Immunogenicity and Safety of a Purified Vero Rabies Vaccine – Serum Free in Comparison with Verorab® and Imovax® Rabies, in a Pre-exposure Regimen in Both Pediatric and Adult Populations and a Single Booster Dose of Purified Vero Rabies Vaccine – Serum Free Administered at 1 Year Post-3-Dose Primary Series, and Between 2 up to 3 Years Post-One Week 2-Dose Primary Series in a Subset of Adults in Thailand

Multi-center, observer-blind, controlled, randomized, Phase III study in 1700 subjects; ie, 505 subjects aged 1 year to < 18 years and 1195 adult subjects aged ≥ 18 years. Subjects will receive 2 or 3 vaccine injections in a primary series.

Booster phase will be conducted in a blinded manner which includes a subset of 170 adult subjects who will receive a single booster dose of Purified Vero Rabies Vaccine – Serum Free 1 year post-3-dose primary series, in addition, to be conducted in an open-label manner which includes a subset of 230 adult subjects who will receive a single booster dose of Purified Vero Rabies Vaccine – Serum Free Between 2 up to 3 years post-one week 2-dose primary series, regardless of the vaccine used in the primary series.

Clinical Study Protocol, Amendment 5

Health Authority File Number(s):	BB-IND #: 015026 EudraCT #: Not applicable
WHO Universal Study Number (UTN):	U1111-1217-3241
Study Code:	VRV12
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur 14 Espace Henry Vallée, 69 007 Lyon, France
Investigational Product(s):	Purified Vero Rabies Vaccine – Serum Free (VRVg): Purified inactivated rabies vaccine prepared on Vero cell line
Form / Route:	Freeze-dried + solvent/Intramuscular
Indication For This Study:	Pre-exposure regimen in pediatric and adult populations
Manufacturer:	Same as Sponsor

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Version and Date of the Protocol:	Version 8.0 dated 12 June 2023

History of Protocol Versions

Version	Date	Comments
1.0	12 March 2019	Internal version not submitted
2.0	26 March 2019	Submitted to EC
3.0	18 July 2019	Superseded by Version 4.0 dated 22 July 2019 due to an administrative change during the development of Amendment 1
4.0	22 July 2019	Version submitted to IEC/IRB; 1st version used in the study
5.0	05 November 2021	Version submitted to IEC/IRB; not used in the study
6.0	31 May 2022	Version submitted to IEC/IRB; used in the study
7.0	17 November 2022	Version submitted to IEC/IRB; used in the study

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	Purified Vero Rabies Vaccine – Serum Free (VRVg): Purified inactivated rabies vaccine prepared on Vero cell line
Active Substance:	Rabies virus – Wistar rabies virus strain PMWI 38 – 1 503 3M – grown on continuous Vero-SF cell cultures, inactivated by betapropiolactone

Title of the Study:	Immunogenicity and Safety of a Purified Vero Rabies Vaccine – Serum Free in Comparison with Verorab® and Imovax® Rabies, in a Pre-exposure Regimen in Both Pediatric and Adult Populations and Single Booster Dose of Purified Vero Rabies Vaccine – Serum Free Administered at 1 Year Post-3-dose Primary Series, and Between 2 up to 3 years Post-One Week 2-dose Primary Series in a Subset of Adults in Thailand
Development Phase:	Phase III
Study Sites:	The study will be conducted in approximately 4 centers in Thailand. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Study" document.
Planned Study Period:	Q4 2019 1st visit, 1st subject (FVFS) to Q3 2025 last contact, last subject (LCLS, consisting of a phone call [PC] and not a visit)
Study Design, Schedule of Study Procedures, and Methodology:	Controlled, randomized, multi-center Primary series will be observer-blinded for both Cohort 1 (3-dose pre-exposure prophylaxis [PrEP] regimen) and Cohort 2 (one week 2-dose PrEP regimen). Booster phase will be conducted in a blinded manner (vaccine received in the primary series) with an adult subset from Cohort 1 and hereafter referred as "Booster Phase Cohort 1" (with booster Dose 1 year after the 1st primary series vaccine injection). Evaluation of immunogenicity persistence after primary series and a booster phase will be conducted in an open-label manner with an adult subset from Cohort 2 and hereafter referred as "Immunogenicity Persistence and Booster Phase Cohort 2" (including blood samples collection at Month [M] 6, M12, M18, pre-booster between M24 up to M36, and post-booster between M24 up to M36+D14; and a booster dose between M24 up to M36). A total of 4 centers in Thailand have been taking part to this study. All the 4 sites participated to Primary Series Cohort 1 and 2 out of the 4 sites participated in Booster Phase Cohort 1. One out of the 4 sites will participate in Cohort 2 (Primary Series Cohort 2 and Immunogenicity Persistence and Booster Phase Cohort 2). A total of 1700 healthy subjects are planned to be enrolled: 505 pediatric subjects (aged 1 year to < 18 years) and 505 adults (aged ≥ 18 years) to be vaccinated according to a 3-dose schedule PrEP regimen (Primary Series Cohort 1), and 690 adults (aged ≥ 18 years) to be vaccinated according to a one week 2-dose PrEP regimen (Primary Series Cohort 2). Randomization will be 3:1:1, (VRVg-2: Verorab vaccine: Imovax Rabies vaccine) in each age group:

	Primary Series Pediatric Subjects: N= 505, in which pediatric subjects were only planned to receive a 3-dose PrEP regimen Primary Series Cohort 1: Group 1: VRVg-2 N=303 Group 2: Verorab N=101 Group 3: Imovax Rabies N=101 Adult Subjects**:** N= 1195, in which: Primary Series Cohort 1**:** 505 adults were planned to receive a 3-dose PrEP regimen Group 1: VRVg-2 N=303 Group 2: Verorab N=101 Group 3: Imovax Rabies N=101 Primary Series Cohort 2: 690 adults are planned to receive one week 2-dose PrEP regimen Group 4: VRVg-2 N=414 Group 5: Verorab N=138 Group 6: Imovax Rabies N=138
	Booster Phase Two subsets of adult subjects will be randomized at enrollment to be part of booster phases. An adult subset from Cohort 1 will receive a booster dose of VRVg-2 at 1 year after the 1st vaccine injection of the primary series, regardless of what type of rabies vaccine was used in the primary series (Booster Phase Cohort 1). An adult subset from Cohort 2 will be followed up for evaluation of immunogenicity persistence after primary series (including blood samples collection at M6, M12, M18, pre-booster between M24 to M36, and post-booster between M24 up to M36+D14) and will receive a booster dose of VRVg-2 between M24 to M36, regardless and not-blinded of what type of rabies vaccine was used in the primary series (Immunogenicity Persistence and Booster Phase Cohort 2). All efforts will be made to ensure that the randomization ratio of the primary series will be maintained in the adult booster subset (Cohort 1) or immunogenicity persistence and booster subset (Cohort 2). Booster Phase Cohort 1 (booster at M12 after the 1st vaccination in the primary series) Adult Subjects: N= 170 (3-dose PrEP regimen)

	Group 1 (primed with VRVg-2) N=102 Group 2 (primed with Verorab) N=34 Group 3 (primed with Imovax Rabies) N=34 Immunogenicity Persistence and Booster Phase Cohort 2 (blood samples collection for evaluation of immunogenicity persistence at M6, M12, M18, pre-booster between M24 to M36 after primary series, and post-booster between M24 up to M36+D14; and a booster dose between M24 up to M36 after the 1st vaccination in the primary series with a new batch of VRVg-2 doses) Adult Subjects: N= 230 (one week 2-dose PrEP regimen) Group 4 (primed with VRVg-2): N=138 Group 5 (primed with Verorab): N=46 Group 6 (primed with Imovax Rabies): N=46 Pediatric subjects aged 1 year to less than 18 years will be in the study for about 7 months (including a 6-month follow-up). Adult subjects aged 18 years and older, will either be in the study for 7 months as the younger population, or they will stay for up to approximately 18 months (N = 170 adult subset in Booster Phase Cohort 1) or up to approximately 42 months (N = 230 adult subset in Immunogenicity Persistence and Booster Phase Cohort 2).
	Visits (V) and PC **Primary series** For pediatric subjects and adults who received the 3-dose PrEP regimen (Primary Series Cohort 1), a total of 5 visits (V01 to V05) and 1 PC have been concluded. For adult subjects who are planned to receive one week 2-dose PrEP regimen (Primary Series Cohort 2), a total of 4 visits (V01 to V04) and 1 PC are outlined. **Immunogenicity Persistence and Booster Phase** Booster Phase Cohort 1: for the primary series 3-dose PrEP regimen + booster phase, a total of 8 visits (V01 to V08) and 2 PCs have been concluded. Immunogenicity Persistence and Booster Phase Cohort 2: for the primary series one week 2-dose PrEP regimen + immunogenicity persistence + booster phase, a total of 10 visits (V01 to V10) and 1 PC are outlined. **Vaccination** Pediatric subjects (505 subjects) and adult subjects (505 subjects) in Primary Series Cohort 1 received a total of 3 injections at D0, D7, and D28 through intramuscular (IM) route. Adult subjects in Primary Series Cohort 2 (690 subjects) will receive a total of 2 injections in the primary series at Day (D)0 and D7 through IM route.

	A subset of 170 adult subjects (Booster Phase Cohort 1) received a booster dose of VRVg-2 after 1 year (M12) regardless of the vaccine used in the primary series and a subset of 230 adult subjects (Immunogenicity Persistence and Booster Phase Cohort 2) will receive a booster dose of VRVg-2 between 2 up to 3 years (M24-M36) regardless of the vaccine used in the primary series. **Blood sampling** Pediatric subjects and adult subjects (Primary Series Cohort 1) provided 3 blood samples: at D0 (prior to the 1st vaccine injection), at D28 (21 days after the 2nd dose vaccine injection), and at D42 (14 days after the 3rd vaccine injection). Adult subjects in Primary Series Cohort 2 will provide 2 blood samples: at D0 (prior to the 1st vaccine injection) and D28 (21 days after the 2nd dose vaccine injection). The adult subset who will be part of the Booster Phase Cohort 1 will have 2 additional blood samples in the booster phase: at M12 (prior to the booster vaccine injection) and M12+D14 (14 days after booster vaccine injection), to evaluate immunogenicity in the booster phase. The adult subset who will be part of the Immunogenicity Persistence and Booster Phase Cohort 2 will have 5 additional blood samples: at M6, M12, M18, pre-booster between M24 up to M36, and post-booster between M24 up to M36+14D to evaluate immunogenicity persistence after the primary series and immunogenicity after booster. **Collection of safety data** All subjects will be kept under observation for 30 minutes after each vaccination to ensure their safety. All subjects will record information on experienced safety events in a diary card (DC) as follows: information about solicited reactions will be recorded during the 7 days following each vaccine injection, about unsolicited injection site reactions during the 28 days after each injection, and about unsolicited systemic adverse events (AEs) between each injection, and during the 28 days following the last injection. Pediatric subjects and adult subjects in Primary Series Cohort 1 recorded safety information in a Memory Aid (MA) from D56 (28 days following the 3rd injection) until M7 for the subjects not involved in the booster phase, and until M12 for the adult subset in the Booster Phase Cohort 1; then from a booster vaccination (M12) until the end of the study (M18) for the adult subset in the Booster Phase Cohort 1. Adult subjects in Primary Series Cohort 2 (not involved in the Immunogenicity Persistence and Booster Phase Cohort 2 subset) will record safety information in a MA from D35 (28 days following the 2nd injection) until M6 (6-month safety follow-up after the last vaccination). Adult subjects in the Immunogenicity Persistence and Booster Phase Cohort 2 subset will record safety information in a safety DC from D35 (28 days following the 2nd injection) until booster vaccination (M24 up to M36); and in a MA from 28 days after booster vaccination until the end of the study (M30 up to M42, 6-month safety follow-up after the booster vaccination). Information about Serious Adverse Events (SAEs), Adverse events of Special Interest (AESIs), and cases of pregnancy were recorded throughout the study

	for pediatrics and adults in Cohort 1; and this is up to 6 months after the booster dose for subset of adults in Cohort 1. Information about SAEs, AESIs, and cases of pregnancy will be recorded until 6 months after the primary series (V05) and until 6 months after the booster dose for subset of adults in Cohort 2. Between the 6-month follow-up visit after primary series (V05) and booster dose visit (V08), AESIs will not be collected, only fatal SAEs and related SAEs will be collected. Study personnel will contact subjects by telephone at 6 months (+14 days) after the last primary vaccine injection (for subjects in Cohort 1, and for subjects in Primary Series Cohort 2 not involved in the Immunogenicity Persistence and Booster Phase Cohort 2 subset) and at 6 months (+14 days) after the booster dose for the collection of SAEs/AESIs.
Interruption of the Study	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the Independent Ethics Committees (IECs)/ Institutional Review Boards (IRBs), or the governing regulatory authorities in the country where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) (CROs) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects/ subjects' parent or legally acceptable representative (LAR) and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	***Immunogenicity*** 1) To demonstrate that VRVg-2 is non-inferior to Verorab and Imovax Rabies vaccines in each age group (pediatric and adult populations) when administered a 3-dose PrEP regimen, in terms of proportion of subjects achieving a rabies virus neutralizing antibody (RVNA) titer ≥ 0.5 International units (IU)/mL at D42, ie, 14 days after the 3rd injection (for Primary Series Cohort 1)
Primary Endpoints:	• RVNA titers (IU/mL) measured by the Rapid Fluorescent Focus Inhibition Test (RFFIT) at D42 for pediatrics and adults (from Primary Series Cohort 1) • Subject with an RVNA titer ≥ 0.5 IU/mL at D42

Secondary Objectives:	***Safety*** • To describe the safety profile of VRVg-2 versus Verorab and Imovax Rabies vaccines, after each vaccine injection, in each age group (for Cohort 1 and Cohort 2). • To describe the safety of single booster dose of VRVg-2 among the subsets of adults following primary series of 3-dose primary series in addition to booster dose at M12 (for Booster Phase Cohort 1) • To describe the safety of single booster dose of VRVg-2 among the subsets of adults following one week 2-dose primary series in addition to booster dose between M24 up to M36 (for Immunogenicity Persistence and Booster Phase Cohort 2) ***Immunogenicity*** • To demonstrate that the observed proportion of subjects in the VRVg-2 group (overall) achieving an RVNA titer ≥ 0.5 IU/mL at D42 is at least 99%, with a lower limit of the 95% confidence interval (CI) of at least 97% (for Primary Series Cohort 1), only if the primary objective is achieved • To demonstrate that VRVg-2 is non-inferior to Verorab and Imovax Rabies vaccines in each age group (pediatric and adult populations), in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D28, ie, 21 days after the 2nd injection (for pooled Primary Series Cohort 1 and Cohort 2), only if the 1st secondary immunogenicity objective is achieved • To demonstrate that 2-dose VRVg-2 at D28 is non-inferior to 3-dose Imovax Rabies at D42 in each age group (pediatric and adult populations, respectively), in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL, only if the 2nd secondary immunogenicity objective is achieved • To demonstrate that the observed proportion of subjects in the VRVg-2 group (overall) achieving an RVNA titer ≥ 0.5 IU/mL at D28 is at least 99%, with a lower limit of the 95% confidence interval (CI) of at least 97% (for pooled Primary Series Cohort 1 and Cohort 2), only if the 3rd secondary immunogenicity objective is achieved • To demonstrate that 2-dose Imovax Rabies at D28 is non-inferior to 3-dose Imovax Rabies at D42 in the overall subjects (pooled pediatric and adult subjects) in Cohort 1, in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL, only if the 4th secondary immunogenicity objective is achieved • To describe the immune response induced by VRVg-2 versus Verorab and Imovax Rabies vaccines at D28 (ie, 21 days after the 2nd injection), and at D42 (ie, 14 days after the 3rd injection) in all age groups (pediatric and adult populations) • To describe the immune response induced by VRVg-2 at D14 after a single dose booster of VRVg-2 administered at M12 after the primary series with VRVg-2, Verorab, or Imovax Rabies vaccines in the subset of adult subjects (for Booster Phase Cohort 1)

	• To describe the persistence of immune response at M6, M12, M18, and pre-booster between M24 up to M36 post-primary series vaccination in the subset of adults who are randomized to receive a booster and completed the 2-dose vaccination in the primary series (for Immunogenicity Persistence and Booster Phase Cohort 2) • To describe the immune response induced by VRVg-2 at D14 after a single booster of VRVg-2 administered between M24 up to M36 after the primary series with VRVg-2, Verorab, or Imovax Rabies vaccines in the subset of adult subjects who are randomized to receive a booster and completed the 2-dose vaccination in the primary series (for Immunogenicity Persistence and Booster Phase Cohort 2)

Secondary Endpoints:	***Immunogenicity*** • RVNA titers (IU/mL) measured by RFFIT, summarized at the subject/ timepoint level: • RVNA titers at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12 and M12+D14 for subjects in the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2 • Subject with an RVNA titers ≥ 0.5 IU/mL at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12 and M12+D14 for subjects in the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2 • Subject with an RVNA titer ≥ lower limit of quantitation (LLOQ) IU/mL at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12 and M12+D14 for subjects in the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in the Immunogenicity Persistence and Booster Phase Cohort 2 • Individual RVNA titer ratio: D28/D0 for subjects in Primary Series Cohort 1 and Cohort 2; D42/D0 for subjects in Primary Series Cohort 1; M12/D0, 14 days after M12/D0, and 14 days after M12/M12, for subjects in Booster Phase Cohort 1; M6/D0, M12/D0, M18/D0, M24 up to M36/D0, 14 days after M24 up M36/D0, and 14 days after M24 up M36/ M24 up to M36 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2 • Individual RVNA titer ratio: D28/D0 for subjects in Primary Series Cohort 1 and Cohort 2; D42/D0 for subjects in Primary Series Cohort 1; M12/D0, 14 days after M12/D0, and 14 days after M12/M12, for subjects in Booster Phase Cohort 1; M6/D0, M12/D0, M18/D0, M24 up to M36/D0, 14 days after M24 up M36/D0, and 14 days after M24 up M36/ M24 up to M36 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2 • Subject with complete or incomplete neutralization at the starting dilution (1/5) of the RFFIT assay at subject with an RVNA titer ≥ LLOQ IU/mL at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12 and M12+D14 for subjects in the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2 ***Safety*** • Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccine injection • Occurrence of solicited (pre-listed in the subject's DC and electronic case report form [CRF]) injection site and systemic reactions occurring within 7 days after each injection

	• Occurrence of unsolicited (spontaneously reported) injection site reactions occurring within 28 days after each injection and unsolicited systemic AEs between each injection and up to 28 days after each injection • Occurrence of SAEs and AESIs within at least 6 months after each vaccination as applicable to Cohort 1 and Cohort 2 SAEs (including AESIs) reporting includes occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] 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 24h), relationship to study procedures, and seriousness criterion. **Note:** The following AESIs will be considered as SAEs and reported to the Sponsor: anaphylactic reactions, encephalitis, and convulsions. For each AESI, the standard case definitions from the Brighton Collaboration will be used. These AESIs have been defined based on existing post-marketing safety data of other rabies vaccines. However, encephalitis and convulsion are no longer considered as safety concern for Verorab and Imovax following a cumulative safety review (scientific literature and reported cases) which concluded on lack of evidence to suspect any causal relationship between these events and Verorab and Imovax. Safety concerns for VRVg are driven based on prior experience with Verorab (biological comparability). Encephalitis and convulsion remain AESI in ongoing studies for continuity purpose only. **Note:** Information about Serious Adverse Events (SAEs), Adverse events of Special Interest (AESIs) and cases of pregnancy were recorded throughout the study for pediatrics and adults in Cohort 1; and this is up to 6 months after the booster dose for subset of adults in Cohort 1. Information about SAEs, AESIs, and cases of pregnancy will be recorded until 6 months after the primary series (V05) and until 6 months after the booster dose for subset of adults in Cohort 2. Between the 6-month follow-up visit after primary series (V05) and booster dose visit (V08), AESIs will not be collected, only fatal SAEs and related SAEs will be collected.
Planned Sample Size:	Total 1700 subjects are planned to be enrolled (505 pediatric subjects and 1195 adults) in 2 Cohorts. The attrition rate is anticipated as 15%. For pediatric subjects: 303 subjects in the VRVg-2 group, and 101 subjects in each of the control groups (Verorab and Imovax Rabies vaccines) will receive 3 doses of vaccinations in the primary series. For adult subjects: 717 subjects in the VRVg-2 group, and 239 subjects in each of the control groups (Verorab and Imovax Rabies vaccines) will be enrolled by 2 Cohorts: • Cohort 1: 303 subjects in the VRVg-2 group, and 101 subjects in each of the control groups received 3-dose primary series • Cohort 2: 414 subjects in the VRVg-2 group, and 138 subjects in each of the control groups will receive one week 2-dose primary series Note: about 1/3 adult subjects are planned to receive a booster vaccination of VRVg-2 (Cohort 1: at 12 months; Cohort 2: at 24 up to 36 months)

Duration of Participation in the Study:	The duration of each subject's participation in the primary series of the study will be approximately 7 months (28 day-vaccination period followed by 6-month safety follow-up period). For the subset of adult subjects in Booster Phase Cohort 1 who received a single booster dose of VRVg-2 (1 booster dose 365 days after primary series followed by 6-month safety follow-up period), the duration will be approximately 18 months. For Primary Series Cohort 2, the duration of each subject's participation in the study will be approximately 7 months (one week vaccination period followed by 6-month safety follow-up period). For the subset of adult subjects in Immunogenicity Persistence and Booster Phase Cohort 2 who will be followed up for evaluation of immunogenicity persistence after primary series (including blood samples collection at M6, M12, M18, and between 24 up to 36 months) and who will receive a single booster dose of VRVg-2 (after the blood sample collection between 24 up to 36 months), the duration will be approximately 30 to 42 months.
Investigational Product:	The investigational product is VRVg: Purified Vero Rabies Vaccine – Serum Free (purified inactivated rabies vaccine prepared on Vero cell line)
Form:	Freeze-dried

Composition:	Each 0.5 mL dose contains:
	Powder (VRVg-2):
	• Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain: ≥ 2.5 IU (potency; NIH); [redacted]
	• Stabilizer*: sufficient quantity (qs)
	• [redacted]
	* *The stabilizer (490 solution) is a mixture of amino acids (including trace amounts of phenylalanine), sugars (including the presence of sorbitol and trace amounts of saccharose), and sodium dihydrogen phosphate, di-sodium phosphate dihydrate, sodium glutamate, di-sodium edetate (EDTA), poloxamer P188 and urea in water for injections.*
	• Diluent:
	  • Sodium chloride: 2 mg
	  • Water for injection: qs 0.5 mL

Route:	IM
Batch Number:	Same batch (number to be disclosed at the time of report) was used for the primary series regardless of the number of doses and for the booster phase for subjects who received a 3-dose PrEP regimen (Primary Series Cohort 1) To be determined for the booster phase for subjects who received one week 2-dose PrEP regimen (Primary Series Cohort 2)
Control Product 1:	Verorab vaccine: purified inactivated rabies vaccine prepared on Vero cell line
Form:	Freeze-dried
Composition:	Each 0.5 mL dose contains: Powder: • Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3 M strain: ≥ 2.5 IU (potency; NIH) • Maltose: qs

	• Human albumin: qs
	• Diluent
	  • Sodium chloride: 2 mg
	  • Water for injection: qs 0.5 mL

Route:	IM
Batch Number:	To be determined
Control Product 2:	Imovax Rabies vaccine: purified inactivated rabies vaccine prepared on human diploid cell cultures
Form:	Freeze-dried
Composition:	Each dose contains: Powder: • Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain: ≥ 2.5 IU (potency; NIH) • Human albumin ≤ 10 mg Diluent: • Water for injection: qs 1 mL
Route:	IM
Batch Number:	To be determined
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1) Aged ≥ 1 year on the day of inclusion[a] 2) Informed consent form (ICF) has been signed and dated by the subject and /or parent(s) or LAR and by an independent witness (if required by local regulations), as necessary; and Assent form (AF) has been signed and dated by the subject, as required. 3) Subject (adult ≥18 years) or subject and parent/LAR (1 year to < 18 years) are able to attend all scheduled visits and to comply with all study procedures.
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to the 1st vaccination until 1 month after each vaccination. To be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, or surgically sterile. 2) Participation at the time of study enrollment or, planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.

