Sponsor: Sanofi **Drug substance:** Purified Vero Rabies Vaccine – Serum Free (VRVg): Purified inactivated rabies vaccine prepared on Vero cell line	**Study Identifiers:** U1111-1238-1726; NCT04594551 **Study code:** VRV00014

Title of the study:

Immunogenicity and Safety of the Purified Vero Rabies Vaccine – Serum Free (VRVg) Using the Zagreb Regimen as Simulated Rabies Post-Exposure Prophylaxis in Healthy Adults in Thailand

Study centers: This study was conducted at 3 centers that enrolled subjects in Thailand.

Study period:

Date first participant enrolled: 11/Oct/2020

Date last participant completed: 23/Jun/2021

Study Status: Completed

Phase of development: III

Objectives:

Primary objective:

Immunogenicity

To describe the immune response induced by VRVg-2 and Verorab vaccines at D14 and D35 when co-administered with HRIG at D0, according to the Zagreb (2-1-1) IM regimen in healthy adult subjects.

Secondary Objectives

Immunogenicity

To describe the immune response induced by VRVg-2 and Verorab vaccines at D90 when co-administered with HRIG at D0, according to the Zagreb (2-1-1) IM regimen in healthy adult subjects.

Safety

To describe the safety profile of VRVg-2 and Verorab vaccines when co-administered with HRIG at D0, after each vaccination.

Methodology:

This was a randomized, observer-blind, controlled, multi-center study.

A total of 201 healthy adult subjects (≥ 18 years old without upper age limit on the day of inclusion) were planned to be enrolled and randomized. The randomization ratio was 2:1 (VRVg-2:Verorab).

1. Group 1: VRVg-2 + HRIG at D0 N=134
2. Group 2: Verorab + HRIG at D0 N=67

Visits and phone calls

A total of 7 visits ([V]01-V07) composing Active Phase of the study, and 1 phone call (6-month safety follow-up) were planned.

Vaccination

All subjects were to receive a total of 3 doses of rabies vaccine (including 4 injections as follows: 2 injections at D0 (V01), 1 injection at D7 (V02), and 1 injection at D21 (V04). In addition, all subjects were to receive concomitant administration of HRIG at D0. All vaccinations were to be given through IM route.

At V01, the 2 vaccinations were to be done on each arm.

In addition, HRIG was to be concomitantly injected at D0 to all subjects, in both Group 1 and Group 2.

Blood sampling

All subjects were to provide 4 blood samples: at D0 (prior to vaccination [VAC]1), at D14 (7 days after VAC2), at D35 (14 days after VAC3), and at D90 (up to 3 months after VAC1). Blood sampling was to be done prior to vaccination and prior to HRIG injection at D0. Each blood sample volume drawn from subjects was to be 6 mL.

Collection of safety data

Subjects were to record information on experienced safety events in a DC as follows: information about solicited injection site and systemic reactions occurring within 7 days after each vaccination; about unsolicited injection site reactions during the 28 days after each vaccination; and about unsolicited systemic AEs or ARs between each vaccination and up to 28 days following the last vaccination.

As the subjects were to receive 2 injections at D0, the injection site reactions (solicited and unsolicited) were assessed on each site of injection.

Subjects were to record safety information in a memory aid from D90 (up to 3 months after VAC1) until the end of the study (Month [M]7).

Information about SAEs, AESIs and cases of pregnancy were recorded by blinded study personnel throughout the study (until 6 months after the last vaccination).

Early safety data review

An early Safety Data Review was not judged necessary in this study.

Number of participants:

It was planned to enroll and randomize 201 subjects: 134 subjects in the VRVg-2 group and 67 subjects in the Verorab group. Assuming a dropout rate of approximately 10%, 120 and 60 subjects were expected to be evaluated, respectively, in the VRVg-2 and Verorab groups.

Table S1: Study VRV00014 sample size

	Group 1 VRVg-2 + HRIG	Group 2 Verorab + HRIG	Total
Planned	134	67	201
Randomized	135	66	201
SafAS	135	66	201
FAS	135	66	201
FASI	117	60	177
PPAS for D14	111	56	167
PPAS for D35	113	55	168

Abbreviations: FAS, full analysis set; FASI, full analysis set for immunogenicity; PPAS, per protocol analysis set; SafAS, safety analysis set

Diagnosis and criteria for inclusion:

The study included healthy male and female subjects ≥ 18 years old without upper age limit on the day of inclusion.

Study products

Investigational product

VRVg-2 (purified inactivated rabies vaccine prepared on Vero cell line - serum-free), freeze-dried (0.5 mL dose).

The route of administration was an IM injection in the deltoid arm.

Control product

Verorab vaccine (purified inactivated rabies vaccine prepared on Vero cell line), freeze-dried (0.5 mL dose).

