PUBLICATION CARD

Non-inferiority study of purified Vero rabies vaccine - serum free in three-dose and two-dose pre-exposure prophylaxis regimens in comparison with licensed rabies vaccines

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INTRODUCTION

Rabies is a viral zoonotic disease, causing 59000 human deaths annually in over 150 countries, with 95% of cases occurring in Africa and Asia

The current recommended schedule for rabies pre-exposure prophylaxis (PrEP) involves **2 doses** of the rabies vaccine, administered on days 0 and 7, updated from the previous **3-dose** schedule on days 0, 7, and 21 or 28

To ensure the vaccine supply and to meet demand, next-generation highly purified Vero cell rabies vaccine (PVRV-NG2) was developed with high level of innovation (serum and antibiotic-free, with low DNA content)

OBJECTIVE

- The main objective was to evaluate the non-inferiority of PVRV-NG2 at D42 compared to 2 standard-of-care rabies vaccines (PVRV and HDCV) when administered as a 3-dose PrEP regimen in each age group (children and adults)

Key Secondary Immunogenicity Objectives

- To demonstrate the NI of 2-dose PVRV-NG2 vs. 2-dose PVRV and HDCV in each age group at D28
- To demonstrate the NI of 2-dose PVRV-NG2 at D28 vs. 3-dose HDCV at D42 in each age group

Safety Objectives

- To evaluate the safety profile of PVRV-NG2 versus PVRV and HDCV after each vaccine injection in each age group

Additional secondary objectives can be found in the publication

METHODS

A phase III, multicentric, observer-blind, controlled, randomized study (NCT04127786) (N=1708)

Location and Period

- **Location:** Thailand (4 centres)
- **Enrolment Period:**
  Cohort 1: Oct 2019 to Feb 2020
  Cohort 2: Sept 2022 to Jan 2023

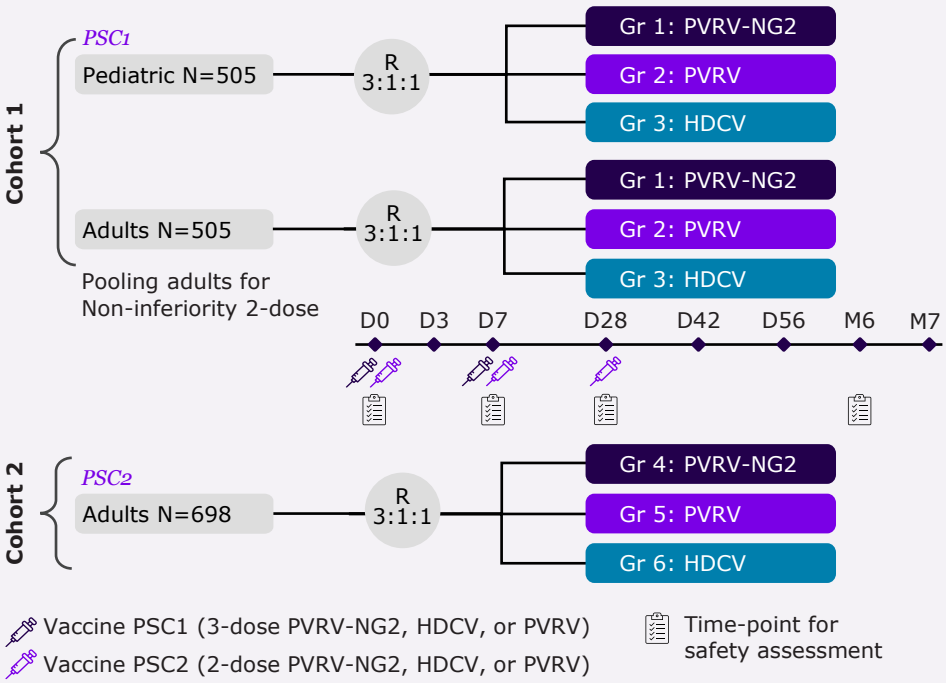
Inclusion Criteria

- Age ≥1 year on the day of inclusion who have never received prior rabies vaccination
- Not been bitten by or exposed to a potentially rabid animal in the previous 6 months