[a] " ≥ 1 year" means from the day of the 1st birthday onwards, with no upper age limit

	3) Receipt of any vaccine in the 4 weeks (28 days) preceding the 1st study vaccination or planned receipt of any vaccine prior to V05 for pediatric subjects and adult subjects in Cohort 1, and prior to V04 for adult subjects in Cohort 2. 4) Previous vaccination against rabies (in pre- or post-exposure regimen) with either the study vaccines or another vaccine. 5) Bite by, or exposure to a potentially rabid animal in the previous 6 months with or without post-exposure prophylaxis. 6) Receipt of immune globulins, blood or blood-derived products in the past 3 months. 7) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months). 8) At high risk for rabies exposure during the study. 9) Known systemic hypersensitivity to any of the study/control vaccine components or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances. 10) Self-reported thrombocytopenia, contraindicating IM vaccination. 11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination. 12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily. 13) Current alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion. 14) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[a]. 15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided. 16) Personal History of Guillain-Barré syndrome. 17) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study.
Statistical Methods:	The statistical analysis will be performed in 4 steps. • The 1st statistical analysis will be done once all immunogenicity data up to D28 (V03, 21 days after the 2nd vaccination) in the primary series of Cohort 2 and all safety data up to D35 (V04, 28 days after the 2nd vaccination) in the primary series of Cohort 2 are available (ie, at the end of 6-month safety follow-up after booster phase in Cohort 1; and up to D35 [V04] in primary series in Cohort 2). The randomization

	and vaccination exposure information for all enrolled subjects will be unblinded at the time of 1st statistical analysis. • The 2nd statistical analysis will be carried out once the 12-month immunogenicity persistence data and safety data in Cohort 2 (V06) are collected. • The 3rd statistical analysis will be carried out once all the immunogenicity and safety data up to 28 days after the booster vaccination in Cohort 2 (V10) are collected. • The 4th statistical analysis will be carried out once the 6-month safety follow-up data post the booster vaccination in Cohort 2 (M30 up to M42) are collected. ***Primary objective: Non-inferiority (NI) testing of 3-dose VRVg-2 versus 3-dose Verorab and Imovax Rabies at D42*** In each age group, the immunogenicity of VRVg-2 will be compared to that of Verorab and Imovax Rabies vaccines at D42 for subjects in Primary Series Cohort 1, ie, 14 days after the 3rd vaccine injection, using a NI testing. For each comparison, the primary parameter will be the difference in the proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 between the 2 compared vaccine groups. The hypotheses tested will be the following: H_0: P_{VRVg-2}-$P_{control} \leq -5\%$ H_1: P_{VRVg-2}-$P_{control} > -5\%$ With P = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 (%). VRVg-2 will be considered as non-inferior to the tested control if the hypothesis H_0 is rejected. For the NI hypotheses, the statistical methodology will be based on the use of the two-sided 95% CI of the difference of proportions of subjects with an RVNA titer ≥ 0.5 IU/mL at D42. The 95% CI for differences will be calculated using the Wilson score method without continuity correction. Each NI will be demonstrated if the lower limit of the 95% CI of the difference of the 2 proportions P_{VRVg-2}-$P_{control}$ is > -5%. The primary objective of NI will be demonstrated if each of the NI between VRVg-2 and both Verorab and Imovax Rabies vaccines is demonstrated in each age group, respectively, in Primary Series Cohort 1. ***Secondary objectives*** The hypotheses of secondary objectives will be tested only if the primary objective is met, and then the key secondary objectives will be evaluated sequentially following a fixed-sequence method. • ***Superiority in the VRVg-2 group at D42***

[a] Chronic illness may include, but is not limited to, neurological, cardiopulmonary, gastrointestinal, renal, genitourinary, metabolic, hematologic, auto-immune, or psychiatric disorders or infection.

	Only if the primary objective is achieved at D42, the 1st secondary objective will be assessed on subjects from the VRVg-2 group for subjects in Primary Series Cohort 1, and this objective will be reached if the observed proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 is higher than or equal to 99% and if the following H_0 hypothesis is rejected: H_0: $P_{VRVg-2} < 97\%$ H_1: $P_{VRVg-2} \geq 97\%$ This objective will be demonstrated if the overall observed proportion of subjects in VRVg-2 group in Primary Series Cohort 1 with an RVNA titer ≥ 0.5 IU/mL at D42 is at least 99.0%, with the lower limit of the 95% CI of the proportion, calculated using the exact binomial distribution (Clopper Pearson method), is higher than or equal to 97%. • ***NI testing of 2-dose VRVg-2 versus 2-dose Verorab and Imovax Rabies at D28*** Only if the 1st secondary objective is achieved, and then based on the same approach as the primary objective testing, the 2nd secondary NI objective of VRVg-2 compared to each of the controls will be tested at D28 in each age group in pooled Primary Series Cohort 1 and Cohort 2 subjects. H_0: P_{VRVg-2}-$P_{control} \leq -5\%$ H_1: P_{VRVg-2}-$P_{control} > -5\%$ With P = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 (%). The secondary immunogenicity objective of NI at D28 will be demonstrated if each of the non-inferiority between VRVg-2 and both Verorab and Imovax Rabies vaccines is demonstrated for each age group, respectively, in pooled Primary Series Cohort 1 and Cohort 2. • ***NI testing of 2-dose VRVg-2 at D28 versus 3-dose Imovax Rabies at D42*** Only if the 2nd secondary objective is achieved, then the following NI hypotheses will be tested in each age group (Pediatric subjects: Cohort 1; Adult subjects: pooled Cohort 1 and Cohort 2), respectively: Pediatric subjects (Cohort 1 only): H_0: $P_{VRVg-2 \text{ at D28 (Group 1)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} \leq -10\%$ H_1: $P_{VRVg-2 \text{ at D28 (Group 1)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} > -10\%$ Adult subjects (Pooled Cohorts 1 and 2): H_0: $P_{VRVg-2 \text{ at D28 (Groups 1+4)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} \leq -10\%$ H_1: $P_{VRVg-2 \text{ at D28 (Groups 1+4)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} > -10\%$ With $P_{VRVg-2 \text{ at D28}}$ = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 for VRVg-2 (%), and $P_{Imovax \text{ Rabies at D42}}$=proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 for Imovax Rabies (%). NI will be demonstrated for each hypothesis if the lower limit of the 95% CI of the difference of the 2 proportions ($P_{VRVg-2 \text{ at D28}}$ -$P_{Imovax \text{ Rabies at D42}}$) is > -10%, with a similar approach as the primary objective testing.

The 3rd secondary objective will be demonstrated if all null hypotheses are rejected.

- ***Superiority in the VRVg-2 group at D28***

Only if the 3rd secondary objective is achieved, and then based on the same approach as the 1st secondary superiority objective testing at D42, the 4th secondary objective of superiority of VRVg-2 group at D28 will be assessed on overall subjects from VRVg-2 group in pooled Primary Series Cohort 1 and Cohort 2, and this objective will be reached if the observed proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 is higher than or equal to 99% and if the following H_0 hypothesis is rejected

H_0: $P_{VRVg\text{-}2} < 97\%$

H_1: $P_{VRVg\text{-}2} \geq 97\%$

This objective will be demonstrated if the overall observed proportion of subjects in VRVg-2 group in pooled Primary Series Cohort 1 and Cohort 2 with an RVNA titer ≥ 0.5 IU/mL at D28 is at least 99.0%, with the lower limit of the 95% CI of the proportion, calculated using the exact binomial distribution (Clopper Pearson method), is higher than or equal to 97%.

- ***NI testing of 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42***

Only if the 4th secondary objective is achieved, then this objective will be tested with the following hypotheses in Imovax Rabies group in overall subjects (pooled pediatric and adult subjects) in Cohort 1 only:

H_0: $P_{\text{Imovax Rabies at D28 (Group 3)}} - P_{\text{Imovax Rabies at D42 (Group 3)}} \leq -10\%$

H_1: $P_{\text{Imovax Rabies at D28 (Group 3)}} - P_{\text{Imovax Rabies at D42 (Group 3)}} > -10\%$

With $P_{\text{Imovax Rabies at D28}}$ = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 for Imovax Rabies in Cohort 1 (%); $P_{\text{Imovax Rabies at D42}}$=proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 for Imovax Rabies in Cohort 1 (%).

The null hypothesis will be rejected, and the objective will be achieved if the lower limit of the two-sided 95% CI for the difference of the 2 proportions ($P_{\text{Imovax Rabies at D28}} - P_{\text{Imovax Rabies at D42}}$) is > -10%, which will be calculated using a generalized linear model (GLM) for repeated measured data with categorical response under binomial distribution (link function=identity).

Other immunogenicity and safety objectives

The analyses will be described by vaccine group, using descriptive statistical methods only without hypothesis testing.

Datasets for analyses:

For primary and key secondary immunogenicity objectives, the per-protocol analysis set (PPAS) will be used as the primary analysis set, and supplementary analysis will be performed on FAS or FASI, if necessary.

For safety objectives, the safety analysis set (SafAS) will be used.

Calculation of sample size:

Primary series:

	Original Plan for Cohort 1: An alpha level of 2.5% (one-sided hypothesis) has been chosen to calculate the sample size. Originally, assuming a proportion of subjects with an RVNA titer ≥ 0.5 IU/mL of 99% for both VRVg-2 and control vaccines in each age group at D42, a clinical acceptable difference of -5% for the difference of proportions at D42 betweenVRVg-2 and the control vaccines, and a power of at least 95% for each of the NI testing in the primary objective, with an unbalanced randomization ratio of 3:1:1 (VRVg-2: Verorab vaccine: Imovax Rabies vaccine), 258 evaluable subjects in the VRVg-2 group, and 86 evaluable subjects in each of the Verorab and Imovax Rabies vaccine groups who are planned to receive 3 vaccinations (at D0, D7, and D28) in primary series in each age group, will be necessary to provide a global power of 81.8% for the primary NI objective, using the Farrington and Manning (FM) method. If the primary objective is met at D42, a total of 516 subjects evaluable in the VRVg-2 group will ensure 85.0% of power for the 1st secondary immunogenicity objective of superiority at D42. If the 1st secondary immunogenicity objective is met, overall power for the 2nd secondary immunogenicity NI objective of 2-dose VRVg-2 at D28 versus 2-dose comparator vaccines at D28 will be higher than 80%. Under the assumption that 15% of subjects will not be evaluable in the PPAS, 303 subjects in the VRVg-2 group and 101 subjects in each of the Verorab and Imovax Rabies vaccine groups must be enrolled in each age group of the study per the original plan, as Primary Series Cohort 1. ***Updated Plan for Cohort 1 and Cohort 2 (Protocol Amendments 2, 3, and 4):*** According to the latest results from the VAJ00001 study and to be conservative, the estimation of proportion of adult subjects with an RVNA titer ≥ 0.5 IU/mL at D28 was adjusted from 99% to 96.5% for both VRVg-2 and control vaccines. With the aim to secure the study power for the 2nd secondary immunogenicity NI objective at D28 and maintain the randomization ratio, 609 evaluable adults in the VRVg-2 group, and 203 evaluable adults in each of the control vaccine group (Verorab and Imovax Rabies) will be necessary to provide a power of 81.7% to demonstrate the 2nd secondary immunogenicity objective at D28, using the FM method. If the 2nd secondary immunogenicity objective is met at D28, a total of 867 subjects evaluable in the VRVg-2 group will ensure 99.2% of power for the secondary objective of superiority for VRVg-2 at D28 in the overall subjects (pooled pediatric and adult subjects). Therefore, under the attrition rate of 15%, 690 additional adults (414 in VRVg-2; 138 in Verorab; 138 in Imovax Rabies) were planned to be enrolled in the study as Cohort 2 to receive 2 vaccinations at D0 and D7 in the primary series. Those 690 additional adults in Cohort 2 were planned to be pooled with the 505 adults enrolled in Cohort 1, for testing the 2nd secondary NI objective at D28. The 414 additional adults in VRVg-2 group in Cohort 2 were planned to be pooled with the 303 pediatric subjects and

	303 adult subjects in VRVg-2 group in Cohort 1, for testing the secondary superiority objective for VRVg-2 at D28. Therefore, a total of 1700 subjects (505 pediatric subjects and 1195 adult subjects) were planned to be enrolled in total by 2 Cohorts, including 505 pediatric subjects and 505 adult subjects in Cohort 1 who are planned to receive 3 doses of vaccinations in the primary series, and 690 adult subjects in Cohort 2 who were planned to receive 2 doses of vaccinations in the primary series. As a consequence, a total of 1708 subjects (505 pediatric subjects and 1203 adult subjects) were actually enrolled, including 505 pediatric subjects and 505 adult subjects in Cohort 1 and 698 adult subjects (including 8 replacements) in Cohort 2. The 3:1:1 design is chosen to optimize the NI testing for immunogenicity and to increase the size of the safety database. ***Updated power estimations with additional objectives (Protocol Amendment 5):*** Based on live blinded data observed from Cohort 1, the estimated attrition rate of Cohort 1 was adjusted from 15% to about 13.5% at both D28 and D42 for pediatric subjects, and adjusted to about 21.0% at D28 and 19.8% at D42 for adult subjects, respectively. Assuming the actual attrition rate of adult subjects in Cohort 2 is similar to Cohort 1, the adjusted estimations for evaluable number of subjects in the PPAS in each age group are as below: • Pediatric subjects (Cohort 1 only): at both D28 and D42, there will be about 261 and 88 evaluable subjects in VRVg-2 group and each of the comparator vaccine groups, respectively. • Adult subjects: at D28, there will be about 570 and 190 evaluable subjects in VRVg-2 group and each of the comparator vaccine groups, respectively (pooled Cohort 1 and Cohort 2); at D42, there will be about 243 and 81 evaluable subjects in VRVg-2 group and each of the comparator vaccine groups, respectively (Cohort 1 only). Moreover, 2 new secondary immunogenicity objectives were added, both with a NI margin of -10%: • To demonstrate the NI of 2-dose VRVg-2 at D28 versus 3-dose Imovax Rabies at D42 in each age group • To demonstrate the NI of 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42 in the overall subjects (pooled pediatric and adult subjects) in Cohort 1 Finally, the primary objective and all 5 key secondary immunogenicity objectives will be evaluated sequentially. Each of the key immunogenicity objective will be tested only if the previous objective is achieved. Based on the updated study objectives and the adjusted number of evaluable subjects in the PPAS, the power to demonstrate each of the key immunogenicity objectives is presented as below:

Key Objectives	Age group	Evaluable N in the PPAS	Power (%)
Primary Objective	Pediatric Subjects (Cohort[C] 1)	VRVg-2: 261 Verorab: 88	95.4[a]
		VRVg-2: 261 Imovax Rabies: 88	95.4 [a]
	Adult Subjects (C1)	VRVg-2: 243 Verorab: 81	93.8 [a]
		VRVg-2: 243 Imovax Rabies: 81	93.8 [a]
			Overall: 80.0 [a]
Secondary Objectives			
#1	Overall (Pooled Pediatric and Adult Subjects in C1)	VRVg-2: 504	**86.3 [b]**
#2	Pediatric Subjects (C1)	VRVg-2: 261 Verorab: 88	95.4 [a]
		VRVg-2: 261 Imovax Rabies: 88	95.4 [a]
	Adult Subjects (Pooled C1+C2)	VRVg-2: 570 Verorab: 190	93.8 [a]
		VRVg-2: 570 Imovax Rabies: 190	93.8 [a]
			Overall: 80.1 [a]
#3	Pediatric Subjects (C1)	VRVg-2 at D28: 261 Imovax Rabies at D42: 88	>99.9 [a]
	Adult Subjects (D28 from Pooled C1+C2, D42 from C1)	VRVg-2 at D28 (Pooled Cohort 1+ Cohort 2): 570 Imovax Rabies at D42: 81	>99.9 [a]
			Overall: >99.9 [a]
#4	Overall (Pooled Pediatric and Adult Subjects in Pooled C1 and C2)	VRVg-2: 831	**98.9 [b]**
#5	Overall (Pooled Pediatric and Adult Subjects in C1 only)	Imovax Rabies at D28: 168 Imovax Rabies at D42: 168	**90.0 [c]**

a Power calculated using Farrington and Manning (FM) method.

b Power calculated using Binomial Exact method.

c Power calculated using simulation (10000 times, assuming correction coefficient [Rho]=0.5), based on general linear model (GLM) for repeated measured data with categorical response under binomial distribution (link function=identify).

Booster Phase

A subset of 170 adults from Cohort 1 (who received 3-dose PrEP regimen in the primary series) were included in the Booster Phase Cohort 1 at M12, in order to have 102 subjects who received the complete schedule with VRVg-2 vaccine (primary series + booster) in the FASB.

	A subset of 230 adults from Cohort 2 (who will receive one week 2-dose PrEP regimen in the primary series) will be included in Immunogenicity Persistence and Booster Phase Cohort 2 (including blood samples collection at M6, M12, M18, pre-booster between M24 up to M36, and post-booster between M24 up to M36+D14, and a booster dose between M24 up to M36), in order to have 117 evaluable subjects who received the complete schedule with VRVg-2 vaccine (primary series + booster), assuming approximate 15% of those 230 adult subjects will not be evaluable for booster immunogenicity evaluation at Year 2 up to Year 3 in the FASB.

Tables of Study Procedures

3-Dose Primary Series – **Pediatrics and Adults (Primary Series Cohort 1)**

Phase III Study, 5 Visits, 1 Phone Call, 3 Vaccinations, 3 Blood Samples, 7 Months Period per Subject

Visit	**V01**	**V02**	**V03**	**V04**	**V05**	**Phone Call**
Visit interval	**VAC1**	**VAC2= VAC1+7D**	**VAC3 = VAC1+28D**	**VAC3+14D**	**VAC3+28D**	**VAC3*+6M**
Indicative days (D)	**D0**	**D7 +1D**	**D28 ±3D**	**D42 ±3D**	**D56 ±3D**	**M7 +14D**
Informed consent signed†	√					
Demographic data	√					
Urine pregnancy test‡	√	√	√			
Physical examination§	√	√	√	√	√	
Past and current significant medical history	√					
Inclusion & exclusion criteria	√					
Randomization/ IRT call	√	√	√			
Blood sampling for serology**	**BL01**		**BL02**	**BL03**		
Vaccine injection	√	√	√			
30-minute observation period	√	√	√			
Diary Card (DC) **Memory Aid (MA)**						
Provided	DC1	DC2	DC3		MA1	
Checked		DC1	DC2	DC3	DC3	MA1
Collected		DC1	DC2		DC3	
Injection site reactions and Systemic Event Assessment	√	√	√	√	√	
Temporary contraindications		√	√			
Definitive contraindications		√	√			
Reportable concomitant medication	√	√	√	√	√	
Termination Record					√	
Pregnancy cases	Collected throughout the entire study period					
SAEs and AESIs	Collected throughout the entire study period					

* VAC3 or last vaccine injection in the event of early terminated subject contacted for the 6 months follow-up period through a phone call

†In addition if applicable, one AF has to be signed by subjects as required by local Ethics Committee or country regulations

‡ For subjects of childbearing potential

§ Complete physical examination at V01 and medically-driven physical examination for remaining visits

** Blood sample volume drawn from subjects aged 1 year to < 2 years will be 3 mL for subjects ≥ 2 years to < 18 years will be 5 mL, and for subjects ≥18 years will be 6 mL

One Week 2-Dose Primary Series – Adults (Cohort 2)

Phase III Study, 4 Visits, 1 Phone Call, 2 Vaccinations, 2 Blood Samples, approximately 7 Months Period per Subject

Visit	V01	V02	V03	V04	Phone Call‡
Visit interval	VAC1	VAC2= VAC1+7D	VAC1+28D	VAC2+28D	VAC2*+6M
Indicative days (D)	D0	D7 +1D	D28 ±3D	D35 ±3D	M6 +14D
Informed consent signed	√				
Demographic data	√				
Urine pregnancy test‡	√	√			
Physical examination§	√	√	√	√	
Past and current significant medical history	√				
Inclusion & exclusion criteria	√				
Randomization/ IRT call	√	√			
Blood sampling for serology**	BL01		BL02		
Vaccine injection	√	√			
30-minute observation period	√	√			
Diary Card (DC) Memory Aid (MA) Provided Checked Collected	DC1	DC2 DC1 DC1	DC2	MA DC2 DC2	MA
Injection site reactions and Systemic Event Assessment	√	√	√	√	
Temporary contraindications		√			
Definitive contraindications		√			
Reportable concomitant medication	√	√	√	√	
Termination Record				√	
Pregnancy cases	Collected throughout the entire study period				
SAEs and AESIs	Collected throughout the entire study period				

* VAC2 or last vaccine injection in the event of early terminated subject contacted for the 6 months follow-up period through a phone call

‡ For subjects of childbearing potential

§ Complete physical examination at V01 and medically-driven physical examination for remaining visits

**Blood sample volume drawn from subjects ≥ 18 years will be 6 mL

‡ Administrative calls: in the interim between 6-month phone call after last vaccination in the primary series and booster dose, the study staff is encouraged (but not obligated) to contact the participants to check on their general well-being and interest to continue with the study

3-Dose Primary Series + M12 Booster – Adult Subset (Cohort 1)

Phase III Study, 8 Visits, 2 Phone Calls, 3 Vaccinations, 1 Booster Dose, 5 Blood Samples, approximately 18 Months Period per Subject

Visit	**V01**	**V02**	**V03**	**V04**	**V05**	**Phone Call**	**V06**	**V07**	**V08**	**Phone Call**
Visit interval	**VAC1**	**VAC2= VAC1+7D**	**VAC3 = VAC1+28D**	VAC3+14D	VAC3+28D	VAC3*+6M	**Booster VAC4= VAC1+12M**	**D14 post-booster dose VAC4+14D**	**D28 post-booster dose VAC4+28D**	**6-month follow-up post-booster dose VAC4+6M**
Indicative days (D)	**D0**	**D7 +1D**	**D28 ±3D**	**D42 ±3D**	**D56 ±3D**	**M7 +14D**	**M12 +14D**	**M12+D14 +1D**	**M12+D28 ±3D**	**M18 +14D**
Informed consent signed	√									
Demographic data	√									
Urine pregnancy test‡	√	√	√				√			
Physical examination§	√	√	√	√	√		√		√	
Past and current significant medical history	√						√			
Inclusion & exclusion criteria	√									
Randomization/ IRT call	√	√	√							
Blood sampling for serology**	**BL01**		**BL02**	**BL03**			**BL04**	**BL05**		
Vaccine injection	√	√	√				√			
30-minute observation period	√	√	√				√			
Diary Card (DC) **Memory Aid (MA)** **Provided** **Checked** **Collected**	DC1	DC2 DC1 DC1	DC3 DC2 DC2	DC3	MA1 DC3 DC3	MA1	DC4 MA1 MA1	DC4	MA2 DC4 DC4	MA2

Visit	**V01**	**V02**	**V03**	**V04**	**V05**	**Phone Call**	**V06**	**V07**	**V08**	**Phone Call**
Visit interval	**VAC1**	**VAC2= VAC1+7D**	**VAC3 = VAC1+28D**	VAC3+14D	VAC3+28D	VAC3*+6M	**Booster VAC4= VAC1+12M**	**D14 post-booster dose VAC4+14D**	**D28 post-booster dose VAC4+28D**	**6-month follow-up post-booster dose VAC4+6M**
Indicative days (D)	**D0**	**D7 +1D**	**D28 ±3D**	**D42 ±3D**	**D56 ±3D**	**M7 +14D**	**M12 +14D**	**M12+D14 +1D**	**M12+D28 ±3D**	**M18 +14D**
Injection site reactions and Systemic Event Assessment	√	√	√	√	√		√			
Temporary contraindications		√	√				√			
Definitive contraindications		√	√				√			
Reportable concomitant medication	√	√	√	√	√		√	√	√	
Termination Record									√	
Pregnancy cases	Collected throughout the entire study period									
SAEs and AESIs	Collected throughout the entire study period									

* VAC3 or last vaccine injection in the event of early terminated subject contacted for the 6 months follow-up period through a phone call
‡ For subjects of childbearing potential
§ Complete physical examination at V01 and medically-driven physical examination for remaining visits
** Blood sample volume drawn will be 6 mL.