The route of administration was an IM injection in the deltoid arm.

Other Product:

IMOGAM® Rabies-HT: HRIG (150 IU/mL). The recommended dose in a post-exposure regimen is 20 IU/kg (or 9 IU/lb) of body weight.

The route of administration was an IM injection in the anterolateral thigh.

Duration of study intervention:

The duration of each subject's participation in the study was approximately 7 months (21-day vaccination period followed by 6-month safety follow-up period).

Criteria for evaluation:

Primary Endpoints

Immunogenicity

The primary endpoints for the evaluation of immunogenicity were:

- Rabies virus neutralizing antibody (RVNA) titers (international units/milliliter [IU/mL]) against rabies virus obtained by the Rapid Fluorescent Focus Inhibition test (RFFIT)
  - Percentage of subjects with an RVNA titer ≥ 0.5 IU/mL at D0, D14, and D35
  - Subjects with an RVNA titer ≥ lower limit of quantification (LLOQ) IU/mL at D0, D14, and D35
  - Individual RVNA titer ratio: D14/D0 and D35/D0

Secondary Endpoints

Immunogenicity

The secondary endpoints for the evaluation of immunogenicity were:

- RVNA titers (IU/mL) against rabies virus obtained by the RFFIT
  - Percentage of subjects with an RVNA titer ≥ 0.5 IU/mL at D90
  - Subjects with an RVNA titer ≥ LLOQ IU/mL at D90
  - Individual RVNA titer ratio: D90/D0

Safety

The secondary endpoints for the evaluation of safety were:

- Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination
- Occurrence of solicited (pre-listed in the subject's diary card (DC) and electronic Case Report Form [eCRF]) injection site and systemic reactions occurring within 7 days after each vaccination
- Occurrence of unsolicited (spontaneously reported) injection site reactions occurring within 28 days after each vaccination and unsolicited systemic AEs/adverse reactions (ARs) between each vaccination and up to 28 days after the last vaccination
- Occurrence of serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study (until 6 months after last vaccination)

SAEs (including AESIs) were reported throughout the study, including occurrence, nature (Medical Dictionary for Regulatory Activities preferred term), time of onset, duration, intensity, action taken, relationship to the product administered (for systemic AEs only), whether the event caused termination from the study, outcome, elapsed time from last administration (if less than 24 hours), relationship to study procedures, and seriousness criterion.

Note: The following AESIs were considered as SAEs and reported to the Sponsor: anaphylactic reactions, encephalitis, and convulsions. For each AESI, the standard case definitions from the Brighton Collaboration was used. These AESIs have been defined based on existing post-marketing safety data of other rabies vaccines

Statistical methods:

The final analysis was conducted after the 6-month safety follow-up period.

All analyses were descriptive, ie, no hypotheses were tested. The Per-Protocol Analysis Set (PPAS), the Full Analysis Set for Immunogenicity (FASI) and the Full Analysis Set (FAS) were used for the main immunogenicity analyses, and the Safety Analysis Set (SafAS) was used for the safety analyses.

The proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at each time point and the 95% confidence interval (CI) using the exact binomial method (Clopper-Person method, quoted by Newcombe) were calculated by vaccine group.

Antibody titers were also described in terms of GMT with their 95% CI in each vaccine group.

All the safety parameters were described in each vaccine group. Proportions and 95% CI were calculated for each endpoint.

Summary Results:

Demographic and Other Baseline Characteristics:

A total of 201 subjects were enrolled: based on the FAS, 133 subjects were aged between ≥ 18 and 40 years old, 63 subjects were aged between ≥ 41 and 64 years old, and 5 subjects were aged ≥ 65 years old. The overall mean age of the subjects was 36.5 (±12.4) years and similar in both treatment groups. There were more males than females in Group 1 (VRVg-2 + HRIG) (86 males [63.7%] and 49 females [36.3%]), and more females than males in Group 2 (Verorab + HRIG) (31 males [47.0%] and 35 females [53.0%]). The male/female ratio was 1.76 in Group 1 and 0.89 in Group 2. All subjects were Asian.

Overall, the demographic and baseline characteristics were similar in all the FAS, FASI, PPAS for D14, and PPAS for D35.

Exposure:

A total of 201 subjects were randomized in the study: 135 subjects to Group 1 (VRVg-2 + HRIG) and 66 subjects to Group 2 (Verorab + HRIG). A total of 200 subjects (99.5%) completed the first 2 doses (D0 and D7) and 199 subjects (99.0%) completed the full vaccination schedule (ie, 3 doses of investigational medicinal product at D0, D7, and D21, with HRIG at D0) and the Active Phase of the study (133 subjects [98.5%] in Group 1 and 66 subjects [100%] in Group 2). All 201 subjects were successfully contacted by phone for 6-month safety follow-up.