Exclusion Criteria

- Any vaccination in the 4 weeks preceding the first study vaccination or following any study vaccinations
- Receipt of Igs, blood, or blood-derived products in the past 3 months
- Known or suspected congenital or acquired immunodeficiency
- Immunosuppressive therapy in the past 6 months
- History of Guillain-Barré syndrome
- Acute illness/infection or febrile illness on the day of vaccination
- Known systemic hypersensitivity
- Pregnancy, or lactation

Figure 1: Study Design



Immunogenicity Assessment

- Blood samples were collected at D0 (before the first vaccination), D28 (21 days after the second vaccination), and D42 (14 days after the last vaccination) in cohort 1 and at D0 and D28 in cohort 2 to measure RVNA using the RFFIT

Safety Assessment

- The safety profile of PVRV-NG2 was assessed throughout the study

* **Booster Phase:** Each PrEP will be followed by a PVRV-NG2 booster dose in a subset of adult participants, at M12 in Cohort 1 and M24-M36 in Cohort 2 (Data not presented)

RESULTS

SAFETY

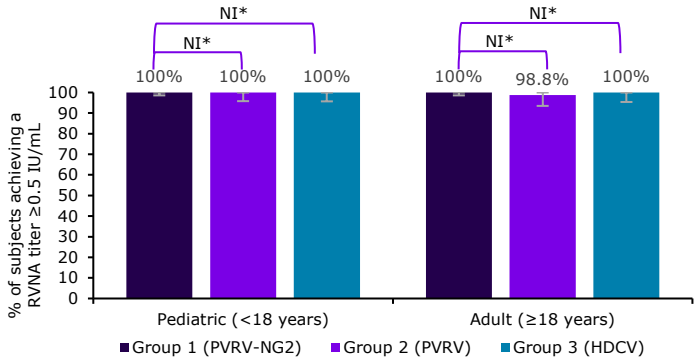
- *No safety concern* was identified
- *Similar rates of solicited and unsolicited AEs* among the 3 groups in each cohort
- The overall safety profile of PVRV-NG2 was comparable to that of PVRV and HDCV

IMMUNOGENICITY OUTCOMES

3-dose PVRV-NG2 was NI to 3-dose PVRV & HDCV at D42

- Non-inferiority of PVRV-NG2 (group 1) was reported at D42 when compared to PVRV (group 2) (difference: 0%, 95% CI: -1.4; 4.3) and HDCV (group 3) (difference: 0%, 95% CI: -1.4; 4.4) in children **(Figure 2)**
- Similarly for adults, non-inferiority of PVRV-NG2 (group 1) was demonstrated at D42 when compared to PVRV (group 2) (difference: 1.2%, 95% CI: -0.6; 6.4) and HDCV (group 3) (difference: 0%, 95% CI: -1.5; 4.6) **(Figure 2)**

Figure 2: Proportion of subjects achieving a RVNA titer ≥0.5 IU/mL - PPAS for D42

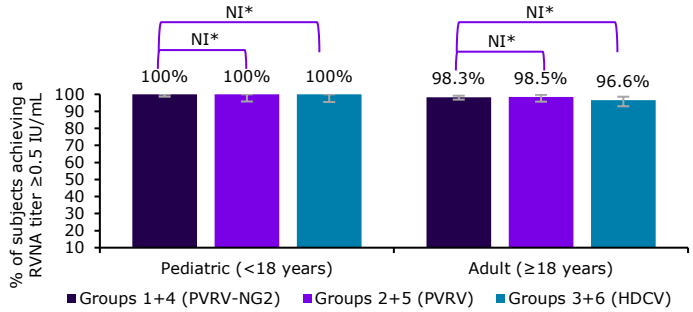


*NI: Non-inferiority

2-dose PVRV-NG2 was NI to 2-dose PVRV & HDCV at D28

- Non-inferiority of 2-dose PVRV-NG2 (groups 1 and 4) was demonstrated at D28 versus 2-dose PVRV (groups 2 and 5) (difference: 0%, 95% CI: -1.4; 4.3) and HDCV (groups 3 and 6) (difference: 0%, 95% CI: -1.4; 4.5) in children **(Figure 3)**
- Also in adults, 2-dose PVRV-NG2 was found to be non-inferior at D28 versus 2-dose PVRV (difference: -0.2%, 95% CI: -1.9; 2.7) and HDCV (difference: 1.8%, 95% CI: -0.5; 5.3) **(Figure 3)**