One Week 2-Dose Primary Series + Blood Samples for Immunogenicity Persistence at M6, M12, M18, pre-booster M24-M36 + M24-M36 Booster – Adult Subset (Cohort 2)

Phase III Study, 10 Visits, 1 Phone Call, 2 Vaccinations, 1 Booster Dose, 7 Blood Samples, approximately 42 Months Period per Subject

Visit	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**Phone Call**
Visit interval	**VAC1**	**VAC2= VAC1+7D**	VAC1+28D	VAC2+28D	VAC2+6M	VAC2+12M	VAC2+18M	**Booster VAC3= VAC1+24M up to 36M**	**D14 post-booster dose VAC3+14D**	**D28 post-booster dose VAC3+28D**	**6-month follow-up post-booster dose VAC3+6M**
Indicative days (D)	**D0**	**D7 +1D**	**D28 ±3D**	**D35 ±3D**	**M6 +14D**	**M12 +14D**	**M18 +14D**	**M24 up to M36 +14D**	**[M24 up to M36+14D] +14D +1D**	**[M24 up to M36+14D] +D28 ±3D**	**M30 up to M42+14D**
Informed consent signed	√										
Demographic data	√										
Urine pregnancy test‡	√	√						√			
Physical examination§	√	√	√	√				√		√	
Past and current significant medical history	√							√			
Inclusion & exclusion criteria	√										
Randomization/ IRT call	√	√									
Blood sampling for serology**	**BL01**		**BL02**		**BL03**	**BL04**	**BL05**	**BL06**	**BL07**		
Vaccine injection	√	√						√			
30-minute observation period	√	√						√			
Diary Card (DC)											

Visit	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**Phone Call**
Visit interval	**VAC1**	**VAC2= VAC1+7D**	VAC1+28D	VAC2+28D	VAC2+6M	VAC2+12M	VAC2+18M	**Booster VAC3= VAC1+24M up to 36M**	**D14 post-booster dose VAC3+14D**	**D28 post-booster dose VAC3+28D**	**6-month follow-up post-booster dose VAC3+6M**
Indicative days (D)	**D0**	**D7 +1D**	**D28 ±3D**	**D35 ±3D**	**M6 +14D**	**M12 +14D**	**M18 +14D**	**M24 up to M36 +14D**	**[M24 up to M36+14D] +14D +1D**	**[M24 up to M36+14D] +D28 ±3D**	**M30 up to M42+14D**
Memory Aid (MA)											
Provided	DC1	DC2						DC3		MA	
Checked		DC1	DC2	DC2					DC3	DC3	MA
Collected		DC1		DC2						DC3	
Diary Card (DC) SAE Follow-Up											
Provided				DC SAE							
Checked					DC SAE	DC SAE	DC SAE	DC SAE			
Collected								DC SAE			
Injection site reactions and Systemic Event Assessment	√	√	√	√				√			
Temporary contraindications		√						√			
Definitive contraindications		√						√			
Reportable concomitant medication	√	√	√	√	√†	√†	√†	√	√	√	
Termination Record										√	
Pregnancy cases	Collected throughout the entire study period***										
SAEs and AESIs	Collected throughout the entire study period***										

‡ For subjects of childbearing potential
§ Complete physical examination at V01 and medically-driven physical examination for remaining visits
** Blood sample volume drawn will be 6 mL
† Only for concomitant medication belonging to categories 2 or 3 (refer to Section 6.9)
***Information about SAEs, AESIs, and cases of pregnancy will be recorded until 6 months after the primary series and until 6 months after the booster dose for adults in Cohort 2. Between the 6-month follow-up visit after primary series (V05) and booster dose visit (V08), AESIs will not be collected, only fatal SAEs and related SAEs will be collected.

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AESI	Adverse event of special interest
AF	Assent Form
AR	Adverse reaction
CBER	Center for Biologics Evaluation and Research
CDM	Clinical Data Management
CI	Confidence Interval
COVID-19	coronavirus disease 2019
CPRV	Chromatographically purified rabies vaccine
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRO	Contract research Organization
CRB	(electronic) Case report book [all the case report forms for a subject]
CRF	(electronic) Case report form
CTA	Clinical trial agreement
CTL	Clinical Team Leader
D	Day
DC	Diary card
EDC	Electronic data capture
EDTA	Di-sodium edetate
EEA	European Economic Area
EMA	European Medicines Agency
FAS	Full Analysis Set
FASB	Full Analysis Set for Booster
FASI	Full Analysis Set for Immunogenicity
FDA	Food and Drug Administration
FITC	Fluorescein isothiocyanate
FM	Farrington and Manning
FVFS	First visit, first subject
FVLS	First visit, last subject

GCDSE	Global Clinical Development Strategy Expert
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
GPV	Global Pharmacovigilance
GSO	Global Safety Officer
HIV	Human immunodeficiency virus
HRIG	Human rabies immunoglobulin
IATA	International Air Transport Association
ICF	Informed consent form
ICH	International Council for Harmonization
ID	intradermal
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	Intramuscular
IME	Important medical event
IND	Investigational new drug (application)
IRB	Institutional Review Board
IRT	Interactive response technology
IU	International units
LAR	Legally acceptable representative
LCLS	Last contact, last subject
LLOQ	Lower limit of quantification
LLT	Lowest level term
M	Month
MA	Memory aid
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NA	Not applicable
NI	Non-inferiority
NSAID	Non-steroidal anti-inflammatory drug
PC	Phone call
PDCO	Pediatric Committee

PEP	Post-exposure prophylaxis
PI	Product Information
PPAS	Per-protocol analysis set
PrEP	Pre-exposure prophylaxis
PVRV	Purified Vero Rabies Vaccine
qs	Sufficient quantity
RFFIT	Rapid Fluorescent Focus Inhibition test
[redacted]	
RIG	rabies immunoglobulin
RMO	Responsible Medical Officer
RNA	Ribonucleic acid
RVNA	Rabies virus neutralizing antibody
SAE	Serious adverse event
SafAS	Safety analysis set
SafASB	Safety analysis set for booster
SF	Serum free
SmPC	Summary of Product Characteristics
SMT	Safety Management Team
TMF	Trial Master File
UN	United Nations
US	United States
V	Visit
VRVg	Purified Vero Rabies Vaccine – Serum Free
WHO	World Health Organization

1 Introduction

1.1 Background

The investigational product assessed in this study is VRVg, a vaccine against rabies.

Rabies is an infectious disease present worldwide, but mainly in developing countries, especially in Africa and Asia, where over 99% of human rabies deaths occur. The epidemiology of human rabies is an exact reflection of the epizootiology of the disease in animals. From the public health viewpoint, the dog or other canid species are the main vectors responsible for most infections in humans (1) (2).

Rabies is responsible for approximately 59 000 human deaths each year. It should be emphasized, however, that the widespread underreporting of rabies cases implies that the actual number of deaths is likely to be higher. Importantly, the majority of deaths occur in children younger than 15 years in poor and rural areas of Asia and Africa (1) (3) (4). The control of rabies in domestic and wild animals through animal control and vaccination programs, and the development of better human rabies vaccines and immunoglobulins remain critical to rabies prevention worldwide.

1.1.1 Rabies Virus

Rabies is caused by Rabies virus, the 1st genotype in the genus *Lyssavirus*, from the *Rhabdoviridae* family. It has 2 known vectors: carnivores (worldwide) and bats (Americas). This genotype is the main cause of rabies in humans. The virus core contains viral ribonucleic acid (RNA), a nucleocapsid protein, a phosphoprotein, and a viral transcriptase. On the outside, there is a matrix protein and a glycoprotein that includes the epitopes that induce neutralizing antibodies (2).

1.1.2 Rabies Disease

Rabies is a disease transmitted by infected (rabid) animals, usually through biting. The incubation period in humans is usually 20-60 days, but can be as short as <1 week, and as long as >6 months, or even several years. At 1st, infection presents with non-specific symptoms, including fever, headache, and malaise. There is often local tingling and severe pruritus at the site of the bite in the days following the contact. This is followed by central neurological signs, including anxiety, agitation, and delirium, often occurring a considerable time after the initial exposure. Periods of irritation are usually alternating with periods during which the patient is fully oriented (2). The virus will then spread from the brain to highly innervated areas, including the salivary glands causing hypersalivation, and other symptoms such as hydrophobia, aerophobia, and hyperventilation. In some cases, a paralytic form rather than an encephalitic form can be seen (5). Fever is usually present, but the sensory abilities of the patient are not affected. Within 2 weeks after onset of the neurological signs, coma usually sets in. There is no known treatment for rabies, and death is generally unavoidable. Few recoveries have been described, but these patients were usually left with permanent severe neurological disabilities.

Infection takes place when saliva from an infected animal (or even human being) comes in contact with mucosal membranes. Immediately after exposure, the virus is still cell-free, allowing prompt

local treatment with disinfectants and antiserum to reduce the risk of infection. In the absence of the latter, the virus, which is highly neurotropic, will access peripheral nerves and possibly muscle cells near the location where the initial contact occurred. Virus shedding in the saliva coincides with the appearance of the 1st clinical symptoms (6) (7).

While rabies is present worldwide, the most affected areas are the tropical countries in Asia, Africa, and Latin America, with over 99% of human rabies deaths occurring in developing countries (8).

In Asia, rabies remains to be a major burden with an estimated 35 172 human deaths per year (8).

In Thailand, the 2018 Surveillance data showed 16 fatal cases from 13 provinces, representing a rate of 0.02 per hundred thousand population. Proportion of males to females is 1:0.60. The most common age group is 35-44 years (25.0%), 55-64 years (25.0%), > 65 years (12.5%) respectively (9). According to the National Disease Surveillance System, in 2020 there were 3 human rabies deaths in different provinces in Thailand (namely Nongkhai, Sakaeo and Sisaket). As to the report covering the period in 2021 up to May 15th, 1 death occurred in Buriram province. The deceased was bitten by his dog that was bitten by a stray dog (10).

Human death from rabies can be effectively prevented either by post-exposure treatment after a rabies exposure or by PrEP to subjects with a high risk of exposure. More than 15 million people receive post-exposure treatments each year after being exposed to animals suspected of having rabies (11). Pre-exposure vaccination is recommended for all individuals at increased risk of contracting rabies, either because of their residence or the nature of their occupation such as laboratory staff, veterinarians, animal handlers, wildlife officers with frequent exposure to potentially infected animals, or persons traveling to rabies enzootic areas (12) (13).

1.1.3 Rabies Vaccines

The currently available vaccines recommended by the World Health Organization (WHO) are prepared on various cell substrates, such as human diploid cells, primary cells of hamster kidney, chicken or duck embryo fibroblasts, and continuous cell lines, like Vero cells (like Purified Vero Rabies Vaccine). These purified and beta-propriolactone-inactivated viral vaccines were developed in the 1960s to replace the 1st rabies vaccines prepared on animal nervous tissue, responsible for neurological disorders (14) (15) (16).

1.2 Background of the Investigational Product

Currently, Sanofi Pasteur has 2 rabies vaccines registered worldwide and available on the market: Imovax® Rabies and Verorab®. Imovax Rabies, a human diploid cell vaccine, was 1st licensed in 1975. It has been registered and marketed in 15 countries, including the United States (US), Canada, Australia, and 9 European Economic Area (EEA) countries. On the other hand, a Purified Vero Rabies Vaccine (PVRV), was 1st licensed in France in 1985 under the commercial name of Verorab and is extensively registered worldwide in 80 countries including 10 EEA countries but not in the US, Canada, and Australia. Both vaccines have a well-defined safety and immunogenicity profile (15) (16).

In addition to Imovax Rabies and Verorab vaccines, Sanofi Pasteur developed a chromatographically purified rabies vaccine (CPRV) prepared on Vero cells that was evaluated in the US and filed in the American Food and Drug Administration (FDA) under IND (BB-IND 6 042) in the 1990s. Although this vaccine was licensed in France and had an adequate immune and safety profiles, it was never commercialized due to industrial constraints.

In an effort to further improve the available rabies vaccines and optimize the manufacturing process and life cycle management, Sanofi Pasteur is developing a PVRV – serum free, henceforth referred to as VRVg.

VRVg is issued from the Wistar Rabies Pitman Moore/WI 38 1503-3M strain. VRVg is highly purified with very low residual DNA content (< 100 pg per dose) and it is produced without raw material derived from human or animal origin and without antibiotics. VRVg is compliant with standards set by the European Union Pharmacopoeia, the WHO, and the US FDA.

[redacted]

The clinical development of VRVg aims at demonstrating adequate immunogenicity versus the reference vaccines, and confirmation of the safety profile of the vaccine in all populations (for PrEP and post-exposure prophylaxis [PEP] of rabies), in order to provide the grounds for worldwide licensure in all age ranges.

VRVg development has been conducted through stepwise adjustments based on various regulatory, pharmaceutical, and /or clinical rationales. As summarized below, 2 formulations referred to as VRVg-1 and VRVg-2, have been subsequently explored and tested in 6 clinical studies. Their performance has been evaluated through the non-inferior immunogenicity to licensed vaccines (whether Verorab or Imovax Rabies vaccines) based on the well-established surrogate clinical endpoint of seroconversion (percentage of subjects achieving a rabies virus neutralizing antibody [RVNA] titer of at least 0.5 international units (IU)/mL, as measured by the Rapid Fluorescent Focus Inhibition test [RFFIT]).

VRVg-1 formulation

VRVg-1 was used in 5 clinical studies comprising both PrEP and simulated PEP regimens[a] (Phase II: VRV01, VRV02, VRV04, and VRV06, and Phase III: VRV08)[b]. VRVg-1 was non-inferior to Verorab vaccine in VRV01 and VRV08 and Imovax Rabies vaccine in VRV06, with the expected level of seroconversions (ie, > 99% subjects with RVNA titer ≥ 0.5 IU/mL).
[redacted]

[a] PrEP regimen: 3 injections at Day D0, D7, and D28; simulated PEP (ESSEN regimen): 5 injections at D0, D3, D7, D14, and D28.

[b] VRV01 (PrEP in adults), VRV02 (PrEP in adults), VRV04 (simulated PEP with HRIG administration at D0 in adults), VRV06 (PrEP in children ≥ 2 years), and VRV08 (simulated PEP in children ≥ 10 years and adults).

[redacted]
Consequently, Sanofi Pasteur decided to modify the initial formulation of VRVg-1 in order to ensure an enhanced vaccine immune response.

The safety profile of VRVg-1 was satisfactory and similar to that of Verorab and Imovax Rabies vaccine, with a trend towards a lower incidence of solicited injection site reactions.

VRVg-2 formulation

This 2nd formulation, referred to as VRVg-2, differs from VRVg-1 in that the antigen (Ag) content is increased, [redacted] A dose-ranging study (VRV11; PEP study in simulated conditions with human rabies immunoglobulin (HRIG) administration at D0 in adults) compared 3 VRVg-2 dosages (low, medium, and high) with increasingly higher Ag amounts than VRVg-1[a], versus VRVg-1 and Imovax Rabies vaccine.

Briefly, VRV11 demonstrated a satisfactory safety profile of all VRVg-2 dosages, VRVg-1 and Imovax Rabies vaccine, with a trend for less adverse reactions in the VRVg groups than in the Imovax Rabies vaccine group in terms of solicited injection site and solicited systemic reactions and less unsolicited adverse events (AEs). Immunology results showed a dose-response relationship between the Ag amount administered and the seroconversion rates at D14, as well as the Geometric Mean Titers (GMTs) at all time points. VRVg-2 High dose was, therefore, the preferred formulation/dosage, since it showed an immune response similar (in terms of seroconversion) or higher (in terms of GMTs) to that of Imovax Rabies vaccine. It should be noted, however, that neither VRVg-2 (3 dosages), nor VRVg-1, nor Imovax Rabies vaccine reached a 99.0% seroconversion rate at D14. A 99% seroconversion rate was reached at D28 by VRVg-2 high dose and Imovax Rabies (Per-Protocol Population). As reported with other licensed vaccines (18) (19) (20), these results might be explained by an interference of the immunoglobulins co-administered through the IM route at D0.

The next step in VRVg clinical development will consist of 2 Phase III non-inferiority (NI) studies which will compare the selected dose in VRV11 (VRVg-2 high dose[b]) with the 2 rabies vaccines marketed by Sanofi Pasteur (Verorab and Imovax Rabies vaccines); ie, this study (VRV12), is being carried out in the pediatric and adult populations using the PrEP regimen. Further, the PEP regimen with D0 HRIG administration is being assessed in the adult population (VRV13).

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[a] [redacted]

[b] For simplicity, VRVg-2 high dose (selected formulation/dose for this and future VRVg studies), will be referred henceforth to as VRVg-2 in this document.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

Vaccination is the most effective preventive measure against rabies. Verorab is WHO-prequalified and specifically recommended by WHO (21). Imovax Rabies is recommended by the Advisory Committee on Immunization Practices (ACIP) (22). Subjects receiving VRVg-2 are expected to be protected against infection in the event of contact with the virus.

Subjects receiving VRVg-2 are expected to be protected against infection in the event of contact with the virus.

Moreover, most of the subjects are expected to have reached RVNA titers ≥ 0.5 IU/mL after completion of the primary series with the 2- or 3-dose PrEP regimen and almost all are to reach this level after a single booster of the vaccine after being primed with those regimens (13) (20) (22) (23). All subjects in the study are healthy therefore each subjects' RVNA titer ≥ 0.5 IU/mL is unnecessary for their life. If a subject had RVNA titers < 0.5 IU/mL at all timepoints after the primary or booster series, the Investigator may decide based on clinical judgment to offer an additional single vaccination of a local licensed rabies vaccine (as chosen by the Investigator) and administer according to the local Summary of Product Characteristics (SmPC) or national guidelines, and if the subject / subject's legally acceptable representative (LAR) agree. Such vaccine is offered outside of the scope of the protocol (ie, no safety nor immunogenicity data will be collected after this vaccine injection), free of charge at the study site.

As a standard approach, subjects may require additional vaccination in the event of exposure to the virus, regardless of the vaccine received in the context of this study.

1.3.2 Potential Risks to Subjects

VRVg-2

[redacted]

Previously, the same order Ag quantity as VRVg-2 to be used in VRV12 has been evaluated in a clinical study during the development of a CPRV vaccine with satisfactory safety profile. [redacted]

Results from the precedent VRV11 study indicated that the safety profile of VRVg-2 (3 distinct doses tested) and VRVg-1 did not significantly differ from each other. Also, a trend for less solicited injection site and solicited systemic reactions, and unsolicited AEs were noted in the VRVg groups compared to the Imovax Rabies vaccine group.

Based on the above, the potential risks of administration of VRVg-2 can be assimilated to those previously observed for VRVg-1 during clinical studies where this formulation was included (pre-exposure regimens VRV01, VRV02, and VRV06, and post-exposure regimens VRV08, VRV04, and VRV11). [redacted] The following suspected adverse reactions and frequencies have been reported:

- Very common (≥ 10%): injection site pain, malaise, headache, and myalgia

- Common (≥ 1% and < 10%): Pyrexia, injection site erythema, injection site swelling
- Uncommon (≥ 0.1% and < 1%): lymphadenopathy, abdominal pain, diarrhea, dry mouth, nausea, asthenia, chills, fatigue, bronchitis, dizziness and somnolence, pharyngolaryngeal pain, pruritus, pruritus generalized, urticaria and flushing; injection site reactions such as injection site discomfort, hemorrhage, induration, hematoma/bruising, and pruritus
- Rare (≥ 0.01% and < 1%): vertigo, vomiting, injection site warmth, injection site anesthesia, immune hypersensitivity, musculoskeletal pain, skin reaction with rash and pruritus, rash (local and generalized)

To note that, the ARs reported only once in humans are not considered as expected ARs when the biological plausibility of the event being triggered by the vaccine is considered very low, and/or when they are symptoms of other listed events. However, if these ARs become common or there is new evidence of the biological plausibility of the event being triggered by the vaccine, the ARs will be considered as expected. Based on this rationale, the following rare cases of ARs (occurrence < 1/1000; only once) fall within this category:

- Oral herpes, sinusitis, abdominal rigidity (low biological plausibility)
- Oral hypoesthesia (symptoms of anxiety-related reactions or hypersensitivity), cold sweat, hyperhidrosis (symptoms of anxiety-related reactions or pyrexia), cough (symptoms of hypersensitivity) (low biological plausibility)

The VRVg-2 dose that will be used in this study has been administered to a limited number of adult subjects (N=80) in VRV11, following a post-exposure regimen (5 injections within 28 days) with HRIG administration on the 1st day of vaccination. The AEs and frequencies reported, matched those of VRVg-1 reported as “Very common”: injection site pain, feeling unwell, headache, and muscle pain, and “Common”: fever, injection site redness and/or swelling, with the addition of injection site paresthesia, injection site hematoma/bruising, injection site pruritus, and diarrhea, also as common events. However, due to the limited sample size (N=80), events were considered as “common” even after a single occurrence of the reaction.

[redacted] Thus, all suspected adverse reactions observed with Verorab (see below) are considered as possible risks for VRVg (including VRVg-1 and VRVg-2).

Thus, all identified and potential risks of Verorab are considered as potential risks for VRVg, even though they have not been observed with VRVg specifically to date.

Verorab Vaccine

The following risks have been identified with the use of Verorab vaccine as currently reported in the approved SmPC:

The following AEs are derivate from several clinical studies where Verorab vaccine has been used in both pre-exposure and post-exposure schedules in adults and children > 2 years old:

Adverse Reactions	**Adults** ≥ 18 years	**Pediatric Population** under 18 years old
	Frequency	**Frequency**
Blood and lymphatic system disorders		
Lymphadenopathy	Common	Common
Immune system disorders		
Allergic reactions (eg, rash, urticaria, pruritus)	Uncommon	Uncommon
Anaphylactic reactions and angioedema	Not known	Not known
Metabolism and nutrition disorders		
Decreased appetite	Uncommon	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness/vertigo	Uncommon	-
Irritability (in infants/young children)	-	Very common
Somnolence (in infants/young children)	-	Very common
Insomnia (in infants/young children)	-	Common
Ear and labyrinth disorders		
Sudden hearing loss, which may persist	Not known	Not known
Respiratory, thoracic and mediastinal disorders		
Dyspnea	Rare	-
Gastrointestinal disorders		
• Nausea	Uncommon	-
• Abdominal pain	Uncommon	Uncommon
• Diarrhea	Uncommon	-
• Vomiting	-	Uncommon
Musculoskeletal and connective tissue disorders		
• Myalgia	Very common	Very common
• Arthralgia	Uncommon	-
General disorders and administration site conditions		
Injection site pain	Very common	Very common
Injection site erythema	Common	Common
Injection site pruritus	Common	-
Injection site swelling	Common	Common

Adverse Reactions	**Adults** ≥ 18 years	**Pediatric Population** under 18 years old
	Frequency	**Frequency**
Injection site induration	Common	-
Malaise	Very common	Very common
Influenza-like syndrome	Common	
Fever	Common	Common
Asthenia	Uncommon	-
Chills	Uncommon	Uncommon
Inconsolable crying (in infants/young children)	-	Very common

Frequency display uses the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10 000 and < 1/1.000); very rare (< 1/10 000); not known (cannot be estimated from the available data)

Imovax Rabies Vaccine

The following risks have been identified with the use of Imovax Rabies as currently reported in the approved SmPC which is the Reference Safety Information for comparator in this study:

Undesirable Effects	Adults ≥ 18 years	Children and Adolescents up to 17 years old
	Frequency	Frequency
Clinical studies		
Blood and lymphatic system disorders		
Lymphadenopathy	Uncommon	-
Gastrointestinal disorders		
Nausea	Common	-
Abdominal pain	Uncommon	-
Diarrhea	Uncommon	-
Vomiting	Uncommon	-
General disorders and administration site conditions		
Injection site pain	Very common	Very common
Malaise	Very common	Very common
Injection site erythema	Common	Common
Injection site swelling/ edema/ induration	Common	Common
Fever	Common	Common
Injection site pruritus	Common	Uncommon
Injection site hematoma/ Ecchymosis	Common	Uncommon
Fatigue/ asthenia	Common	-
Shivering	Uncommon	-
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Uncommon	Uncommon
Paresthesia	Uncommon	-
Musculoskeletal and connective tissue disorders		
Myalgia	Very common	Very common
Arthralgia	Uncommon	Uncommon

Undesirable Effects	Adults ≥ 18 years	Children and Adolescents up to 17 years old
	Frequency	**Frequency**
Immune system disorders		
Allergic reaction with skin involvement or respiratory involvement	Uncommon	-
Angioedema	Rare	-
POST-MARKETING EXPERIENCE		
Nervous system disorders		
Encephalitis	Not known	Not known
Convulsions	Not known	Not known
Neuropathies	Not known	Not known
Immune system disorders		
Anaphylactic reactions	Not known	Not known
Serum sickness-like reactions	Not known	Not known

Frequency display uses the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10 000 and < 1/1.000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be excluded despite strict control procedures and extraction/purification processes. This also applies to unknown or emerging viruses and other pathogens.