Immunogenicity Results:

At D0, all evaluable subjects in the PPAS for D14 and for D35 had RVNA titer < 0.2 IU/mL.

Primary objective:

Based on the PPAS for D14, the numbers of subjects who achieved RVNA titer ≥ 0.5 IU/mL at D14 (ie, 7 days after the 2nd dose) were 101 (91.0% [95% CI: 84.1; 95.6]) in Group 1 (VRVg-2 + HRIG) and 53 (94.6% [95% CI: 85.1; 98.9]) in Group 2 (Verorab + HRIG); and 109 (98.2% [95% CI: 93.6; 99.8]) subjects in Group 1 and 55 (98.2% [95% CI: 90.4; 100]) subjects in Group 2 had RVNA titer ≥ 0.2 IU/mL. The GMTs were similar in Group 1 (2.15 [95% CI: 1.75; 2.64]) and in Group 2 (2.34 [95% CI: 1.76; 3.11]).

Based on the PPAS for D35, all subjects in Group 1 (VRVg-2 + HRIG) and Group 2 (Verorab + HRIG) achieved RVNA titer ≥ 0.5 IU/mL at D35 (ie, 14 days after the 2nd dose). The GMTs had increased from D0 and D14, and were similar in Group 1 (7.83 [95% CI: 6.79; 9.03]) and in Group 2 (8.95 [95% CI: 7.33; 10.9]).

Secondary objective:

At D90 (ie, 69 days after the 3rd dose), based on the PPAS for D35, the numbers of subjects who achieved RVNA titer ≥ 0.5 IU/mL were 102 (90.3% [95% CI: 83.2; 95.0]) in Group 1 (VRVg-2 + HRIG) and 52 subjects (94.5% [95% CI: 84.9; 98.9]) in Group 2 (Verorab + HRIG); and 111 subjects (98.2% [95% CI: 93.8; 99.8]) in Group 1 and 55 subjects (100% [95% CI: 93.5; 100]) in Group 2 had RVNA titer ≥ 0.2 IU/mL. The GMTs decreased from D35 and tended to be numerically lower in Group 1 (1.51 [95% CI: 1.29; 1.77]) than in Group 2 (1.98 [95% CI: 1.56; 2.52]), with overlapping CIs.

Safety Results:

The following results were based on the SafAS.

No immediate unsolicited AEs were reported after any injection in any group.

Within 7 days after any vaccine injection, the proportion of subjects who reported at least 1 solicited reaction was similar in Group 1 (VRVg-2 + HRIG) and Group 2 (Verorab + HRIG) (43.0% and 40.9%, respectively).

Within 7 days after any vaccine injection, the proportion of subjects who reported at least 1 solicited injection site reaction was similar in Group 1 and Group 2 (37.8% and 39.4%, respectively). Pain was the most frequently reported solicited injection site reaction in both groups, with 37.8% and 39.4% of subjects in Group 1 and Group 2, respectively. There was no Grade 3 injection site reaction.

Within 7 days after any vaccine injection, the proportion of subjects who reported at least 1 solicited systemic reaction tended to be numerically higher in Group 1 (34.8% [95% CI: 26.8; 43.5]) than in Group 2 (21.2% [95% CI: 12.1; 33.0]), with overlapping CIs. Myalgia was the most frequently reported solicited systemic reaction in both groups, in 30.4% (95% CI: 22.8; 38.9) and 21.2% (95% CI: 12.1; 33.0) of subjects in Group 1 and Group 2, respectively. Transient Grade 3 solicited systemic reactions after any vaccination were reported only by 2 subjects (1.5%) in Group 1.

Within 28 days after any vaccine injection, the proportion of subjects who reported at least 1 unsolicited AE tended to be numerically higher in Group 1 (20.0% [95% CI: 13.6; 27.7]) than in Group 2 (9.1% [95% CI: 3.4; 18.7]) with overlapping CIs. All these unsolicited AEs were non serious. The proportion of subjects who reported at least 1 unsolicited AE assessed as related to the study vaccines was 0.7% in Group 1 and 1.5% in Group 2, respectively. These unsolicited ARs were non-serious and all were injection-site haemorrhages (among the SOC “General disorders and administration site conditions”), which started during the time period from D0 to D3, and resolved within 8 to 14 days. There was no Grade 3 unsolicited AEs / ARs after any vaccination.

During the study, there were no AEs leading to study discontinuation, no AESIs, and no deaths. One subject (0.7%) in Group 1 reported 1 SAE (exposure to communicable disease i.e., "suspected exposure to rabies, World Health Organization category 3 (dog bite) (unknown)") during the safety follow-up period and was assessed as not related to the study vaccines by the Investigator and the Sponsor.

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