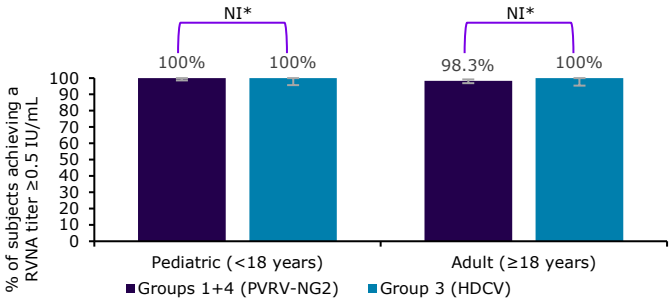
Figure 3: Proportion of subjects achieving a RVNA titer ≥0.5 IU/mL - PPAS for D28



2-dose PVRV-NG2 at D28 was NI to 3-dose HDCV at D42

- Both in children and adults, non-inferiority of 2-dose PVRV-NG2 (groups 1 and 4) was achieved at D28 versus 3-dose HDCV (groups 3) at D42 with a difference of 0% (95% CI: -1.4; 4.4) and -1.7% (95% CI: -3.1; 3.0) respectively **(Figure 4)**
- The sufficiency of 3-dose PVRV-NG2 (group 1) at D42 was demonstrated as 100% of participants achieved an RVNA titer ≥0.5 IU/mL, with the lower limit of the 95% CI being 99.3%, meeting the ≥97% sufficiency margin
- Also, the sufficiency of 2-dose PVRV-NG2 at D28 was 98.8% (95% CI, 97.9–99.4)
- *Other secondary objectives* such as sufficiency of the 3 or 2-dose PVRV-NG2 were considered to have been *met from a clinical standpoint*

Figure 4: Proportion of subjects achieving a RVNA titer ≥0.5 IU/mL - PPAS



LIMITATIONS

- The recruitment time periods for cohort 1 and cohort 2 were different and the study was conducted in only 1 country, with cohort 2 recruited at a single center
- Additionally, very few participants younger than age 2 years and older than age 65 years were recruited

SUMMARY

1. This study demonstrated that the immune response in terms of proportion of participants reaching RVNA titer ≥0.5 IU/mL induced by 2-dose PVRV-NG2 at D28 was not inferior to 2-dose of the control vaccines, and also not inferior to 3-dose of HDCV
2. PVRV-NG2 was well tolerated, with a similar safety profile to the current licensed PVRV & HDCV standard of care

Glossary: ACIP, Advisory Committee on Immunization Practices; AE, adverse event; CI, confidence interval; D, day; GBS, Guillain-Barré syndrome; HDCV, human diploid cell vaccine (Imovax Rabies®, Sanofi); Igs, immunoglobulins; N, number; PrEP, pre-exposure prophylaxis; PPAS, per-protocol analysis set; PVRV, purified Vero cell vaccine (Verorab®, Sanofi); PVRV-NG, purified Vero cell vaccine-next generation; RFFIT, rapid fluorescent focus inhibition test; RVNA, rabies virus neutralizing antibody; WHO, World Health Organization; yo, years old

Reference: Chokephaibulkit K, *et al.* Non-inferiority study of purified Vero rabies vaccine - serum free in three-dose and two-dose pre-exposure prophylaxis regimens in comparison with licensed rabies vaccines. *Clin Infect Dis.* 2024; doi: 10.1093/cid/ciae581

Declaration: This study was funded by Sanofi

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