1.3.3 Benefit and Risk Assessment During COVID-19 Pandemic

A potential benefit of the PrEP in an endemic country is the study subjects to be primed against rabies in the context of coronavirus disease 2019 (COVID-19) and potential situations of lockdown that may limit access to healthcare infrastructures.

Rabies vaccines would not cause immune suppression. Therefore, the risk of the subjects having COVID-19 will be similar to the general population. However, the risk of exposure to infected people cannot be completely excluded as the subjects may need to be exposed to public areas (eg, commute to the site and at the site).

Risk mitigation:

- The study staff will comply and abide by local regulations and measures to mitigate the spread of COVID-19 infection as prescribed by the local authorities. The study (Cohort 2) will not start until the local confinement measures linked to the COVID-19 pandemic are lifted by the local authorities.

The Sponsor will perform a risk assessment of the study and implement measures that prioritize subject safety (main criteria) and data validity in agreement with the Investigators, IRB/EC, Thai

FDA, Central Research Ethics Committee in Thailand and European Medicines Agency (EMA) applicable recommendations (24) (25). These assessments will be documented.

1.4 Rationale for the Study

Previous Phase II clinical study (VRV11) concluded that VRVg-2 compared favorably in terms of seroconversion rate and GMTs (all time points), to Imovax Rabies in a simulated PEP ESSEN Regimen with HRIG administration at D0, in the adult population.

Following up on these results, the objective of phase III VRV12 is to demonstrate the vaccine's adequate immunogenicity and non-inferior immune response versus current Rabies vaccines-Standard of Care (Verorab or Imovax Rabies vaccines) and to confirm its satisfying safety profile in the pediatric and adult population in a PrEP regimen. See Section 5.1.2 for further details.

2 Study Objectives

2.1 Primary Objective

To demonstrate that VRVg-2 is non-inferior to Verorab and Imovax Rabies vaccines in each age group (pediatric and adult populations) when administered as a 3-dose PrEP regimen, in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D42, ie, 14 days after the 3rd injection (for Primary Series Cohort 1).

The endpoint(s) for the primary objective(s) are presented in Section 9.1.2.

2.2 Secondary Objectives

Safety

- To describe the safety profile of VRVg-2 versus Verorab and Imovax Rabies vaccines, after each vaccine injection, in each age group (for Cohort 1 and Cohort 2).
- To describe the safety of a single booster dose of VRVg-2 among the subsets of adults following primary series of 3-dose primary series in addition to booster dose at M12 (for Booster Phase Cohort 1)
- To describe the safety of a single booster dose of VRVg-2 among the subsets of adults following one week 2-dose primary series in addition to booster dose between M24 up to M36 (for Immunogenicity Persistence and Booster Phase Cohort 2)

Immunogenicity

- To demonstrate that the observed proportion of subjects in the VRVg-2 group (overall) achieving an RVNA titer ≥ 0.5 IU/mL at D42 is at least 99%, with a lower limit of the 95% confidence interval (CI) of at least 97% (for Primary Series Cohort 1), only if the primary objective is achieved

- To demonstrate that VRVg-2 is non-inferior to Verorab and Imovax Rabies vaccines in each age group (pediatric and adult populations), in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D28, ie, 21 days after the 2nd injection (for pooled Primary Series Cohort 1 and Cohort 2), only if the 1st secondary immunogenicity objective is achieved
- To demonstrate that 2-dose VRVg-2 at D28 is non-inferior to 3-dose Imovax Rabies at D42 in each age group (pediatric and adult populations, respectively), in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL, only if the 2nd secondary immunogenicity objective is achieved
- To demonstrate that the observed proportion of subjects in the VRVg-2 group (overall) achieving an RVNA titer ≥ 0.5 IU/mL at D28 is at least 99%, with a lower limit of the 95% confidence interval (CI) of at least 97% (for pooled Primary Series Cohort 1 and Cohort 2), only if the 3rd secondary immunogenicity objective is achieved
- To demonstrate that 2-dose Imovax Rabies at D28 is non-inferior to 3-dose Imovax Rabies at D42 in the overall subjects (pooled pediatric and adult subjects) in Cohort 1, in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL, only if the 4th secondary immunogenicity objective is achieved
- To describe the immune response induced by VRVg-2 versus Verorab and Imovax Rabies vaccines at D28 (ie, 21 days after the 2nd injection), and at D42 (ie, 14 days after the 3rd injection) in all age groups (pediatric and adult populations)
- To describe the immune response induced by VRVg-2 at D14 after a single booster dose of VRVg-2 administered at M12 after the primary series with VRVg-2, Verorab, or Imovax Rabies vaccines in the subset of adult subjects (for Booster Phase Cohort 1)
- To describe persistence of the immune response at M6, M12, M18, and pre-booster between M24 up to M36 post-primary series vaccination in the subset of adults who are randomized to receive a booster and completed the 2-dose vaccination in the primary series (for Immunogenicity Persistence and Booster Phase Cohort 2)
- To describe the immune response induced by VRVg-2 at D14 after a single booster dose of VRVg-2 administered between M24 up to M36 after the primary series with VRVg-2, Verorab, or Imovax Rabies vaccines in the subset of adult subjects who are randomized to receive a booster and completed the 2-dose vaccination in the primary series (for Immunogenicity Persistence and Booster Phase Cohort 2)

The endpoint(s) for the secondary objective(s) are presented in Section 9.2.1.2 for safety and in Section 9.2.2.1 for immunogenicity.

3 Investigators and Study Organization

A total of 4 centers in Thailand have been taking part to this study. All the 4 sites participated to Primary Series Cohort 1 and 2 out of the 4 sites participated in Booster Phase Cohort 1. One out of the 4 sites will participate in Cohort 2 (Primary Series Cohort 2, and Immunogenicity Persistence and Booster Phase Cohort 2). Details of the study centers and the Investigators at each center, are provided in the "List of Investigators and Centers Involved in the Study" document.

Monitoring and Data Management activities will be conducted by a Contract Research Organization (CRO), under the responsibility of the Sponsor.

No independent data monitoring committee (IDMC) is planned to be set up for this study as the investigational vaccine was shown to be safe and well-tolerated in a previous clinical study conducted with VRVg-2 (ie, VRV11), and several other clinical studies conducted with the precedent formulation VRVg-1 (ie, VRV01 in adults, VRV08 in subjects from 10 years of age, VRV02 in adults, VRV04 in adults, VRV06 in children, VRV11 in adults). It is also to be noted, that VRVg constitutes an improvement of Verorab in terms of the purification process, and technological innovation in vaccine manufacturing and characterization. [redacted] Consequently, the wide post-marketing experience of Verorab vaccine and adequate safety profile is considered supportive of VRVg safety profile.

There will be an internal Safety Management Team (SMT) review performed on a regular basis as part of an ongoing safety review. This SMT led by the Global Safety Officer (GSO) includes core representatives from the Global Pharmacovigilance (GPV) Department and the Clinical Department. Reviews will be performed in a blinded manner.

4 Independent Ethics Committee/ Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the 1st subject, this protocol, the informed consent form (ICF), the assent form (AF), the subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and/ or receive favorable opinion from, the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and/ or the Sponsor are responsible for obtaining this approval and/ or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IEC/ IRB (the names and qualifications of the members attending and voting at the meetings).

According to the local requirements, the Investigator will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All Serious Adverse Events (SAEs) occurring during the study that are related to the product administered will be reported by the Investigator to the IEC / IRB, according to the IEC/ IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This will be a multi-center, observer-blind, controlled, randomized, Phase III study in 1700 healthy subjects (505 pediatric subjects [aged 1 year to < 18 years] and 1195 adults subjects [aged ≥18 years]). Pediatric subjects (505 subjects) and adult subjects (505 subjects) in Primary Series Cohort 1 received primary series of 3 vaccine injections of VRVg-2 (Group 1), Verorab vaccine (Group 2) or Imovax Rabies vaccine (Group 3), at day [D] 0, D7, and D28. Adult subjects in Primary Series Cohort 2 will be vaccinated according to a one week 2-dose schedule PrEP regimen of either VRVg-2 (Group 4), Verorab vaccine (Group 5) or Imovax Rabies vaccine (Group 6) at D0 and D7.

Primary series will be observer-blinded for both Cohort 1 (3-dose PrEP regimen) and Cohort 2 (one week 2-dose PrEP regimen). Booster Phase Cohort 1 will be conducted in a blinded manner (vaccine received in the primary series) with an adult subset from Cohort 1 (with booster dose 1 year after the 1st primary series vaccine injection). Evaluation of immunogenicity persistence after primary series and a booster phase will be conducted in an open-label manner with an adult subset from Cohort 2 (Immunogenicity Persistence and Booster Phase Cohort 2) (see Section 6.6 for details).

A total of 4 centers in Thailand have been taking part to this study. All the 4 sites participated to Primary Series Cohort 1 and 2 out of the 4 sites participated in Booster Phase Cohort 1. One out of the 4 sites will participate in Cohort 2 (Primary Series Cohort 2, and Immunogenicity Persistence and Booster Phase Cohort 2).

A subset of 170 adult subjects from Primary Series Cohort 1 received a booster dose of VRVg-2 after 1 year (M12) regardless the vaccine used in the primary series. A subset of 230 adult subjects from Primary Series Cohort 2 will be followed up for evaluation of immunogenicity persistence after primary series (including blood sample collection at M6, M12, M18, and pre-booster between M24 up to M36) and will receive a booster dose of VRVg-2 between M24 up to M36 regardless of the vaccine received in the primary series. The randomization and vaccination during the primary series and booster phase for Cohort 1 were conducted in a blinded manner (see Section 6.6). Similarly, for Cohort 2, randomization and vaccination from the enrollment up to V04 (28 days after the last vaccination in the primary series) will be conducted in a blinded manner, and then the study data will be locked and unblinded for the 1st statistical analysis as defined in Section 12.4.

The booster dose vaccination in the Immunogenicity Persistence and Booster Phase Cohort 2 will be conducted in an open-label manner with a new batch of VRVg-2; as a reminder, the laboratory analysts will remain blinded during the whole study.

All efforts will be made to ensure that the randomization ratio of the primary series will be maintained in the booster subsets.

For Primary Series Cohort 1, the duration of each subject's participation in the study will be approximately 7 months (28 day-vaccination period followed by a 6-month safety follow-up period). For the subset of adult subjects in Booster Phase Cohort 1 who received a single booster dose of VRVg-2, the duration will be approximately 18 months (1 booster dose 365 days after primary series followed by 6-month safety follow-up period).

For Primary Series Cohort 2, the duration of each subject's participation in the study will be approximately 7 months (one week vaccination period followed by a 6-month safety follow-up period). For the subset of adult subjects in Immunogenicity Persistence and Booster Phase Cohort 2 who will be followed up for evaluation of immunogenicity persistence after primary series (including blood sample collection at M6, M12, M18, and pre-booster between M24 up to M36) and who will receive a single booster dose of VRVg-2 (between M24 up to M36), the duration will be approximately 30 to 42 months.

Vaccination will be administered through the intramuscular (IM) route. Subjects will be randomized 3:1:1 (Groups 1, 2, and 3 in Cohort 1; and Groups 4, 5, and 6 in Cohort 2; respectively) with the resulting number of subjects assigned to each study group shown in Table 5.1.

Table 5.1: Distribution of Subjects According to Vaccination Group

			Vaccine	Number of adult subjects	Number of pediatric subjects
Primary Series	Cohort 1 3-dose PrEP regimen	Group 1	VRVg-2	303	303
		Group 2	Verorab	101	101
		Group 3	Imovax Rabies	101	101
	Cohort 2 one week 2-dose PrEP regimen	Group 4	VRVg-2	414	NA
		Group 5	Verorab	138	NA
		Group 6	Imovax Rabies	138	NA
Booster Phase	Cohort 1 (M12)	Group 1	VRVg-2 (primed with VRVg-2)	102	NA
		Group 2	VRVg-2 (primed with Verorab)	34	NA
		Group 3	VRVg-2 (primed with Imovax Rabies)	34	NA
	Cohort 2 (M24 up to M36)	Group 4	VRVg-2 (primed with VRVg-2)	138	NA
		Group 5	VRVg-2 (primed with Verorab)	46	NA
		Group 6	VRVg-2 (primed with Imovax Rabies)	46	NA

NA: Not applicable

Pediatric subjects and adult subjects in Primary Series Cohort 1 provided 3 blood samples: at D0 (prior to the 1st vaccine injection), at D28 (21 days after the 2nd vaccine injection), and D42 (14 days after the 3rd vaccine injection). Adult subjects in Primary Series Cohort 2 will provide

2 blood samples: at D0 (prior to the 1st vaccine injection) and D28 (21 days after the 2nd dose vaccine injection).

The adult subset of subjects who were part of the Booster Phase Cohort 1 had 2 additional blood samples: at M12 (prior to the booster vaccine injection), and M12 +D14 (14 days after booster vaccine injection).
The adult subset of subjects who will be part of the Immunogenicity Persistence and Booster Phase Cohort 2 will have 5 additional blood samples: at M6, M12, M18, pre-booster between M24 up to M36, and post-booster between M24 up to M36+D14 (14 days after booster vaccine injection).

Safety will be assessed in all subjects during the vaccination period and up to 28 days after vaccinations, in terms of occurrence of AEs, SAEs and Adverse Events of Special Interest (AESIs). In addition, SAEs and AESIs will be collected up to 6 months after the last vaccination in all subjects. The duration of the safety follow-up is planned to be until 6 months after the last dose of vaccine in the primary series and up to approximately 18 or approximately 30 to 42 months for the subsets of adult subjects who will receive the single booster dose (Cohorts 1 and 2, respectively). For adult subjects in Immunogenicity Persistence and Booster Phase Cohort 2, between the 6-month follow-up visit after primary series (V05) and booster dose visit (V08), AESIs will not be collected, only fatal SAEs and related SAEs will be collected.

5.1.2 Justification of the Study Design

VRV12 will use the PrEP regimen. In detail, the performance of VRVg-2 will be demonstrated through the NI to both Verorab vaccine and Imovax Rabies vaccine, in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL[a] at D42 (ie, 14 days after the 3rd vaccine injection [primary objective]).

In VRV12, safety and immunogenicity data will be generated in the pediatric population (aged 1 year to < 18 years) and in adults (aged ≥ 18 years). The age range and the design have been approved by EMA, Pediatric Committee (PDCO), Center for Biologics Evaluation and Research (CBER) (including the Pediatric Study Plan)[b]. The inclusion of subjects aged < 2 years was a PDCO request since this group is also at risk of rabies. For example, in a recent study conducted in the Philippines (27), 2.8% (17/600) were bitten subjects aged between 11 months and 2 years. It has been reported around 1% of children aged < 2 years had animal attacks in Thailand (28). Moreover, it is expected an adequate safety and immunogenicity profile in this age based on the results observed with VRVg-1 in children aged > 2 years and data obtained with Verorab in children aged ≤ 2 years in PrEP (28) (29) (30) and PEP (31) (32) (33).

[a] An RVNA titer ≥ 0.5 IU/mL is the worldwide recognized surrogate marker of protection for the rabies vaccines.

[b] [redacted]

The 3-dose schedule of PrEP immunization in Primary Series Cohort 1 is based on ACIP 2008 recommendations on PrEP (ie, 3 IM dose schedule on D0, D7, and D21 or D28) (34). It should be noted that the latest guidance from the WHO from April 2018 recommends a PrEP regimen consisting of 2 IM doses instead of 3 (D0 and D7) (13).

Both guidelines were covered by the original study design. Recently, the ACIP guidelines adopted the same one week 2-dose PrEP regimen in February and June 2021 meetings (35), hence the amendment of the protocol to collect more data and information to substantiate the safety and immunogenicity of the one week 2-dose regimen for PrEP rabies immunization. This recommendation has been adopted by the director of Centers for Disease Control and Prevention and will become official after it is published in the Morbidity and Mortality Weekly Report.

The study design of VRV12 will enable the evaluation of the NI against the reference vaccines after 3 doses (primary objective) and after 2 doses (secondary objectives), to cover the recommended PrEP regimens by both guidelines. Further, the VRV12 study intends to document a single booster dose after the 3-dose and one week 2-dose PrEP regimens for people whose occupation puts them at continual or frequent risk of exposure according to the WHO guidelines (34) (35) (36) and to accommodate CBER recommendations [redacted]. Previous studies conducted with VRVg-1 showed an adequate immune response at D14 after a single dose of booster in adults, which also supports the current design of the study. The inclusion of children for the booster subset was not justified due to ethical reasons and due to the available evidence of similar immune responses to rabies vaccines in children and adults. Regarding the time of the booster, the US ACIP 2008 guidelines recommended that an IM booster dose of vaccine should be administered if the serum titer falls to maintain a serum titer corresponding to a value of at least complete neutralization at a 1:5 serum dilution by the RFFIT, every 6 months for the continuous risk category and up to 2 years for the frequent risk category group. Therefore, the time of the single booster and persistence assessment was set for 1 year after the 3-dose PrEP regimen. The new US ACIP 2021 guidelines recommended the time of the booster according to 5 different risk categories. The widest time window is recommended for the population who have elevated risk of recognized exposures that is sustained (eg, animal care professionals, veterinary students, etc.), who will have a serological test once between 1 and 3 years or a booster dose no sooner than 21 days and no later than year 3. Therefore, a single booster between 2 up to 3 years will be administered after 2-dose primary series in this Amendment 3 of the VRV12 protocol, a pre-booster blood sample will be taken at M24 up to M36, and a post-booster blood sample will be taken at 14 days after M24 up to M36 to evaluate immunogenicity of booster in Cohort 2. [redacted] two major additional objectives were added ie, the evaluation of superiority in VRVg-2 group after 2 doses in the overall population from VRVg-2 group and the assessment of immunogenicity persistence at M6, M12, and M18 after the 2-dose regimen in the primary series of Cohort 2.

Moreover, in an effort to maximize the value of the data generated with VRV12 actual sample size, 2 new secondary objectives were added: to demonstrate the NI of a 2-dose VRVg-2 at D28 versus 3-dose Imovax Rabies at D42 in each age group; and to demonstrate the NI of a 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42 in each age group, both with a NI margin of -10% for each of these 2 new secondary objectives.

The reference vaccines (Verorab and Imovax Rabies vaccines) are both current standards of care employed globally. Their inclusion as controls/comparators aims to support VRVg licensure

worldwide. [redacted]

The selection of Thailand as the country for VRV12 is driven by the enzootic character of rabies in Thailand, which enables the conduct of rabies studies in the pediatric population, and also because both Verorab and Imovax Rabies are licensed in Thailand and can be used as controls[a].

An early Safety Data Review is not judged necessary in this study. Data from the initial VRVg formulation (VRVg-1) in the adult population (VRV01, VRV08, VRV02, and VRV04) and pediatric population (VRV08 and VRV06) have consistently indicated a favorable safety profile comparable to the Verorab and Imovax Rabies vaccines. In addition, the safety profile of VRVg-2 (all dosages) has been shown to be comparable to that of VRVg-1 in the adult population (VRV11). No safety concerns are therefore expected with VRVg-2. An internal ongoing safety review will be performed by the SMT, which includes safety signal detection.

5.1.3 Study Plan

The study plan is summarized in the Table of Study Procedures

Recruitment and Information of Subjects:

Before inclusion in the study, the Investigator will orally inform potentially eligible subjects and/or their parents about the study. They will be given an oral description of the study design, presenting the general benefits and risks related to the study. They will be informed that they may return and receive further information and sign the full informed consent during the recruitment period. The process of subject recruitment and any oral or written information that will be provided to the subjects must be documented. This will be available in the Investigator's file and the Trial Master File (TMF).

It should be noted that subjects who may have been pre-screened may not necessarily be included in the study if the required number of subjects have already been recruited.

Informed consent and assent, if applicable will be obtained before inclusion of the subject in the study (see Section 5.2).

Study Description:

After having signed the ICF/AF, eligible subjects will be included in the study, and will provide the initial blood sample.

Eligible pediatric subjects and adult subjects in Primary Series Cohort 1 received a total of 3 injections (1 injection at D0, D07, and D28) and adult subjects in Primary Series Cohort 2 will receive a total of 2 injections in the primary series (at D0 and D7).

A subset of 170 adult subjects (Booster Phase Cohort 1) received a single booster injection of VRVg-2 at M12 after the 1st vaccination of the primary series, and a subset of 230 adult subjects (Immunogenicity Persistence and Booster Phase Cohort 2) will receive a booster dose of VRVg-2 between 24 up 36 months (M24 up to M36) regardless of the vaccine used in the primary series.

[a] [redacted]

All subjects will be observed for safety for 30 minutes after each vaccination, and any AE/reaction occurring between each vaccination and up to 28 days after the last vaccination will be recorded by the subjects in a diary card (DC). The Investigator or delegate will transcribe the DC information into the electronic case report form (CRF) after interviewing the subject. In addition, all SAEs and AESIs will be recorded throughout the study, ie, up to 6 months after the last injection of the primary series and post-booster dose.
Immunogenicity will be assessed in pediatric subjects and adult subjects in Primary Series Cohort 1 included in the study, before the 1st vaccine injection (VAC1) (D0), before VAC3 (D28), and 14 days after VAC3 (D42), and at D0 (prior to the 1st vaccine injection) and D28 (21 days after the one week 2-dose vaccine injection) in adult subjects in Primary Series Cohort 2.

For the adult subset in Booster Phase Cohort 1, the immunogenicity of the booster dose will be assessed before VAC4 (M12) and 14 days after VAC4 (M12 +D14). For the adult subset in Immunogenicity Persistence and Booster Phase Cohort 2, the persistence of immune response after primary series will be assessed at M6, M12, M18, and pre-booster between M24 up to M36, and the immunogenicity of the booster dose will be assessed before booster (M24 up to M36), and 14 days after booster (M24 up to M36+D14).

Blood Sampling:

Pediatric subjects and adult subjects in Primary Series Cohort 1 provided a total of 3 blood samples[a] and adult subjects in Primary Series Cohort 2 will provide 2 blood samples to assess the immune response induced by the rabies vaccines. The subsets of adult subjects from Booster Phase Cohort 1 and Immunogenicity Persistence and Booster Phase Cohort 2 will provide 2 and 5 more blood samples, respectively.

Table 5.2 and Table 5.3 below outline the schedule of blood sampling and vaccine injection.

[a] Blood sample volume drawn from subjects 1 year to <2 years will be 3 mL, for subjects ≥2 years to <18 years will be 5 mL, and for subjects ≥18 years will be 6 mL.

