and well tolerated after each injection and until 6 months after the last dose. The vaccine had a similar safety profile to Verorab with regards to the nature, frequency, duration and severity of AEs and ARs. With around 26% of subjects who reported at least one solicited reaction, the younger subjects in both groups tended to report more reactions than the older subjects (around 20%), regardless of whether they received PVRV-NG or Verorab. No safety signals emerged and reactogenicity did not increase with the successive injections.

Through this Phase III clinical trial, it was confirmed that the next-generation serum-free PVRV-NG vaccine, an evolution over the reference vaccine Verorab, is both safe and immunogenic, offering a new alternative for the prophylaxis of rabies.

Role of the funding source
Sanofi Pasteur was involved in all stages of the trial, including study design, data collection, analysis and interpretation, preparation of this article, and decision to submit the article for publication.

Contributors
All authors contributed to the conception, design or conduct of the trial, or the analysis and interpretation of data and they have all approved the final version of this manuscript.

Conflicts of interest
RL, LH, Jl, ZM, BH, YW, XW declare they have no conflicts of interest. MM, FGM, SP are Sanofi Pasteur employees.

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References