Table 5.2: Blood sampling and vaccination schedule for the 3-dose PrEP regimen + M12 booster

	Primary series **Pediatrics and Adults (Cohort 1)**						**Booster phase** **Adult Subset from Cohort 1**			
	V01	**V02**	**V03**	**V04**	**V05**	**Phone call**	**V06**	**V07**	**V08**	**Phone call**
Visit interval	VAC1	VAC2= VAC1+7D	VAC3= VAC1+ 28D	VAC3+ 14D	VAC3+ 28D	VAC3+ 6M	VAC4= VAC1+ 12M	VAC4+ 14D	VAC4+ 28D	VAC4+6M
Blood sampling*	BL01		BL02	BL03			BL04	BL05		
Vaccine Injection	x	x	x				x			

*Blood sample volume drawn from subjects aged 1 year to < 2 years will be 3 mL, for subjects ≥ 2 years to < 18 years will be 5 mL, and for subjects ≥ 18 years will be 6 mL

Table 5.3: Blood sampling and vaccination schedule for the one week 2-dose PrEP regimen + immunogenicity persistence at M6, M12, M18, and pre-booster M24 up to M36 + M24 up to M36 booster

	Primary series Adults (Cohort 2)				Immunogenicity Persistence and Booster phase Adult Subset from Cohort 2						
	V01	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**Phone call**
Visit interval	VAC1	VAC2= VAC1+7D	VAC1+ 28D	VAC2+ 28D	VAC2+ 6M	VAC2+ 12M	VAC2+ 18M	VAC3= VAC1+ 24M up to 36M	VAC3+ 14D	VAC3+ 28D	VAC3+ 6M
Blood sampling*	BL01		BL02		BL03	BL04	BL05	BL06	BL07		
Vaccine Injection	x	x						x			

*Blood sample volume drawn from subjects ≥ 18 years will be 6 mL

Collection of Safety Data:

At each visit, study staff will either check and/or collect the safety DCs provided to all subjects to report safety data. A Memory Aid (MA) will be provided to the subjects at V05 (all pediatric subjects and adult subjects in Primary Series Cohort 1), at V08 (adult subjects in Booster Phase Cohort 1), at V04 (adult subjects in Primary Series Cohort 2), and at V10 (adult subjects in Immunogenicity Persistence and Booster Phase Cohort 2) to collect SAEs and AESIs up to the end of the study.

Pediatric subjects and adult subjects in Primary Series Cohort 1 will record safety information in a MA from D56 (28 days following the 3rd injection) until M7 (ie, end of the 6-month follow-up after primary series) for the subjects not involved in the booster phase, and until M12, and then up to the end of the study (M18) for the adult subset involved in the booster phase (Booster Phase Cohort 1).

Adult subjects in Primary Series Cohort 2 will record safety information in a MA from D35 (28 days following the 2nd injection) until M6 (ie, end of the 6-month follow-up after primary series). Adult subjects in Immunogenicity Persistence and Booster Phase Cohort 2 will record safety information:

- In a safety DC from D35 (28 days following the 2nd injection) up to the booster vaccine injection at M24-M36.

- In a MA from 28 days after the booster dose up to the end of the study (ie, 6 month-follow-up post-booster vaccine injection)

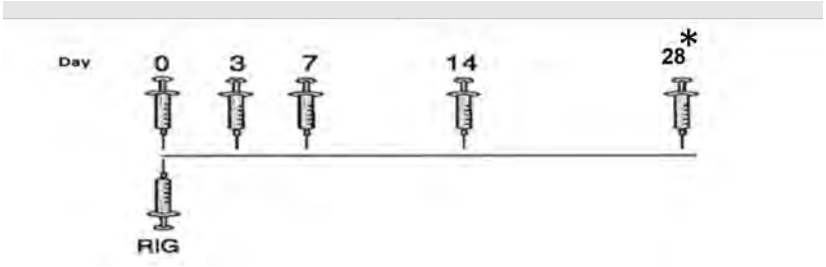
Management of Subjects in Case of Rabies Exposure

The management of subjects in case of rabies exposure will follow the local practice. PEP is recommended for people with WHO category II or III exposures. For category III, PEP indicated with rabies vaccine and rabies immunoglobulin (RIG) (37).

Category	Contact type	Procedure
I (Contact without infection)	Touching or feeding animals, licks on intact skin	Clean the contact area No vaccination require
II (Contact with possibility of infection)	Category II Nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin	Washing, flushing the wound Rabies vaccine
III (Contact with high possibility of infection)	Single or multiple transdermal bites or scratches; contamination of mucous membrane with saliva from licks Having wound, contact animal secretions, carcass of animal body, animal brain. Pealing animal skin, dissect animal body. Take any raw meat or product made from rabies infected animal	Washing, flushing the wound Rabies vaccine plus RIG as soon as possible

- Vaccination can be given in 2 different routes:

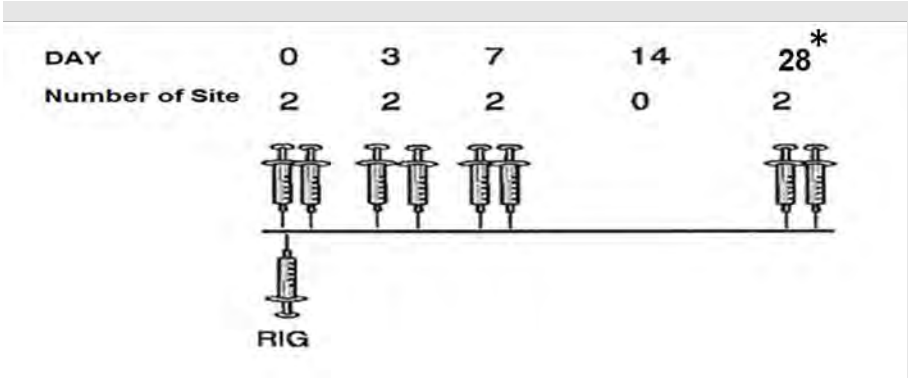
  1. IM route



*According to Thai National Recommendation, D30 is also acceptable

According to 2018 WHO guidelines, one site IM dose can be given at D0, D3, D7, and between D14–D28.

  2. Intradermal (ID)



*According to Thai National Recommendation, D30 is also acceptable

As a Sponsor procedure, subjects will not receive any further investigational/control product, but can stay in the study for safety collection and blood sampling

5.1.4 Visit Procedures

5.1.4.1 For Cohort 1

Visit (V) 01 (D0): Inclusion, Randomization, Blood Sample, and Vaccination

1) After signature of the ICF and/ or AF, as applicable, inclusion and exclusion criteria will be checked.
2) Collect demographic data.
3) Urine pregnancy test, if woman of childbearing potential.
4) Conduct a physical examination, including temperature, weight and height to determine the Body Mass Index.
5) Obtain past and current medical history.
6) For woman of childbearing potential, check the use of effective methods of contraception (example of effective methods of contraception include hormonal implants, intrauterine devices [hormonal or non-hormonal], adequate compliance with oral contraceptive pills, hormonal patch and adequate condom use with spermicide [sponge, contraceptive foam or cream]).
7) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
8) Contact the Interactive Response Technology (IRT) system for randomization; allocation of subject number, dose number/product assignment, and booster phase involvement.
9) A blood sample will be collected (3 mL for subject 1 year to < 2 years, 5 mL for subjects ≥ 2 to < 18 years, and 6 mL for subjects ≥ 18 years).
10) Review warnings and precautions to vaccination.

11) Inject the appropriate study vaccine (VAC1) on the opposite side to that of the blood sampling.
12) Keep the subject under observation for 30 minutes and record any adverse reaction in the source document.
13) The 1st diary card (DC1), the thermometer and the ruler will be provided to the subject or subjects' parents/ LAR and explanation on how to use them will be given by the blinded staff member.
14) Remind the subject or subjects' parent/ LAR to bring back the DC when they return for V02 at a specified date and time.
15) Subject or subject's parent/ LAR will be reminded to notify the site in case of SAE and AESI.
16) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
17) The source documents and relevant CRF pages for this visit will be completed.

V02 (7 [+1] days after VAC1): Collection of Safety Information and Vaccination

1) DC1 will be collected and checked by the blinded Investigator/staff, different from the person performing the vaccination.
2) Urine pregnancy test, if woman of childbearing potential.
3) Conduct a physical examination, including temperature.
4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
5) Check contraindication for subsequent vaccinations (see Section 5.2.7).
6) Contact the IRT system for dose number/product assignment (see Section 6.6).
7) Subjects will receive the 2nd injection (VAC2) from the unblinded staff member in the opposite arm as compared to VAC1 and will stay at the center for the 30-minute observation period following vaccination. Safety assessment will be made by the blinded Investigator, different from the person performing the vaccination.
8) DC2 will be provided to the subject or the subjects' parent/ LAR.
9) The source documents and the relevant CRF pages for this visit will be completed.
10) Remind the subject or subjects' parent/ LAR to bring back the DC when they return for V03 at a specified date and time.
11) Remind the subject or subjects' parent/ LAR to notify the site in case of a SAE and AESI.
12) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
13) Complete the relevant source document information and CRF pages for this visit.

V03 (28 [±3] days after VAC1) for Pediatrics and Adults in Primary Series Cohort 1: Collection of Safety Information, Blood Sample, and Vaccination

1) DC2 will be collected and checked by the blinded Investigator/staff, different from the person performing vaccination.
2) Urine pregnancy test, if woman of childbearing potential for subjects in Primary Series Cohort 1.
3) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
4) Conduct a physical examination, including temperature.
5) Check contraindication for subsequent vaccinations (see Section 5.2.7) for subjects in Primary Series Cohort 1.
6) Contact the IRT system for dose number/product assignment (see Section 6.6) for subjects in Primary Series Cohort 1.
7) A blood sample will be collected (3 mL for subject 1 year to < 2 years, 5 mL for subjects ≥ 2 to < 18 years, and 6 mL for subjects ≥ 18 years).
8) Only subjects from pediatric subjects and adult subjects in Primary Series Cohort 1 will receive the 3rd injection (VAC3) from the unblinded staff member in the opposite arm as compared to VAC2 and will stay at the center for the 30-minute observation period following vaccination. Safety assessment will be made by the blinded Investigator, different from the person performing the vaccination.
9) DC3 will be provided only to pediatric subjects and adult subjects in Primary Series Cohort 1 or the subjects' parent/ LAR.
10) The source documents and the relevant CRF pages for this visit will be completed.
11) Remind the subject or subjects' parent/ LAR to bring back the DC when they return for V04 at a specified date and time.
12) Remind the subject or subjects' parent/ LAR to notify the site in case of a SAE and AESI.
13) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
14) Complete the relevant source document information and CRF pages for this visit.

V04 (42 [±3] days after VAC1) for Pediatrics and Adults in Primary Series Cohort 1: Collection of Safety Information and Blood Sample

1) DC3 will be checked by the blinded Investigator/ staff, different from the person performing the vaccination and will be given back to subjects or subjects' parent/ LAR.
2) Conduct a physical examination, including temperature.
3) A blood sample will be collected only (3 mL for subject 1 year to < 2 years, 5 mL for subjects ≥ 2 to < 18 years, and 6 mL for subjects ≥ 18 years).

4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
5) Subject or subject's parent/ LAR will be reminded to notify the site in case of SAE and AESI.
6) The source documents and relevant CRF pages for this visit will be completed.

V05 (56 [±3] days after VAC1) for Pediatrics and Adult Subjects in Primary Series Cohort 1: Collection of Safety Information

1) DC3 will be collected and checked by the blinded Investigator/staff, different from the person performing the vaccination.
2) Conduct a physical examination.
3) Give the MA1 to record any SAEs or AESIs that may occur during the safety follow-up.
4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
5) Subject or subject's parent/LAR will be reminded to notify the site in case of SAE and AESI.
6) The source documents and relevant CRF pages for this visit will be completed.
7) Complete the study termination record.

6-month Safety Follow-up Phone Call (PC) (M7+14D) after the Primary Series

Subject or subject's parent/ LAR will be contacted by phone by the blinded personnel 6 months after the 3rd vaccination. Information recorded in MA1 will be checked.

Further details on the visit procedures can be found in the Operating Guidelines.

V06 (12 months [+14 days] after VAC1): Collection of Safety Information, Blood Sample, and Booster Injection - for Adult Subjects in Booster Phase Cohort 1

1) MA1 will be collected and checked by the blinded Investigator/staff, different from the person performing vaccination.
2) Urine pregnancy test, if woman of childbearing potential.
3) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
4) A blood sample will be collected (6 mL).
5) Conduct a physical examination, including temperature.
6) Obtain past and significant current medical history. Check contraindication for subsequent vaccinations (see Section 5.2.7).
7) Subjects will receive the booster injection (VAC4) from the unblinded staff member in the opposite arm as compared to VAC3 and will stay at the center for the 30-minute observation period following vaccination. Safety assessment will be made by the blinded Investigator, different from the person performing the vaccination.
8) DC4 will be provided to the subject.

9) The source documents and the relevant CRF pages for this visit will be completed.
10) Remind the subject or to bring back the DC when they return for V07 at a specified date and time.
11) Remind the subject to notify the site in case of a SAE and AESI.
12) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
13) Complete the relevant source document information and CRF pages for this visit.

V07 (12 months + 14 [+1] days after VAC1): Collection of Safety Information and Blood Sample - for Adult Subjects in Booster Phase Cohort 1

1) DC4 will be checked by the blinded Investigator/staff, different from the person performing the vaccination.
2) A blood sample will be collected (6 mL).
3) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
4) Subject will be reminded to notify the site in case of SAE and AESI.
5) The source documents and relevant CRF pages for this visit will be completed.

V08 (12 months + 28 [±3] days after VAC1): Collection of Safety Information - for Adult Subjects in Booster Phase Cohort 1

1) DC4 will be collected and checked by the blinded Investigator/staff, different from the person performing the vaccination.
2) Conduct a physical examination.
3) Give the subject the MA2 to record any SAEs or AESIs that may occur during the safety follow-up.
4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
5) Subject will be reminded to notify the site in case of SAE and AESI.
6) The source documents and relevant CRF pages for this visit will be completed.
7) Complete the study termination record.

6-month Safety Follow-up PC After Booster Injection (M18+14D): for Adult Subjects in Booster Phase Cohort 1

1) Subject will be contacted by phone by the blinded personnel 6 months after the booster vaccination. Information recorded in MA2 will be checked.

Further details on the visit procedures can be found in the Operating Guidelines.

5.1.4.2 For Cohort 2

Visit (V) 01 (D0): Inclusion, Randomization, Blood Sample, and Vaccination

1) After signature of the ICF, inclusion and exclusion criteria will be checked.
2) Collect demographic data.
3) Urine pregnancy test, if woman of childbearing potential.
4) Conduct a physical examination, including temperature, weight and height to determine the Body Mass Index.
5) Obtain past and current medical history.
6) For woman of childbearing potential, check the use of effective methods of contraception (example of effective methods of contraception include hormonal implants, intrauterine devices [hormonal or non-hormonal], adequate compliance with oral contraceptive pills, hormonal patch and adequate condom use with spermicide [sponge, contraceptive foam or cream]).
7) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
8) Contact the IRT system for randomization; allocation of subject number, dose number/product assignment, and booster phase involvement.
9) A blood sample will be collected (6 mL).
10) Review warnings and precautions to vaccination.
11) Inject the appropriate study vaccine (VAC1) on the opposite side to that of the blood sampling.
12) Keep the subject under observation for 30 minutes and record any adverse reaction in the source document.
13) The 1st diary card (DC1), the thermometer and the ruler will be provided to the subject and explanation on how to use them will be given by the blinded staff member.
14) Remind the subject to bring back the DC when they return for V02 at a specified date and time.
15) Subject will be reminded to notify the site in case of SAE and AESI.
16) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
17) The source documents and relevant CRF pages for this visit will be completed.

V02 (7 [+1] days after VAC1): Collection of Safety Information and Vaccination

1) DC1 will be collected and checked by the blinded Investigator/staff, different from the person performing the vaccination.
2) Urine pregnancy test, if woman of childbearing potential.
3) Conduct a physical examination, including temperature.
4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
5) Check contraindication for subsequent vaccinations (see Section 5.2.7).
6) Contact the IRT system for dose number/product assignment (see Section 6.6).
7) Subjects will receive the 2nd injection (VAC2) from the unblinded staff member in the opposite arm as compared to VAC1 and will stay at the center for the 30-minute observation period following vaccination. Safety assessment will be made by the blinded Investigator, different from the person performing the vaccination.
8) DC2 will be provided to the subject.
9) The source documents and the relevant CRF pages for this visit will be completed.
10) Remind the subject to bring back the DC2 when they return for V03 at a specified date and time.
11) Remind the subject to notify the site in case of a SAE and AESI.
12) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
13) Complete the relevant source document information and CRF pages for this visit.

V03 (28 [+3] days after VAC1): Collection of Safety Information and Blood Sample

1) DC2 will be checked by the blinded Investigator/staff, different from the person performing vaccination.
2) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
3) Conduct a physical examination, including temperature.
4) A blood sample will be collected (6 mL).
5) Remind the subject to notify the site in case of a SAE and AESI.
6) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
7) Complete the relevant source document information and CRF pages for this visit.

V04 (35 [±3] days after VAC1): Collection of Safety Information

1) DC2 will be collected and checked by the blinded Investigator/ staff, different from the person performing the vaccination.
2) Conduct a physical examination, including temperature.
3) Give the MA (to adult subjects who will only participate in Primary Series Cohort 2) or DC SAE (to adult subjects who will participate to the Immunogenicity Persistence and Booster Phase Cohort 2) to record SAEs or AESIs that may occur during the safety follow-up.
4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
5) Subject will be reminded to notify the site in case of SAE and AESI.
6) Complete the study termination record for adult subjects who will only take part to the Primary Series Cohort 2
7) The source documents and relevant CRF pages for this visit will be completed.

6-month Safety Follow-up PC (M6+14D) After the Primary Series – for Adult Subjects in Primary Series Cohort 2

1) Subject will be contacted by phone by the blinded personnel 6 months after the 2nd vaccination. Information recorded in MA1 will be checked.
2) Further details on the visit procedures can be found in the Operating Guidelines.

V05 (6 months +14D after VAC2): 6-month Safety Follow-up after the Primary Series and Blood Sample - for Adult Subjects in Immunogenicity Persistence and Booster Phase Cohort 2

1) DC SAE will be checked by the Investigator/staff, different from the person performing vaccination.
2) A blood sample will be collected (6 mL).
3) Collect reportable categories 2 and 3 concomitant medications in the CRF (see Section 6.9).
4) Subject will be reminded to notify the site in case of SAE and AESI.
5) The source documents and relevant CRF pages for this visit will be completed.

V06 (12 months +14 days after VAC2): Collection of Safety Information and Blood Sample - for Adult Subjects in Immunogenicity Persistence and Booster Phase Cohort 2

1) DC SAE will be checked by the Investigator/staff, different from the person performing vaccination.
2) A blood sample will be collected (6 mL).

3) Collect reportable categories 2 and 3 concomitant medications in the CRF (see Section 6.9).
4) Subject will be reminded to notify the site in case of SAE (to Investigator: note that only fatal SAEs and related SAEs need to be reported at this visit).
5) The source documents and relevant CRF pages for this visit will be completed.

V07 (18 months +14 days after VAC2): Collection of Safety Information and Blood Sample - for Adult Subjects in Immunogenicity Persistence and Booster Phase Cohort 2

1) DC SAE will be checked by the Investigator/staff, different from the person performing vaccination.
2) A blood sample will be collected (6 mL).
3) Collect reportable categories 2 and 3 concomitant medications in the CRF (see Section 6.9).
4) Subject will be reminded to notify the site in case of SAE (to Investigator: note that only fatal SAEs and related SAEs need to be reported at this visit).
5) The source documents and relevant CRF pages for this visit will be completed.

V08 (between 24 and up to 36 months +14 days after VAC1): Collection of Safety Information, Blood Sample, and Booster Injection - for Adult Subjects in Immunogenicity Persistence and Booster Phase Cohort 2

1) DC SAE will be checked and collected by the Investigator/staff, different from the person performing vaccination.
2) Urine pregnancy test, if woman of childbearing potential.
3) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
4) A blood sample will be collected (6 mL).
5) Conduct a physical examination, including temperature.
6) Obtain past and significant current medical history. Check contraindication for subsequent vaccinations (see Section 5.2.7).
7) Subjects will receive the booster injection (VAC3) from the unblinded staff member in the opposite arm as compared to VAC2 and will stay at the center for the 30-minute observation period following vaccination.
8) DC3 will be provided to the subject.
9) Subject will be reminded to notify the site in case of SAE and AESI.
10) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy
11) The source documents and the relevant CRF pages for this visit will be completed.
12) Remind the subject to bring back the DC3 when they return for V09 at a specified date and time.

V09 ([between 24 months and up to 36 months+14D] +14 [+1] days after VAC1): Collection of Safety Information and Blood Sample - for Adult Subjects in Immunogenicity Persistence and Booster Phase Cohort 2

1) DC3 will be checked by the Investigator/staff.
2) A blood sample will be collected (6 mL).
3) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
4) Subject will be reminded to notify the site in case of SAE and AESI.
5) The source documents and relevant CRF pages for this visit will be completed.

V10 ([between 24 months and up to 36 months+14D] +28 [±3] days after VAC1): Collection of Safety Information and Blood Sample - for Adult Subjects in Immunogenicity Persistence and Booster Phase Cohort 2

1) DC3 will be collected and checked by the Investigator/staff.
2) Conduct a physical examination.
3) Give the subject the MA to record any SAEs or AESIs that may occur during the safety follow-up.
4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
5) Subject will be reminded to notify the site in case of SAE or AESI.
6) The source documents and relevant CRF pages for this visit will be completed.
7) Complete the study termination record.

6-month Safety Follow-up PC after the Booster Injection (M30 up to M42 +14D): for Adult Subjects in Immunogenicity Persistence and Booster Phase Cohort 2

Subject will be contacted by phone by the Investigator/staff 6 months after the booster vaccination. Information recorded in MA will be checked.

Further details on the visit procedures can be found in the Operating Guidelines.

5.1.4.3 Follow-up for Cohorts 1 and 2

Follow-up of Subjects With RVNA Titer ≤ 0.5 IU/mL After Completion of the 2- or 3-dose PrEP Regimen With Rabies Vaccine (and Booster Dose for Adult Subset):

As stated in Section 1.3.1, if a subject had RVNA titers < 0.5 IU/mL at all timepoints after the primary or booster series, the Investigator may decide based on clinical judgment to offer an additional single vaccination of a local licensed rabies vaccine (as chosen by the Investigator) and administer according to the local SmPC / Product Information (PI) or national guidelines, and if the subject / subject's LAR agree. Adult subjects randomized in the Immunogenicity Persistence

and Booster Phase Cohort 2 need to complete all the visits in this phase before being offered to receive benefit vaccine if the Investigator deemed necessary.

Follow-up of Subjects With Related AEs or With AEs That Led to Study/Vaccination Discontinuation:

Unless a subject or subject's parent/LAR refuses further contact, each subject who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the subject's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the product administered
- The AE caused the discontinuation of the subject from the study or vaccination

5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ as, for example, the study will not start until all the appropriate regulatory and ethical approvals have been obtained.

FVFS (first visit, first subject) to LCLS (last contact, last subject): October 2019 – September 2025

Inclusion period – FVFS to FVLS (first visit, last subject): October 2019 – February 2023

Primary vaccination period: October 2019 – February 2023

Booster vaccination period: October 2020 – March 2025

End of study Booster Phase Cohort 1: August 2021

End of study Immunogenicity Persistence and Booster Phase Cohort 2: September 2025

Date of Final Clinical Study Report: March 2026

5.1.6 End of study definition

A subject is considered to have completed the study if the subject has completed the last contact planned in the Table of Study Procedures.

The end of the study is defined as the date that the last results have been released for samples collected at Visit 9, Cohort 2, related to primary and secondary endpoints. The end of the study must be achieved no later than 9 months after the last contact of the last subject in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Before the start of the study, the Investigator or delegate will contact an appropriate pool of potential subjects or parent of potential subjects and invite them to participate in the study. The site will ensure that any advertisements used to recruit subjects (letters, pamphlets, posters) are submitted to the Sponsor prior to submission to the IEC/ IRB for approval.

Recruitment procedures and materials will be submitted for IEC/ IRB approval or favorable opinion before implementation.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject and/or an appropriate and LAR voluntarily confirms his or her willingness to participate or let his/her child participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF and /or AF. A separate AF will be provided for subjects aged 13 to less than 18 years or for subjects aged 7 to 12 years. The AF is in addition to, not in place of, an ICF that is signed by the parent/ LAR.

In accordance with GCP, prior to signing and dating the consent form, the subject and/or parent/LAR must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate and must have sufficient time and opportunity to ask any questions.

The actual ICF and AFs used at each center may differ, depending on local regulations and IEC/ IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC/ IRB prior to the form being used.

If new information becomes available that may be relevant to the subject's or LAR's willingness to continue participation in the study, this will be communicated to him/ her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF and via a revised AF or an addendum to the original AF.

Informed consent forms and AFs will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy will be kept by the subject or subject's parent/LAR.

Documentation of the consent process should be recorded in the source documents.

In the context of this clinical study, subject will be receiving different vaccination regimens, ie, 2- or 3-dose PrEP regimen. Subject has the chance of receiving vaccine not yet licensed (VRVg-2) or the vaccine that was previously licensed in Thailand (Imovax® Rabies) or currently licensed there (Verorab®). In addition, subject or subject's parent/LAR needs to give consent and comply with other study-related activities which are not usually part of the treatment process, ie, blood draws, filling up of DCs, MA, scheduled visits, phone calls from study staff and, if woman of childbearing potential, other procedures such as urine pregnancy test before each vaccination or

follow-up of the subject's health and the newborn's health in case of pregnancy will be carried out.

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria to be eligible for study enrollment:

1) Aged ≥ 1 year on the day of inclusion[a]
2) ICF has been signed and dated by the subject and/or parent(s) or LAR and by an independent witness (if required by local regulations), as necessary; and AF has been signed and dated by the subject, as required
3) Subject (adult ≥ 18 years) or subject and parent/LAR (1 year to < 18 years) are able to attend all scheduled visits and to comply with all study procedures.

5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from study enrollment:

1) Subject is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to the 1st vaccination and 1 month after each vaccination. To be considered of non-childbearing potential, a female must be pre-menarche[b] or post-menopausal for at least 1 year, or surgically sterile.
2) Participation at the time of study enrollment or, planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.
3) Receipt of any vaccine in the 4 weeks (28 days) preceding the 1st study vaccination or planned receipt of any vaccine prior to V05 for pediatric subjects and adult subjects in Cohort 1, and prior to V04 for adult subjects in Cohort 2.
4) Previous vaccination against rabies (in pre- or post-exposure regimen) with either the study vaccines or another vaccine.
5) Bite by, or exposure to a potentially rabid animal in the previous 6 months with or without PEP.
6) Receipt of immune globulins, blood or blood-derived products in the past 3 months.

[a] " ≥ 1 year" means from the day of the 1st birthday onwards, with no upper age limit

[b] Pre-menarche females will declare by themselves that they have not yet started menstruation. If a young female subject reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward.

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7) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).
8) At high risk for rabies exposure during the study[a].
9) Known systemic hypersensitivity to any of the study/control vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances[b].
10) Self-reported thrombocytopenia, contraindicating IM vaccination.
11) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination.
12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.
13) Current alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion.
14) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[c].
15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
16) Personal History of Guillain-Barré syndrome.
17) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study.

If the subject has a primary physician who is not the Investigator, if feasible the site should contact this physician with the subject's consent to inform him/ her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

[a] Such as veterinarians and their staff, animal handlers, rabies researchers, and certain laboratory workers.

[b] The components of VRVg-2 are listed under Section 6 Investigational Product and in the Investigator's Brochure Section 3.2. The components of Verorab and Imovax Rabies vaccines are listed under Section 6 Control Products, eg, traces of polymyxin B, streptomycin, or neomycin.

[c] Chronic illness may include, but is not limited to, neurological, cardiopulmonary, gastrointestinal, renal, genitourinary, metabolic, hematologic, auto-immune, or psychiatric disorders or infection.

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the subject is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the case report book (CRB). The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment

The reporting of signs and symptoms in lieu of a diagnosis is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and the information collected will not be coded. Its purpose is to assist in the later interpretation of safety data collected during the study. Given the current COVID-19 pandemic, the medical history must actively include if suspected/ confirmed COVID-19 happened and the dates. The use of medications (prescribed or out-of-the-counter) such as chloroquine and hydroxychloroquine within at least 2 months before enrollment and during the conduct of the study should be recorded, given their interference with rabies vaccines (38).

5.2.7 Contraindications for Subsequent Vaccinations

5.2.7.1 Temporary Contraindications

Should a subject experience one of the conditions listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the Table of Study Procedures (except for VAC2 in Cohort 2 which can be given after resolution of temporary contraindication(s) to permit the subject fully benefit from the rabies vaccination). If any dose is delayed, the subsequent doses should be delayed according to the original time interval.

- Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C).
- For Primary Series Cohort 2: unplanned administration of a vaccine other than the study vaccine between D0 and last primary vaccination (D07-VAC2). Since this is a PrEP study and the subjects will benefit from the rabies vaccination, the subject can receive the 2nd rabies primary dose at least 4 weeks after receipt of another vaccine (out of window) but will be excluded from the Per-Protocol Analysis Set (PPAS) – see Section 12.2.4.
- For Immunogenicity Persistence and Booster Phase Cohort 2: administration of a vaccine other than the study vaccine 4 weeks prior to or planned administration within 4 weeks after booster vaccination, only if the delayed booster vaccination can still be maintained within the

allowed time window (M24-36 +14 days). If the allowed time window cannot be applied; please refer to Section 5.2.7.2.

- Note: Vaccinations other than study vaccine consist of prohibited therapies within 28 days before and after each study vaccination (Section 6.9), their administration results in exclusion from PPAS and protocol deviation. The decision whether or not this would consist of a significant non-compliance with the protocol (condition for withdrawal from the study) depends on Investigator's judgment. There are no restrictions for receipt of other vaccines, including COVID-19 vaccination, in other study time frames: between V05 (Cohort 1) or V04 (Cohort 2) and 4 weeks before booster visit, or > 28 days after booster vaccination.

5.2.7.2 Definitive Contraindications

Should a subject experience 1 of the conditions listed below, the Investigator will discontinue vaccination:

- Pregnancy, as indicated by a positive urine test.
- Anaphylactic or other significant allergic reaction to the previous dose of vaccine.
- Immunoglobulin, blood or blood-derived products received in the past 3 months or ongoing at the visit.
- Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy in the past 6 months or ongoing at the visit, or long-term systemic corticosteroid therapy (for more than 2 consecutive weeks in the past 3 months before the visit).
- Human immunodeficiency virus (HIV) seropositivity.
- Thrombocytopenia, bleeding disorder or receipt of anticoagulants contraindicating IM vaccination.
- For Primary Series Cohort 1: administration of a vaccine other than the study vaccine between D0 and last primary vaccination (VAC3) or planned administration before V05.
- For Booster Phase Cohort 1: administration of a vaccine other than the study vaccine 4 weeks prior to or planned administration within 4 weeks after booster vaccination.
- For Immunogenicity Persistence and Booster Phase Cohort 2: administration of a vaccine other than the study vaccine 4 weeks prior to or planned administration within 4 weeks after booster vaccination, only if the temporary contraindication for the booster (see Section 5.2.7.1) could not be applied since it would not permit to keep visits schedule within the allowed window.
- An SAE related to the study vaccines following a vaccination.
- Any potential contact with rabies virus during the course of the study.
- Reporting of Guillain-Barré syndrome.

Subjects with a definitive contraindication will continue to be followed up for the study-defined safety and immunogenicity assessments, as applicable.

5.2.8 Coronavirus Disease 2019 (COVID-19) Vaccine

Should the COVID-19 vaccination campaign be implemented during the study for the population eligible to participate or participating in the study, applicable country recommendations will be implemented. If a subject is eligible to participate, it is recommended the subject prioritize the COVID-19 vaccination and delay the time of the enrollment according to the exclusion criterion specified in Section 5.2.5. If the subject was already enrolled in the study, when possible and unless recommended otherwise, as per national public health policies or Investigator judgment, a 4-week interval between any study vaccine dose and the COVID vaccine dose(s) is desirable.

When the subject is already enrolled in the study if a COVID-19 vaccine dose is received during one study vaccine solicited reactogenicity period it would not be possible to differentiate systemic reactions between them. Likewise, if the COVID-19 vaccine is received between a study vaccine dose and the collection of blood, it will not be possible (at this point) to rule out an immunogenicity interaction. Therefore, in any of the 2 situations, it is recommended that the subject will not be withdrawn from the study and should continue within the full analysis set (FAS).

The type of COVID-19 vaccine received (including tradename) and the date/time of its administration(s) should be documented in the concomitant medications CRF.

Wherever possible, the site of injection of study vaccines should be in the limb separate from the limb in which the COVID-19 vaccine is administered (if it has already been administered). Likewise, and if on the control of the study site, any COVID-19 vaccine scheduled to be received after administration of study vaccines should not be received in the same limb as study vaccines. Where it is not possible to have study vaccines and COVID-19 vaccine administered in separate limbs, a distance of at least 1 inch/ 2.5 cm should be maintained between the 2 administration sites.

5.2.9 Conditions for Withdrawal

Subjects and/or subject's parent/LAR will be informed that they have the right to withdraw and/or withdraw their child from the study at any time.

- At the discretion of the Investigator or Sponsor due to safety concerns or significant non-compliance with the protocol (based on the Investigator's judgment), without the subject's permission (withdrawal)
- At the request of the subject (dropout)

The following will result in automatic withdrawal or exclusion of a subject from the study:

- Significant non-compliance with the protocol, based on the Investigator's judgment

The reason for a withdrawal or dropout should be clearly documented in the source documents and in the CRB.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "AEs") or for another reason.

Withdrawn subjects may be replaced.

Subjects included in the Immunogenicity Persistence and Booster Phase Cohort 2 (adult subset) will not be withdrawn from the study if they fail to come to one or more visits prior to booster dose (at M6, M12, and/or M18).

5.2.10 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (ie, documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents.

5.2.11 Classification of Subjects Who Discontinue the Study

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the CRB. Reasons are listed below from the most significant to the least significant (refer to the CRF completion instructions for additional details and examples):

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.2.1.1. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.10. The certified letter was sent by the Investigator and returned unsigned, and the subject or parent/guardian did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant non-compliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, administration of other vaccine, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration) • If the subject experiences a definitive contraindication that is not an SAE or AE • The subject or the parent/guardian signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit
Withdrawal by Subject or Parent / Guardian / Legally Acceptable Representative	To be used: • When the subject or parent/guardian indicated unwillingness to continue in the study • When the subject or parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.12 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the study because of an AE or a protocol deviation.

For subjects where the reason for early termination was lost to follow-up or if the subject withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

If the subject's status at the end of the study is "Withdrawal by Subject or Parent / Guardian / LAR", the site will attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.2.13 Follow-up and Reporting of Pregnancies

Pregnancy is an exclusion criterion for enrollment in this study, but a subject could potentially become pregnant during her participation. In case of pregnancy during the primary series and if at least 1 dose of the study vaccine(s) has been administered, the subject will not be discontinued from the study, but no further vaccination will be administered until after delivery (if applicable and still within the study vaccination window). However, the subject will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

All pregnancy cases should be reported if they occurred:

- Throughout the entire study period (for subjects in Cohort 1 and for subjects in Primary Series Cohort 2)
- From the first vaccination in Primary Series until the end of the 6-month follow-up after Primary Series or from the Booster Injection until the end of the 6-month follow-up after Booster Injection (for subject in Immunogenicity Persistence and Booster Phase Cohort 2).

To report the pregnancy case, the Investigator must fill out Pregnancy Reporting forms in the electronic data capture (EDC) system and inform the Sponsor within 1 month of identifying a pregnancy case.

If the EDC system is not available, the Investigator must fill out a paper Pregnancy Reporting Form (provided by the Sponsor at the start of the study) and inform the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome (ie, details about the delivery and the newborn, or about pregnancy termination) and must update the Pregnancy Reporting forms even after the end of the study. This information should be provided to the Sponsor within 1 month of delivery.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, blighted ovum, fetal death, stillbirth, and congenital anomalies reported in the baby are always considered as SAEs, and the information should be provided to the Global Pharmacovigilance (GPV) Department regardless of when the SAE occurs (eg, even after the end of the study).

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's Responsible Medical Officer (RMO) for advice on how to address any study-related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department (please refer to Section 10).

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.6.

5.4 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (eg, those that affect the conduct of the study or the safety of subjects) require IEC / IRB approval, and must also be forwarded to regulatory authorities.

An administrative / non-substantial amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs / IRBs must approve all amendments linked to administrative changes.

The Investigator is responsible for ensuring that changes to an approved study, during the period for which IEC / IRB approval has already been given, are not initiated without IEC/ IRB review and approval, except to eliminate apparent immediate hazards to subjects.

5.4.1 VRV12 Amendments Justification

Amendment 2

As explained in Section 5.1.2, the VRV12 study was planned to document the NI of the 3-dose PrEP regimen recommended by the ACIP 2008 guidelines (34) as a primary endpoint and the one week 2-dose PrEP regimen recommended by the WHO 2018 guidelines, [redacted]

Protocol amendment 2 was developed to conservatively adjust the estimation of seroconversion rate at D28 for adults subjects in VRVg-2 and the control vaccines from 99% to 96.5% according to the latest results from VAJ00001 study and to ensure the statistical power of the secondary objective to demonstrate that VRVg-2 is non-inferior to Verorab and Imovax Rabies vaccines in each age group (pediatric and adult population), in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D28 based on the above-adjusted estimation. This will be

accomplished by increasing the sample size of the adult population assuming a lower estimation of seroconversion rate at D28 based on the following rationale:

- Originally, the sample size and statistical power calculated for the NI assessment at D28 after the one week 2-dose PrEP regimen vaccination was based on available literature at the time (39) (40) (41) (42) (43) (44) (45) (46), which showed pediatric and adult population may have around 99% of seroconversion rates between 2 weeks (D21) and 3 weeks (D28) after the 2nd vaccination dose using Verorab or Imovax Rabies intramuscularly. However, to be on the conservative side, this seroconversion rate assumption should be adjusted to take into account the latest results of the VAJ00001 study conducted by the Sponsor. The VAJ00001 study was carried out to document the NI of the one week 2-dose PrEP regimen versus the 3-dose PrEP regimen using Imovax rabies, and to describe the immunogenicity and safety of the one week 2-dose PrEP regimen using IM or intradermal routes with Verorab or Imovax Rabies vaccines in healthy subjects aged 2 up to 65 years in the Philippines. The one week 2-dose PrEP arms using IM route showed that 100% of the pediatric population achieved RVNA titer ≥ 0.5 IU/mL at D21 for both vaccines, while 93.9% of the adult population who received Imovax Rabies and 97.1 % who received Verorab achieved RVNA titer ≥ 0.5 IU/mL at D21 in the PPAS. Therefore, the estimation of seroconversion rate at D28 for adult population was adjusted from 99% to 96.5%.
- There are differences and similarities between VAJ00001 and VRV12 studies that should be taken into account to reassess the assumptions of the VRV12 study:
  - The age of the population included: variability of primary immune response to rabies vaccines has been previously described, some individuals responding earlier and producing high titers (early/high responders) while others respond later and produce lower titers (late/low responders), this is particularly relevant in adults (47) (48). VRV12 study will include subjects who are older than 65 years old and tend to be late/ low responders.
  - The time points used to assess the one week 2-dose PrEP regimen: The timepoint 21 days after the 1st injection (ie, 14 days after the 2nd dose) may be too early to observe seroconversion in all subjects in the VAJ00001 study. Clinical studies evaluating the kinetics of the immune response after rabies injection in naïve healthy individuals have shown that following primary vaccination series of Imovax Rabies at D0, D7, and D28, neutralizing antibodies were formed as early as 7 days of vaccination, while the highest IgG antibody titers were found at 2–4 weeks after a 3rd injection (49) (50) (51) (52). Although the timepoint at D28 may benefit the assessment of the one week 2-dose PrEP in the VRV12 Study, there is limited evidence in the current literature of how the kinetics of the immune response will be 3 weeks after a 2nd injection in the elderly population.
  - The RFFIT method: both studies will use the same RFFIT method. This has been recently validated (53) and the known variability of the method should be considered (54) (55).
- There are scientific rationale and product constraints that justifies increasing only the adult population by receiving a one week 2-dose PrEP regimen, as follows:
  - It is expected that the estimation of seroconversion rate at D42 is 99.0% for both adult and pediatric populations and so that the statistical power for the primary objective at D42 is the same as the original estimations. Therefore, there is no need to increase the sample size for the primary objective.

[redacted]

Therefore, the increase of the sample size will ensure the evaluation of immunogenicity of the one week 2-dose PrEP regimen at D28 which is anticipated to be the most used worldwide since it is recommended by the new ACIP 2021 guidelines and the WHO 2018 guidelines. The adjusted assumption of seroconversion and the updated calculation of the sample size and statistical power for the key objectives in the primary series are explained in Section 12.5.

In addition, as explained in Section 5.1.2, protocol amendment 2 also incorporated a single booster between 2 and up to 3 years with a new batch of VRVg-2 as recommended in the new ACIP 2021 guidelines. The booster evaluation is confirming the assessment of the PrEP regimens, since it is expected good boostability of immunity in subjects at risk of rabies exposure (eg, one single IM booster dose) or primed patients who were exposed to rabies and will receive a PEP regimen (eg, one IM dose at D0 and D3). In the VAJ00001 study, a high immune response was observed in all age classes after the simulated PEP regimens which confirm the efficiency of these PrEP and PEP regimens in subjects aged 2 up to 65 years. These findings are consistent with those from recent studies (56) (57) (58) (59) and confirmed the adequate priming conferred by the one week 2-dose PrEP regimen in all subjects. The VRV12 results of a single IM booster dose are expected to document the boostability after the one week 2-dose PrEP regimen.

Amendment 3

[redacted] this protocol amendment 3 adds a secondary objective to demonstrate the acceptability of the immune response at D28 of a 1-week 2-dose PrEP regimen. It also adds the evaluation of persistence of the immune response at M6, M12, M18 and pre-booster between M24 up to M36 after a 2-dose primary series in the subset of adults who are randomized to be part of the Immunogenicity Persistence and Booster Phase Cohort 2.

Amendment 4

As stated in Section 1.3.1, most of the subjects are expected to have reached RVNA titers ≥ 0.5 IU/mL after the completion of the 2- or 3-dose PrEP regimen of rabies vaccine (and booster dose for adult subsets) (61) (62). Depending on Investigator's clinical judgment, subjects with RVNA titers < 0.5 IU/mL at all timepoints may be offered an additional injection of a local licensed rabies vaccine chosen by the Investigator and administered according to the local SmPC / PI or national guidelines and if the subject / subject's LAR agree. Such vaccine is offered outside of the scope of the protocol (ie, no safety nor immunogenicity data will be collected after this vaccine injection), free of charge at the study site. This is the Investigator's responsibility to decide which vaccine will be the most appropriate for giving real benefit to the subject.

Moreover, Section 5.2.9 was updated to avoid any unnecessary subjects' withdrawal due to missing visits (at M6, M12, and/or M18) during the Immunogenicity Persistence and Booster Phase Cohort 2 (adult subset). Section 6.7 was updated to clarify the subject number assigning rule was different between Cohort 1 and Cohort 2, due to different IRT settings.

Amendment 5

Protocol amendment 5 adds 2 secondary objectives to demonstrate the NI of a 2-dose VRVg-2 PrEP at D28 versus 3-dose Imovax Rabies PrEP at D42 in each age group, and also to

demonstrate NI of 2-dose Imovax Rabies PrEP at D28 versus 3-dose Imovax Rabies PrEP at D42 in each age group, both with a NI margin of -10%for each of these 2 new secondary objectives.

5.5 Interruption of the Study

The study may be discontinued if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on the advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in Thailand where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by applicable regulatory requirements. The Investigator shall promptly inform the study subjects/subjects' parents/guardians and should assure appropriate subject therapy and/or follow-up.

6 Products Administered

6.1 Identity of the Investigational Products

The investigational product is VRVg: PVRV – Serum Free (purified inactivated rabies vaccine prepared on Vero cell line):

- VRVg-2 is the formulation used.

Form: freeze-dried

Route: IM injection into the deltoid muscle (or anterolateral thigh for toddlers)

6.1.1 Composition

Each 0.5 mL dose of VRVg-2 reconstituted vaccine contains:

- Powder (VRVg-2):
  - Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain: ≥ 2.5 IU (potency; NIH); [redacted]
  - Stabilizer*: sufficient quantity (qs)
  - [redacted]

* *The stabilizer (490 solution) is a mixture of amino acids (including trace amounts of phenylalanine), sugars (including the presence of sorbitol and trace amounts of saccharose), and sodium dihydrogen phosphate, di-sodium phosphate dihydrate, sodium glutamate, di-sodium edetate (EDTA), poloxamer P188 and urea in water for injections.*

- Diluent:
  - Sodium chloride: 2 mg
  - Water for injection: qs 0.5 mL

Powder and diluent batch numbers are to be determined.

6.1.2 Preparation and Administration

The procedures for preparing and administering VRVg-2 are as follows:

The products will be placed at room temperature for few minutes (in order to bring the liquid to room temperature). The diluent, contained in a pre-filled syringe, will be injected into the vial containing the powder of rabies virus. The mixture will then be gently swirled to obtain a homogenous suspension. To administer the vaccine, the entire volume of the solution (approximately 0.5 mL) is withdrawn and injected with a new needle intramuscularly in the deltoid (or anterolateral thigh for toddlers), within 1 hour after reconstitution of the vaccine. Vaccinations should be performed on alternative sides, at least 3 cm apart from the previous injection site; eg, the 1st injection in the left deltoid, the 2nd in the right deltoid and so on (or anterolateral thigh for toddlers).

Note: The freeze-dried vaccine is white homogenous; after reconstitution, the vaccine is limpid to opalescent and colorless.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.5.1), and extraneous particulate matter and/ or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor.

As there are no preservatives in the vaccine, the mixture must be administered immediately (within 1 hour) after reconstitution.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1 000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.1.3 Dose Selection and Timing

[redacted] The dose selected for the present study is based upon results obtained in VRV11 study (Phase II dose ranging study).

6.2 Identity of Control Product 1

Verorab®: purified inactivated rabies vaccine prepared on Vero cell line

Form: freeze-dried

Route: IM injection into the deltoid muscle (or anterolateral thigh for toddlers)

6.2.1 Composition

Each 0.5 mL dose contains:

- Powder:
  - Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain: ≥ 2.5 IU (potency; NIH)
  - Maltose: qs
  - Human albumin: qs

- Diluent
  - Sodium chloride: 2 mg
  - Water for injection: qs 0.5 mL

Powder and diluent batch numbers are to be determined.

6.2.2 Preparation and Administration

Preparation and administration of the Verorab vaccine will follow the same steps as preparation and administration of the investigational vaccine, VRVg-2, as described in Section 6.1.2.

Note: The powder is a white homogeneous pellet; after reconstitution, the vaccine is a limpid homogeneous solution.

Precautions for use are the same as for VRVg-2 and are described in Section 6.1.2.

In addition, traces of neomycin, streptomycin, and polymyxin are used during the production process of Verorab and can be found in the final product. Therefore, caution must be exercised when the vaccine is administered to subjects with hypersensitivity (not known or not disclosed by the subject) to these antibiotics and other antibiotics of the same class. Appropriate treatment in case of anaphylactic reactions to these antibiotics must therefore be available.

6.2.3 Dose Selection and Timing

Verorab vaccine will be administered according to the recommendations described in the package insert of the licensed vaccine.

6.3 Identity of Control Product 2

Imovax® Rabies: purified inactivated rabies vaccine prepared on human diploid cell cultures

Form: freeze-dried

Route: IM injection into the deltoid muscle (or anterolateral thigh for toddlers)

6.3.1 Composition

Each dose contains:

- Powder:
  - Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain: ≥ 2.5 IU (potency; NIH)
  - Human albumin: 50 mg

- Diluent:
  - Water for injection: qs 1 mL

Powder and diluent batch numbers are to be determined.

6.3.2 Preparation and Administration

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.2, with the exception that the diluent volume is approximately 1 mL and, hence, the entire volume of the vaccine solution to be injected is approximately 1 mL.

Note: The freeze-dried vaccine is creamy white to orange; after reconstitution, the vaccine is pink to red.

Each dose may contain undetectable traces of neomycin, used during vaccine production. Therefore, caution must be exercised when the vaccine is administered to subjects with hypersensitivity (not known or not disclosed by the subject) to this antibiotic and other antibiotics of the same class. Appropriate treatment in case of anaphylactic reactions to these antibiotics must therefore be available.

6.3.3 Dose Selection and Timing

Imovax Rabies vaccine will be administered according to the recommendations described in the package insert of the licensed vaccine.

6.4 Identity of Other Product(s)

Not applicable

6.5 Product Logistics

6.5.1 Labeling and Packaging

Each dose of the different rabies vaccines (VRVg, Verorab and Imovax Rabies vaccines) will be in an individual box that will be identified by a dose number. Each box will contain a vial with the powder of rabies virus and a pre-filled syringe containing the diluent. Each box of vaccine dose will bear both detachable and fixed labels for identification. The labeling of vials, syringes and boxes will be done according to Thai regulation requirements.

6.5.2 Product Shipment, Storage, and Accountability

6.5.2.1 Product Shipment

The Investigational Product Manager or designee will contact the Investigator or a designee to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (ie, verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative and request authorization from Sanofi Pasteur to use the product. See Operating Guidelines for further instructions.

6.5.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this responsibility.

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C and should be protected from light. The vaccines must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccines are at the study site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.5.2.3 Product Accountability

The person in charge of product management at the site will maintain records of product delivery to the study site, product inventory at the site, the dose(s) given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the CRB. If applicable, information may also be entered into the subject's vaccination card.

The Sponsor's monitoring staff will verify the study site's product accountability records against the record of administered doses in the CRBs and the communication from the IRT (if applicable).

In case of any expected or potential shortage of product during the study, the Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

6.5.3 Replacement Doses

If a replacement dose is required (eg, because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.5.4 Disposal of Unused Products

Unused or wasted products will be either disposed of or returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the study period.

6.5.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigator(s) will be informed of what needs to be done.

6.6 Blinding and Code-breaking Procedures

The study will be conducted in an observer-blind manner for all vaccinations (except for the booster vaccination in Immunogenicity Persistence and Booster Phase Cohort 2):

- Unblinded staff member(s), independent of the safety evaluation and other study evaluations, will prepare and administer the vaccine
- The blinded staff member(s), including the Investigator (for Cohort 1 and Primary Series Cohort 2), in charge of safety assessment, will not know which vaccine is administered
- The subject and subject's parent/ LAR will remain blinded (for Cohort 1 and Primary Series Cohort 2) and will not know which vaccine is administered: the product will not be prepared in their presence and the product will be hidden.

The blinded staff members, including the Investigator (for Cohort 1 and Primary Series Cohort 2), responsible for safety assessment will not attend the vaccination session. However, they will remain available in case of emergency (eg, anaphylactic shock).

In addition to the subjects, health care providers, data collectors, outcome assessors (eg, Investigator who assess the safety), the Sponsor personnel (eg, Clinician, Data Management, Biostatistician) will remain blinded until the 1st statistical analysis. The laboratory analysts who will be involved in the blood sample testing will remain blinded during the whole study.

The code may be broken in the event of an AE only when the identification of the vaccine received could influence the treatment of the subject. Code-breaking should be limited to the subject(s) experiencing the AE.

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO if a subject’s code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking CRF is to be completed.

A request for the code to be broken may also be made:

- by the GPV Department through an internal system for reporting to health authorities in the case of an SAE as described in ICH E2A. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (ie, the subject’s vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

The IEC / IRB must be notified of the code-breaking. All documentation pertaining to the event must be retained in the site’s study records and, in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

The code will be broken at the time of the 1st statistical analysis (ie, 28 days after the 2nd vaccination which is at the end of vaccination active phase in the primary series of Cohort 2). However, the laboratory personnel who conducts the serology test for blood sample will remain blinded during the whole study.

6.7 Randomization and Allocation Procedures

An IRT system will be used. The full detailed procedure for randomization will be described in the Operating Guidelines given to the Investigator and the staff in charge of these operations at each site.
Separate randomization listings will be created for Cohort 1 and Cohort 2, respectively.
At V01 (D0), the qualified staff member will contact the IRT system to assign a subject number of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). The 1st digit of the subject identifier will be a predefined figure ("0" for pediatric population and "1" for adult population). The 2nd digit of the subject identifier will represent the adult subjects participating in the booster phase or not ("0" for adults included only in the Primary Series Cohort 1 without booster vaccination, "1" for adult included in the Primary Series Cohort 1 with the booster phase at M12 [Booster Phase Cohort 1], "2" for adult included only in the Primary Series Cohort 2 without booster vaccination, and "3" for adults included in the Primary Series Cohort 2 with the evaluation of Immunogenicity Persistence (at M6, M12, M18, and pre-booster between M24 up to M36 after primary series) and Booster Phase at M24 up to M36 [Immunogenicity Persistence and Booster Phase Cohort 2]). In Cohort 1, the last 3 digits of the subject's identifier represent the enrollment sequence of the subject in each site, and the subject number will be sequential regardless of the participation in the booster phase. In Cohort 2, the last 3 digits of the subject's identifier represent the sequence number of a subject's randomization sequence at D0 in each vaccination schedule subset (primary series only, or primary series with immunogenicity persistency and booster phase) within each site, and the sequence number will be start from 001 within each stratum.
Some examples:

- Subject 764000100005 is the 5th pediatric enrolled in Center Number 1 and will only be part of the Primary Series in Cohort 1 (764 being the Thailand country code)
- Subject 764000211005 is the 5th adult enrolled in Center Number 2 and will be part of the Booster Phase Cohort 1
- Subject 764000212008 is the 8th adult enrolled to participate in the Primary Series only without Immunogenicity Persistence and Booster Phase in Cohort 2, in Center Number 2
- Subject 764000213008 is the 8th adult enrolled to participate in the Primary Series with Immunogenicity and Persistence and Booster Phase in Cohort 2, in Center Number 2
- Subject 764000210006 is the 6th adult enrolled in Center Number 2, and will only be part of the Primary Series in Cohort 1 and not be part of the Booster Phase Cohort 1 (subject number will be continuous regardless of the participation in the booster phase)

The IRT system will define which product/dose number will be administered for each vaccination and will determine, at D0, if the subject from the adult population will participate to the booster phase or not.

Randomization, managed by the IRT system, will be performed using the permuted block method with stratification on centers and age group (adults [≥18 years] and children [1 year to < 12 years and ≥ 12 to < 18 years]). This guarantees, at any time and in each center and each age group, the right number of subjects with respect to the randomization scheme that has been defined for the study.

Subject numbers should not be reassigned for any reason. The Clinical Quality Assessment (CQA) Department at Sanofi Pasteur will hold the randomization codes of doses in a secured location.

6.8 Treatment Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified study personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the study site, product inventory at the site, dose(s) given to each subject, and the disposal of unused or wasted doses

6.9 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications and other therapies (eg, blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during study participation.

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of 1st vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of each vaccination to the end of the solicited and unsolicited follow-up period.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], steroids/corticosteroids and other immunomodulators)
- Category 2: medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Global Clinical Immunology [GCI] department, steroids/corticosteroids, immune-suppressors,

immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)

- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, steroids/corticosteroids)

Additionally, given the COVID-19 pandemic and the possible use of medications with or without medical prescription, medications that interfere with the immune response should be actively evaluated. For instance, chloroquine or hydroxychloroquine received within at least 2 months before and during data collection should be clearly reported due to the possible interference with rabies vaccines (38) (62). For use of COVID-19 vaccines during the study period, please refer to Section 5.2.8.

The information reported in the CRB for each reported medication will be limited to:

- Trade name.
- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables.
- Medication category (1, 2, or 3).
- Start and stop dates.

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a category 1 medication in this specific instance.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the pre-listed categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected:

- At V01, V03, and V04 for pediatrics and adults in Cohort 1, as well as at V06 and V07 for adults who will also participate in Booster Phase Cohort 1.
- At V01 and V03 for adults in Primary Series Cohort 2, as well as at V05, V06, V07, V08, and V09 for adults who will also participate in Immunogenicity Persistence and Booster Phase Cohort 2.

See the Tables of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

Blood[a] will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label and will attach the label to the tube. When vaccination and blood sample collection occur at the same visit and vaccine is given only in one of the arms, blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours to allow the blood to clot.

Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of + 2°C to + 8°C up to a maximum of 24 hours. The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes.

These tubes are pre-labeled with adhesive labels that identify the study code, the subject's number, and the sampling stage.

The subject's number and the date of sampling, the number of aliquots obtained, and the subject's consent for future use of his/her samples are to be specified on a sample identification list. These previous items, as well as the date and time of preparation, are to be recorded in the source document. Space is provided on the sample identification list to record comments regarding the quality of samples.

7.3 Sample Storage and Shipment

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented in the appropriate form during the entire study. If it rises above -10°C for any period of time, the Clinical Samples Logistics representative must be notified. See the Operating Guidelines for further details.

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Clinical Samples Logistics representative. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

[a] Blood sample volume drawn from subjects 1 year to < 2 years will be 3 mL, for subjects ≥ 2 years to < 18 years will be 5 mL, and for subjects ≥ 18 years will be 6 mL.

Samples will be shipped to GCI at Sanofi Pasteur. The address is provided in the Operating Guidelines.

Any unused part of the serum samples will be securely stored for any testing directly related to this study at the Sanofi Pasteur serology laboratory (GCI) for up to 25 years after the end of the study.

7.4 Future Use of Stored Serum Samples for Research

Subjects or subjects' parent/LAR will be asked to indicate in the ICF whether they will permit the future use of any leftover stored serum samples for additional research not related to this study. If they consent, leftover serum samples will be securely stored at GCI for up to 25 years after the end of the study. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs/AFs, CRBs, SAE reporting forms, DCs, MAs, and other study documents, as well as with the following study materials: all study vaccines, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

The means for performing EDC will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the study.

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and/ or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Safety

There are no primary objectives for safety.

9.1.2 Immunogenicity

9.1.2.1 Immunogenicity Endpoints

The primary endpoint(s) for the evaluation of immunogenicity are:

- RVNA titers (IU/mL) measured by the RFFIT at D42 for pediatrics and adults in Primary Series Cohort 1:
  - Subject with an RVNA titer ≥ 0.5 IU/mL at D42

9.1.2.2 Immunogenicity Assessment Methods

The assay method to quantify neutralizing antibodies against rabies virus in human serum samples is the RFFIT. The method involves reaction of rabies virus specific antibodies present in serum with a standardized challenge dosage of rabies virus (CVS-11) in a micro-neutralization cell culture. The presence of non-neutralized rabies virus in the serum-virus mixture is detected in the infected cells by direct fluorescence antibody method using fluorescein isothiocyanate (FITC) conjugated anti-rabies monoclonal immunoglobulin. The rabies virus in micro-neutralization cell culture is enumerated in scanned images generated from a cell imaging reader. The absence of infectivity (no fluorescent cells) constitutes a positive neutralization reaction, indicating the presence of RVNA in the serum. On the contrary, the infection of cells in culture indicates the absence of RVNA in the serum.

The highest dilution of the serum that neutralizes 50% of the challenge virus is the endpoint antibody titer. The RVNA concentration is expressed in IU/mL and is determined by calibrating the 50% neutralization endpoint antibody titer of the test serum to the 50% neutralization endpoint titer of an internal reference serum which was calibrated against the 1st or 2nd WHO international standard for anti-rabies immunoglobulin. Titers (IU/mL) will be obtained in duplicates for each tested sample, and the individual geometric mean of duplicates calculated as needed.

LLOQ for the RFFIT assay is 0.2 IU/mL. Samples calculated to a value less than LLOQ will be reported as < LLOQ.

Virus neutralization will also be assessed as complete (absence of fluorescent cells) or incomplete (presence of fluorescent cells) at the subject/timepoint level at the starting dilution (1/5) of the RFFIT assay. Samples may be assessed in duplicates and the result summarized as: complete or incomplete (if both duplicates show complete or incomplete neutralization, respectively) or undetermined, if duplicates give different results.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Safety

9.2.1.1 Safety Definitions

The following definitions are taken from the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore, an AE may be:

- A new illness
- The worsening of a pre-existing condition
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

Surgical procedures are not AEs; they are the actions taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the study period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (eg, asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3 (see Section 9.2.1.3.3). This is not the same as *serious,* which is based on subject/ event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose.

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability/ incapacity[c]
- Is a congenital anomaly/ birth defect
- Is an important medical event (IME)

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new-onset diabetes, or autoimmune disease.

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the product administered) that occur within the 1st 30 minutes after vaccination.

Solicited Reaction:

A solicited reaction is an "expected" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRB (eg, injection site pain or headache occurring between D0 and D7 post-vaccination).

By definition, solicited reactions are to be considered as being related to the product administered.

For injectable vaccines, solicited reactions can either be solicited injection site reactions or solicited systemic reactions.

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[a] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or outpatient treatment with no hospitalization.

[c] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

Unsolicited AE/ AR:

An unsolicited AE is an observed AE that does not fulfill the conditions pre-listed in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D7 is a solicited reaction (ie, pre-listed in the protocol and CRB), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

An injection site reaction is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions. They are considered to be related to the product administered.

Systemic AE:

Systemic AEs are all AEs that are not injection or administration site reactions. They, therefore, include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Adverse Event of Special Interest (AESI):

An AESI is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

AEs of special interest are AEs that are considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine. The following AESIs are defined: anaphylactic reactions, encephalitis, and convulsions.

9.2.1.2 Safety Endpoints

The secondary endpoints for the evaluation of safety are:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccine injection
- Occurrence of solicited (pre-listed in the subject's DC and electronic CRF) injection site and systemic reactions occurring within 7 days after each injection
- Occurrence of unsolicited (spontaneously reported) injection site reactions occurring within 28 days after each injection and unsolicited systemic AEs up to 28 days after each injection
- Occurrence of SAEs and AESIs within at least 6 months after each vaccination as applicable to Cohort 1 and Cohort 2.
- SAEs (including AESIs) reported throughout the study, including occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] 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 24h), relationship to study procedures, and seriousness criterion

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

Note: Information about SAEs, AESIs, and cases of pregnancy were recorded throughout the study for pediatrics and adults in Cohort 1; and this is up to 6 months after the booster dose for subset of adults in Cohort 1. Information about SAEs, AESIs, and cases of pregnancy will be recorded until 6 months after the primary series (V05) and until 6 months after the booster dose for subset of adults in Cohort 2. Between the 6-month follow-up visit after primary series (V05) and booster dose visit (V08), AESIs will not be collected, only fatal SAEs and related SAEs will be collected.

9.2.1.3 Safety Assessment Methods

At each visit, the blinded Investigator or a delegate will perform a clinical or medically-driven physical examination and will ask the subject or subject's parent/LAR about any solicited reactions and unsolicited AEs recorded in the DC and/or MA, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.2.1.3.1 Immediate Post-vaccination Observation Period

Subjects will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination observation should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the CRB, as follows:

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected)
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination
- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10

9.2.1.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 After Each Vaccination)

After each vaccination, subjects or subjects' parent/LAR will be provided with a DC, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the DC on the day of vaccination and for the next 7 days (ie, D0 through D7) until resolution:

- Daily temperature, with the route by which it was taken

- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event (eg, medication)

  The action(s) taken by the subject or subject's parent/LAR to treat and/or manage any **solicited reactions** will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination

Table 9.1 to Table 9.3 and Table 9.4 to Table 9.5 present, respectively, the injection site reactions and systemic reactions that are pre-listed in the DCs and CRB, together with the intensity scales.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales in infants and toddlers aged ≤ 23 months

CRB term (MedDRA lowest level term [LLT])*	**Injection site tenderness**	**Injection site erythema**	**Injection site swelling**
MedDRA PT†	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
Diary card term	Tenderness	Redness	Swelling
Definition	Pain when the injection site is touched or injected limb mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale§	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3: Cries when injected limb is mobilized, or the movement of the injected limb is reduced	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

* The MedDRA (Version 22.0 or higher) lowest level term (LLT) will be used in the protocol and CRF

† The MedDRA LLT will be used in the protocol and in analyzing and reporting the reactions (clinical study report, summary documents)

§ For the subjective reaction of tenderness, parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.2: Solicited injection site reactions: terminology, definitions, and intensity scales in children (aged 2 through 11 years)

CRB term (MedDRA lowest level term [LLT])*	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
MedDRA PT†	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale§	Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform usual activities	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

* The MedDRA (Version 22.0 or higher) lowest level term (LLT) will be used in the protocol and CRF

† The MedDRA LLT will be used in the protocol and in analyzing and reporting the reactions (clinical study report, summary documents)

§For the subjective reaction of pain, subjects or parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.3: Solicited injection site reactions: terminology, definitions, and intensity scales in adolescents and adults (aged ≥ 12 years)

CRB term (MedDRA lowest level term [LLT])*	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
MedDRA PT†	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale§	Grade 1: A type of AEs that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of AEs that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject. Grade 3: A type of AEs that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

* The MedDRA (Version 22.0 or higher) lowest level term (LLT) will be used in the protocol and CRF

† The MedDRA LLT will be used in the protocol and in analyzing and reporting the reactions (clinical study report, summary documents)

§For the subjective reaction of pain, subjects or parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

Table 9.4: Solicited systemic reactions: terminology, definitions, and intensity scales in infants and toddlers aged ≤ 23 months

CRB term (MedDRA lowest level term [LLT])*	**Fever**	**Vomiting**	**Crying abnormal**	**Drowsiness**	**Appetite lost**	**Irritability**
MedDRA PT†	**Pyrexia**	**Vomiting**	**Crying**	**Somnolence**	**Decreased appetite**	**Irritability**
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the toddler and despite caregiver responses that would normally be soothing
Intensity scale§	Grade 1: ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F	Grade 1: 1 episode per 24 hours	Grade 1: < 1 hour	Grade 1: Sleepier than usual or less interested in surroundings	Grade 1: Eating less than normal	Grade 1: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	Grade 2: 2–5 episodes per 24 hours	Grade 2: 1–3 hours	Grade 2: Not interested in surroundings or did not wake up for a feed / meal	Grade 2: Missed 1 or 2 feeds / meals completely	Grade 2: Requiring increased attention
	Grade 3: > 39.5°C **or** > 103.1°F	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	Grade 3: Inconsolable

* The MedDRA (Version 22.0 or higher) lowest level term (LLT) will be used in the protocol and CRF

† The MedDRA LLT will be used in the protocol and in analyzing and reporting the reactions (clinical study report, summary documents)

§ For all reactions but fever, parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Table 9.5: Solicited systemic reactions: terminology, definitions, and intensity scales in children (aged 2 through 11 years), adolescents or adults (aged ≥ 12 years)

CRB term (MedDRA lowest level term [LLT])*	**Fever**	**Headache**	**Malaise**	**Myalgia**
MedDRA PT†	**Pyrexia**	**Headache**	**Malaise**	**Myalgia**
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale§	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of AEs that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AEs that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AEs that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

CRB term (MedDRA lowest level term [LLT])*	**Fever**	**Headache**	**Malaise**	**Myalgia**
MedDRA PT†	**Pyrexia**	**Headache**	**Malaise**	**Myalgia**
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of AEs that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.	Grade 2: A type of AEs that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.	Grade 2: A type of AEs that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of AEs that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AEs that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AEs that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

***** The MedDRA (Version 22.0 or higher) lowest level term (LLT) will be used in the protocol and CRF

† The MedDRA LLT will be used in the protocol and in analyzing and reporting the reactions (clinical study report, summary documents)

§ For all reactions but fever, subjects or parents / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important Notes for the Accurate Assessment of Temperature:

Subjects or subjects' parents/legally acceptable representatives are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC/MA, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is axillary for toddlers and children; oral for adolescent and adults. Pre-vaccination temperature is also systematically collected by the Investigator on the source document. Tympanic thermometers must not be used.

9.2.1.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, subjects or subjects' parents/legally acceptable representatives will be instructed to record any other medical events that may occur between each vaccination and during the 28-day period after the last vaccination and the booster vaccination. Space will be provided in the DC for this purpose.

Information on SAEs will be collected and assessed throughout the study, from inclusion until 6 months after the last vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports). In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE.
See Section 10 for further details on SAE reporting.

For each unsolicited AE (whether serious or non-serious), the following information is to be recorded:

- Start and stop dates[a]
- Intensity of the event:

  For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.1 to Table 9.5).

  All other unsolicited AEs will be classified according to the following intensity scale:

[a] The stop date of all related AEs will be actively solicited. For other events, the Investigator will provide the stop date when it becomes available. AEs for which no stop date was obtained during the course of the study will be considered as ongoing at the end of the study.

  - Grade 1: A type of AEs that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Grade 2: A type of AEs that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
  - Grade 3: A type of AEs that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.2.1.3.5.
- Action taken for each AE (eg, medication)

  The action(s) taken by the subject or subject's parent/LAR to treat and/or manage any unsolicited AEs will be classified in the CRB using the following list (all applicable items should be checked):
  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination
- Whether the AE was serious

  For each SAE, the Investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)
- Whether the AE caused study discontinuation

9.2.1.3.4 Adverse Events of Special Interest

The following AESIs will be assessed during the overall conduct of the study:

- Anaphylactic reactions
- Encephalitis
- Convulsions

These AESIs are considered by the Sponsor to be relevant for the monitoring of the safety profile of investigational products. They will be collected during the entire participation of a subject in the study and are to be reported as SAEs according to the procedure described in Section 10.

These AESIs have been defined based on existing post-marketing safety data of other rabies vaccines. For each AESI, the standard case definitions from the Brighton Collaboration will be used (63) (64) (65).

9.2.1.3.5 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the product administered as either ***not related*** or ***related***, based on the following definitions:

Not related – The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the given vaccination

Related – There is a "reasonable possibility" that the AE was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all AEs reported at the injection site (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

AEs likely to be related to the product, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

9.2.2 Immunogenicity

9.2.2.1 Immunogenicity Endpoints

The secondary endpoints for the evaluation of immunogenicity are:

- RVNA titers (IU/mL) measured by RFFIT, summarized at the subject/ timepoint level:
- RVNA titers at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12 and M12+D14 for subjects in the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2
- Subjects with an RVNA titer ≥ 0.5/mL at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12 and M12+D14 for subjects in the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2
- Subject with an RVNA titer ≥ LLOQ IU/mL at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12 and M12+D14 for subjects in the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2
- Individual RVNA titer ratio: D28/D0 for subjects in Primary Series Cohort 1 and Cohort 2, and D42/D0 for subjects in Primary Series Cohort 1; M12/D0, 14 days after M12/D0, and 14 days after M12/M12 for subjects in Booster Phase Cohort 1; M6/D0, M12/D0,

M18/D0, M24 up to M36/D0, 14 days after M24 up to M36/D0, and 14 days after M24 up to M36/M24 up to M36 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2

- Subject with complete or incomplete neutralization at the starting dilution (1/5) of the RFFIT assay at subject with an RVNA titer ≥ LLOQ IU/mL at D0 and D28 for subjects in Primary Series Cohort 1 and Cohort 2, and D42 for subjects in Primary Series Cohort 1; M12 and M12+D14 for the Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for the Immunogenicity Persistence and Booster Phase Cohort 2

9.2.2.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 9.1.2.2.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 Observational Endpoints and Assessment Methods

There are no observational objectives in this study.

10 Reporting of Serious Adverse Events

To comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product(s). It is the responsibility of the Investigator to request all necessary documentation (eg, medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The Investigator (licensed physician [MD or DO]) must validate the information entered on the AE CRF by completing the Investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form as well as the appropriate Safety Complementary Information

CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the Global Clinical Development Strategy Expert (GCDSE) with relevant SAE information details.

If the EDC system is unavailable, the site must notify the Sponsor, using the paper version of the CRB, as described in the Operating Guidelines.

The Investigator must complete the paper copies of the AE CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by one of the following means:

- In PDF format to the following e-mail address, using a method of transmission that includes password protection: CL-CPV-Receipt@sanofi.com
- Fax: +33 (0) 1 60 49 70 70

When the EDC system becomes available, the Investigator must transcribe the information from the paper forms into the EDC system.

If there is a need for urgent consultation, the Investigator is to contact the RMO. If the RMO cannot be reached, the Investigator may contact the Call Center as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (eg, outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the AE CRF and the appropriate Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPV Department and the CRA. Copies of documents (eg, medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the subject must always be respected when forwarding this information.

10.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Any SAE that occurs after a subject has completed the study but that is likely to be related to the investigational product(s), other products (eg, a benefit vaccine), or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

The causal relationship between the SAE and the product administered will be evaluated by the Investigator as described in Section 9.2.1.3.5.

Following this, the Sponsor's GSO will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The causal relationship to study procedures will be also assessed in the CRB.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

The Sponsor's RMO will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators will be responsible for informing the IECs or IRBs that reviewed the study protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual DCs, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study subjects for the recording of daily safety information as described in Section 9.2.1.3. These DCs will include pre-listed terms and intensity scales (see Table 9.1 to Table 9.5) as well as areas for free text to capture additional safety information or other relevant details. Subjects or subjects' parents/legally acceptable representatives will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects or subjects' parents/legally acceptable representatives on how to correctly use these tools.

The 6-month safety follow-up will be done by interviewing subjects either during a visit or over the telephone using a questionnaire to capture SAEs and AESIs, if applicable. A MA/DC SAE may be provided to the subjects or subjects' parents/LAR at the preceding study visit to help them record information on events occurring between this visit and the 6-month follow-up.

Relevant information will be transcribed into the AE CRF. Any SAEs captured during this 6-month follow-up period will be reported and followed up as per the normal process for reporting SAEs. For periods between the 6-month safety follow-up and the next booster vaccination, the relevant information will be collected as described in Tables of Study Procedures and Visit Procedures (see Section 5.1.4).

At specified intervals, the blinded Investigator or an authorized designee will interview the subjects or subjects' parents/legally acceptable representatives to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the DC will 1st be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of the Sponsor, using a validated electronic records/ electronic signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRBs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in study personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any study personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trial will be initiated in the EDC system at the time of the 1st data entry to track all modifications and ensure database integrity.

The Investigator is responsible for the timeliness, completeness, and accuracy of the information in the CRBs; must provide explanations for all missing information; and must sign the CRB using an e-signature.

11.2 Data Management

Management of SAE and Pregnancy Data

During the study, SAE data (reported on the AE, Death, and Safety Complementary Information CRFs) and pregnancy data (reported by the Investigator on ePregnancy Forms) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the GSO and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information from the GPV database cases will be reconciled with that in the clinical database.

Management of Clinical and Laboratory Data

Clinical data, defined as all data reported in the CRB, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.

During the study, clinical data reported in the CRBs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and/ or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical data will be submitted to the Investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

The validation of the immunogenicity data will be performed at the laboratory level following the laboratory's procedures. Information from the laboratory will be checked for consistency before integration into the clinical Datawarehouse.

After integration of all corrections in the complete set of data, and after the SAE information available from CDM and the GPV Department has been reconciled, the database will be released for statistical analysis.

11.3 Data Review

A blind review of the data is anticipated through the data review process led by Data Management before database lock.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

The statistical analysis will be performed under the responsibility of the Sponsor's Biostatistics platform with the SAS software, at least version 9.4 (SAS Institute, Cary, North Carolina, USA).

More details of the study objectives, statistical hypotheses, and success criteria will be provided in the statistical analysis plan (SAP), where applicable.

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 Hypotheses

In each age group of Primary Series Cohort 1, the immunogenicity of VRVg-2 will be compared to that of Verorab and Imovax Rabies vaccines at D42, ie, 14 days after the 3rd vaccine injection, using NI testing. For each comparison, the primary parameter will be the difference in the proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 between the 2 compared vaccine groups. The hypotheses tested will be the following:

H_0: $P_{VRVg\text{-}2}$-$P_{control} \leq -5\%$

H_1: $P_{VRVg\text{-}2}$-$P_{control} > -5\%$

With P = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 (%).

VRVg-2 will be considered as non-inferior to the tested control if the hypothesis H_0 is rejected.

12.1.1.2 Statistical Methods

For the NI hypotheses testing, the statistical methodology will be based on the use of the two-sided 95% CI of the difference of proportions of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 between the vaccine groups. The 95% CI for differences will be calculated using the Wilson score method without continuity correction (66).

NI will be demonstrated if the lower limit of the 95% CI of the difference of the 2 proportions P_{VRVg-2}-$P_{control}$ is > -5%.

The primary objective of NI will be demonstrated if each of the NI between VRVg-2 and both Verorab and Imovax Rabies vaccines is demonstrated in each age group, respectively, in Primary Series Cohort 1.

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Hypotheses

The secondary hypotheses testing will be considered only if the primary objective is met, and then the secondary objectives will be evaluated sequentially following a fixed-sequence method as specified below (67) (68) (69).

- **Superiority in the VRVg-2 group at D42**

Only if the primary objective is achieved at D42, the 1st secondary objective will be assessed on overall subjects from the VRVg-2 group in Primary Series Cohort 1, and this objective will be reached if the observed proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 is higher than or equal to 99% and if the following H_0 hypothesis is rejected.

H_0: $P_{VRVg-2} < 97\%$

H_1: $P_{VRVg-2} \geq 97\%$

With P = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 (%).

- **NI testing of 2-dose VRVg-2 versus 2-dose Verorab and Imovax Rabies at D28**

Only if the 1st secondary objective is achieved at D42, the 2nd secondary NI objective at D28 will be assessed on each age group of pooled Primary Series Cohort 1 and Cohort 2. The immunogenicity of VRVg-2 will be compared to that of Verorab and Imovax Rabies vaccines at D28, ie, 21 days after the 2nd vaccine injection, using NI testing. For each comparison, the primary parameter will be the difference in the proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 between the 2 compared vaccine groups. The hypotheses tested will be the following:

H_0: P_{VRVg-2}-$P_{control} \leq -5\%$

H_1: P_{VRVg-2}-$P_{control} > -5\%$

With P= proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 (%).

- **NI testing of 2-dose VRVg-2 at D28 versus 3-dose Imovax Rabies at D42**

Only if the 2nd secondary objective is achieved, then the following NI hypotheses will be tested in each age group (Pediatric subjects: Cohort 1; Adult subjects: pooled Cohort 1 and Cohort 2), respectively:

Pediatric subjects (Cohort 1 only):

H_0: $P_{VRVg-2 \text{ at D28 (Group 1)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} \leq -10\%$

H_1: $P_{VRVg\text{-}2 \text{ at D28 (Group 1)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} > -10\%$

Adult subjects (Cohorts 1 and 2):

H_0: $P_{VRVg\text{-}2 \text{ at D28 (Groups 1+4)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} \leq -10\%$

H_1: $P_{VRVg\text{-}2 \text{ at D28 (Groups 1+4)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} > -10\%$

With $P_{VRVg\text{-}2 \text{ at D28}}$ = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 for VRVg-2 (%), and $P_{Imovax \text{ Rabies at D42}}$ = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 for Imovax Rabies (%).

- **Superiority in the 2-dose VRVg-2 group at D28**

Only if the 3rd secondary NI objective is achieved, the 4th secondary superiority objective at D28 will be assessed on overall subjects from the VRVg-2 group in pooled Primary Series Cohort 1 and Cohort 2, and this objective will be reached if the observed proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 is higher than or equal to 99% and if the following H_0 hypothesis is rejected:

H_0: $P_{VRVg\text{-}2} < 97\%$

H_1: $P_{VRVg\text{-}2} \geq 97\%$

With P= proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 (%).

- **NI testing of 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42**

Only if the 4th secondary objective is achieved, then the 5th secondary NI objective will be tested with the following hypotheses in Imovax Rabies group in overall subjects (pooled pediatric and adult subjects) in Cohort 1 only:

H_0: $P_{Imovax \text{ Rabies at D28 (Group 3)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} \leq -10\%$

H_1: $P_{Imovax \text{ Rabies at D28 (Group 3)}} - P_{Imovax \text{ Rabies at D42 (Group 3)}} > -10\%$

With $P_{Imovax \text{ Rabies at D28}}$ = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 for Imovax Rabies in Cohort 1 (%), and $P_{Imovax \text{ Rabies at D42}}$ = proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42 for Imovax Rabies in Cohort 1 (%).

12.1.2.2 Statistical Methods

- **Superiority in the VRVg-2 group at D42**

Only if the primary objective is achieved at D42, the superiority testing will be assessed on overall subjects from VRVg-2 group in Primary Series Cohort 1, and will be demonstrated if the overall observed proportion of subjects in VRVg-2 group in Cohort 1 with an RVNA titer ≥ 0.5 IU/mL at D42 is at least 99.0%, with the lower limit of the 95% CI of the proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D42, calculated using the exact binomial distribution (Clopper Pearson method) (70), is higher than or equal to 97%.

- **NI testing of 2-dose VRVg-2 versus 2-dose Verorab and Imovax Rabies at D28**

Only if the 1st secondary superiority objective in the VRVg-2 group at D42 is achieved, based on

the same approach as the primary objective testing, the NI of VRVg-2 compared to each of the controls will be tested at D28 in each age group in pooled Primary Series Cohort 1 and Cohort 2 subjects, based on the use of the two-sided 95% CI of the difference of proportions at D28, calculated using the Wilson score method without continuity correction (66). The secondary immunogenicity objective of NI at D28 will be demonstrated if each of the non-inferiority between VRVg-2 and both Verorab and Imovax Rabies vaccines is demonstrated in each age group, respectively, in pooled Primary Series Cohort 1 and Cohort 2.

- **NI testing of 2-dose VRVg-2 at D28 versus 3-dose Imovax Rabies at D42**

NI will be demonstrated for each hypothesis if the lower limit of the 95% CI of the difference of the 2 proportions ($P_{VRVg\text{-}2\ at\ D28}$ -$P_{Imovax\ Rabies\ at\ D42}$) is > -10%, with a similar approach as the testing for primary objective.

The 3rd secondary immunogenicity objective will be demonstrated if all null hypotheses are rejected.

- **Superiority in the VRVg-2 group at D28**

Only if the 3rd secondary objective is achieved, based on the same approach as the secondary superiority objective testing at D42, the superiority of VRVg-2 group at D28 will be assessed on overall subjects from VRVg-2 group in pooled Primary Series Cohort 1 and Cohort 2, and the superiority objective at D28 will be demonstrated if the overall observed proportion of subjects in VRVg-2 group in pooled Cohort 1 and Cohort 2 with an RVNA titer ≥ 0.5 IU/mL at D28 is at least 99.0%, with lower limit of the 95% CI of the proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28, calculated using the exact binomial distribution (Clopper Pearson method) (70), is higher than or equal to 97%.

- **NI testing of 2-dose Imovax Rabies at D28 versus 3-doses Imovax Rabies at D42**

The null hypothesis will be rejected, and this objective will be achieved if the lower limit of the two-sided 95% CI of the difference of the 2 proportions ($P_{Imovax\ Rabies\ at\ D28}$ -$P_{Imovax\ Rabies\ at\ D42}$) is > -10%, which will be calculated using a generalized linear model (GLM) for repeated measured data with categorical response under binomial distribution (link function=identity) (71).

- **Other secondary immunogenicity and safety objectives**

All other secondary endpoints will be described by age group and vaccine group using descriptive statistical methods without hypothesis testing, as follows.

Immunogenicity Endpoints

The analysis of RVNA titers after vaccination series will be done per age group and vaccine group, using the endpoints defined in Section 9.1.2.1. The analysis of booster results will be done overall and according to the vaccine received in the primary series.

Assuming that $\log_{10}$ transformation of the titers/ratios follows a normal distribution, at first, the mean and 95% CI will be calculated on $\log_{10}$ (titers/ratios) using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, in order to provide GMTs/GMTRs and their 95% CIs.

The exact binomial distribution for percentages (Clopper Pearson's method), quoted by Newcombe (70) will be used for the single proportions.

Reverse Cumulative Distribution Curves will be plotted in all vaccine groups at D0, D28 for subjects in Primary Series Cohort 1 and Cohort 2, and at D42 for subjects in Primary Series Cohort 1; at M12, M12+D14 for subjects in Booster Phase Cohort 1; at M6, M12, M18, between M24 up to M36, and between M24 up to M36+D14 for subjects in Immunogenicity Persistence and Booster Phase Cohort 2.

Safety Endpoints

The safety analysis will report the occurrence of solicited reactions and the incidence of unsolicited AEs, including SAEs and AESIs, over the safety observation period by age group and vaccine group. Injection site reactions will be collected up to 7 days after each injection, systemic AEs will be collected between each vaccination and up to 28 days after the last injection. The following AEs will be considered as AESIs: anaphylactic reactions, encephalitis and convulsions. In order to avoid any under-estimation of the incidences, the number of subjects with documented safety will be used as the denominator of the frequencies.

For safety parameters, 95% CIs of point estimates of proportion will be calculated using the exact binomial distribution (Clopper Pearson method) for proportions (70).

12.1.3 Exploratory Analyses

With the aim to provide the same standards and granularity in terms of investigational results across VRVg studies, and comply with health authorities requirements (72), the possible influence of several covariates on the safety and immunogenicity results will be studied using descriptive statistics. Thus, the main immunogenicity and safety parameters will be described according to gender, age group (1 year to < 12 years and ≥ 12 years for children; and 18 to 40 years, 41 to < 65 years, and ≥ 65 years for adults), ethnicity (only if more than 5% of subjects had different ethnicity), race (only if more than 5% of subjects had different race), and center. Race and ethnicity will be defined according to current guidelines (72).

Other analyses will be defined in the SAP, if applicable.

12.2 Analysis Sets

12.2.1 Full Analysis Set

The FAS is defined as the subset of randomized subjects who received at least 1 dose of the study vaccines in the primary series.

The Full Analysis Set for Immunogenicity (FASI) is defined as a subset of the FAS, including all subjects from FAS who have a baseline titer lower than 0.5 IU/mL.

FAS for Immunogenicity Persistence (FASP) is defined as the subset of randomized subjects from Cohort 2 who received a complete primary rabies vaccination series (ie, one week 2-dose PrEP regimen), and have at least one valid post-vaccination serology result at M6, M12, M18 or M24 up to M36.

FASI for Immunogenicity Persistence (FASIP) is defined as the subset of FASP, including all subjects from the FASP with a baseline titer lower than 0.5 IU/mL.

The Full Analysis Set for Booster at M12 (FASB1) is defined as the subset of subjects who received the booster dose at M12, after a complete primary rabies vaccination series (ie, 3-dose pre-exposure regimen) in Cohort 1.

The Full Analysis Set for Booster at M24 up to M36 (FASB2) is defined as the subset of subjects who received the booster dose between M24 up to M36, after a complete primary rabies vaccination series (ie, one week 2-dose pre-exposure regimen) in Cohort 2.

The Full Analysis Set for Immunogenicity for Booster at M12 (FASIB1) is defined as the subset of FASB1, including all subjects from FASB1 who have a baseline titer lower than 0.5 IU/mL.

The Full Analysis Set for Immunogenicity for Booster at M24 up to M36 (FASIB2) is defined as the subset of FASB2, including all subjects from FASB2 who have a baseline titer lower than 0.5 IU/mL.

The analysis of immunogenicity addresses endpoints involving pre- and post-injection titers. The analysis will include all available data for each time point.

12.2.2 Safety Analysis Set

The Safety Analysis Set (SafAS) is defined for each dose as the subset of subjects having received this dose. All subjects will have their safety analyzed after each dose according to the vaccine they actually received and for the primary series, and after any dose according to the vaccine received at the first dose.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately). Thus, if a subject does not receive any vaccine at a given visit or if the vaccine received does not correspond to any protocol group at a specific dose, the subject is excluded from the SafAS at this dose; however, the subject will be included in the analysis for all doses combined (referred to as analysis “after any dose”) according to the 1st dose received that corresponds to a protocol group.

The Safey Analysis Set for booster (SafASB) is defined as the subset of subjects who received the booster dose (VRVg-2 vaccine). The corresponding vaccination group will be determined by the actual vaccination group in the Primary Series Cohort 1 (Groups 1, 2, and 3) or Cohort 2 (Groups 4, 5, and 6).

12.2.3 Per-Protocol Analysis Set

The PPAS is defined for each key objective. Adherence to the definition of the PPAS may also be decided during the blinded data review, ie, before breaking the code and locking the database.

12.2.3.1 Per-Protocol Analysis Set for D42

The PPAS for D42 is a subset of the FAS which will be used for primary objective assessment at D42 (V04) for subjects in Primary Series Cohort 1. The subjects presenting with at least one of the following relevant protocol deviations before D42 (ie, 14 days after the 3rd vaccine injection) will be excluded from the PPAS for D42:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the 3-dose vaccination schedule
- Subject received a vaccine other than the one that he/ she was randomized to receive
- Preparation and/ or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
  - Vaccination Dose 2 in [D07-D09]
  - Vaccination Dose 3 in [D25-D31]
- Subject did not provide post-dose 3 serology sample at V04 in the proper time window [D11, D17] post the third vaccination (ie, VAC3 +14D ±3D) or a post-dose 3 serology sample was not drawn at V04
- Subject received a protocol-prohibited therapy/medication/vaccine (belonging to categories 2 and 3) before V04 (D42)
- Subject's serology sample is missing or did not produce valid test results at D0 or D42
- Seropositive subject at D0, ie, RVNA titer ≥ LLOQ
- Subject developed a protocol-specified withdrawal criterion during the study but was not withdrawn before V04 (D42)

12.2.3.2 Per-Protocol Analysis Set for D28

The PPAS for D28 is also subset of the FAS, which will be used for secondary NI objective evaluation at D28 (V03) for subjects in Primary Series Cohort 1 and Cohort 2. The subjects presenting with at least one of the following relevant protocol deviations before D28 (ie, 21 days after the 2nd vaccine injection) will be excluded from the PPAS for D28:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the 2-dose vaccination schedule at D0 (V01) and D7 (V02)
- Subject received a vaccine other than the one that he/ she was randomized to receive at the 1st 2 doses
- Preparation and/or administration of vaccine was not done as per-protocol at D0 (V01) and D7 (V02)
- Subject did not receive 2nd vaccine injection in the proper time window
  - Vaccination Dose 2 in [D07-D09]
- Subject did not provide post-dose 2 serology sample at V03 in the proper time window [D25-D31] or a post-dose 2 serology sample was not drawn at V03

- Subject received a protocol-prohibited therapy/medication/vaccine (belonging to categories 2 and 3) before V03 (D28)
- Subject's serology sample is missing or did not produce valid test results at D0 or D28
- Seropositive subject at D0, ie, RVNA titer ≥ LLOQ
- Subject developed a protocol-specified withdrawal criterion during the study but was not withdrawn before V03 (D28)

12.2.3.3 Per-Protocol Analysis Set for Booster at M12

The PPAS for Booster at M12 (V07) is a subset of the FASB1, which will be used for evaluation of immunogenicity objective in the booster phase of Cohort 1, for a subset of adults who received a 3 doses regimen and received a single booster dose of VRVg-2 one year after the first vaccination of the primary series (ie, at M12). The adult subjects in Booster Phase Cohort 1, presenting with at least one of the following relevant protocol deviations before M12+D14 (ie, 14 days after the booster dose injection) will be excluded from the PPAS for Booster at M12:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject received a vaccine other than the one that he/ she was randomized to receive in either primary series or booster phase
- Preparation and/ or administration of vaccine was not done as per-protocol in either primary series or booster phase
- Subject did not receive booster vaccine in the proper time window at V06
  - Vaccination 4 in [M12, M12 +14D] after Vaccination Dose 1
- Subject did not provide post-booster dose serology sample at V07 in the proper time window [D14, D15] post the booster vaccination (VAC 4) or a post-booster dose serology sample was not drawn at V07
- Subject received a protocol-prohibited therapy/medication/vaccine (belonging to categories 2 and 3) before V07 (M12 + D14)
- Subject's serology sample is missing or did not produce valid test results at V06 (booster vaccination) or V07 (D14 after booster vaccination)
- Seropositive subject at D0, ie, RVNA titer ≥ LLOQ
- Subject developed a protocol-specified withdrawal criterion during the study but was not withdrawn before V07 (M12 + D14)

12.2.3.4 Per-Protocol Analysis Set for Booster at M24 up to M36

The PPAS for Booster at M24 up to M36 (V09) is a subset of the FASB2, which will be used for evaluation of immunogenicity objective in the booster phase for Cohort 2, for a subset adult who received a one week 2-dose regimen in the primary series, and received a single booster dose of

VRVg-2 between 2 up to 3 years after the first vaccination of the primary series (ie, at M24 up to M36). The adult subjects in Immunogenicity Persistence and Booster Phase Cohort 2 presenting with at least one of the following relevant protocol deviations before M24 up to M36+D14 (ie, 14 days after the booster dose injection) will be excluded from the PPAS for Booster at M24 up to M36:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject received a vaccine other than the one that he/ she was randomized to receive in either primary series or booster phase
- Preparation and/ or administration of vaccine was not done as per-protocol in either primary series or booster phase
- Subject did not receive booster vaccine in the proper time window at V08
  - Vaccination 3 in [between M24 up to M36, between M24 up to M36 +14D after Vaccination dose 1]
- Subject did not provide post-booster dose serology sample at V09 in the proper time window [D14, D15] post the booster vaccination (VAC 3), or a post-booster dose serology sample was not drawn at V09 (D14 after booster vaccination)
- Subject received a protocol-prohibited therapy/medication/vaccine (belonging to categories 2 and 3) before V09 (D14 after booster vaccination)
- Subject's serology sample is missing or did not produce valid test results at V08 (booster vaccination) or V09 (D14 after booster vaccination)
- Seropositive subject at D0, ie, RVNA titer ≥ LLOQ
- Subject developed a protocol-specified withdrawal criterion during the study but was not withdrawn before V09 (D14 after booster vaccination)

12.2.4 Other Analysis Set(s)

Other analysis sets will be defined in the SAP, if applicable.

12.2.5 Populations Used in Analyses

For the primary and key secondary immunogenicity objectives with hypothesis testing, the analyses will be performed on the PPAS primarily, and then on the FASI / FAS as supplementary analysis, if necessary. The subjects will be analyzed by the vaccine group to which they were randomized in the primary series.

The safety analysis will be performed on the SafAS, and the subjects will be analyzed according to the vaccine they actually received in the primary series.

More detail for the analysis populations will be defined in the SAP, if necessary.

The safety analysis for booster phase will be performed on the SafASB, and the subjects will be analyzed according to the vaccine they actually received in the first dose in primary series.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done as it is expected that the degree of missing safety data will be very low.

Missing data in vaccine studies are mostly due to dropouts. The dropouts due to AEs or lost to follow-up subjects will be identified and discussed in the study report.

12.3.2 Immunogenicity

No replacement will be done as it is expected that the degree of missing safety data will be very low.

No test or search for outliers will be performed.

12.4 Interim / Preliminary Analysis

The statistical analysis will be performed in 4 steps:

- The 1st statistical analysis will be done once all immunogenicity data up to D28 (V03, 21 days after the 2nd vaccination) in the primary series of Cohort 2 and all safety data up to D35 (V04, 28 days after the 2nd vaccination) in the primary series of Cohort 2 are available (ie, at the end of 6-month safety follow-up after booster phase in Cohort 1; and up to D35 [V04] in primary series in Cohort 2). The randomization and vaccination exposure information for all enrolled subjects will be unblinded at the time of 1st statistical analysis.
- The 2nd statistical analysis will be carried out once the 12-month immunogenicity persistence data and safety data in Cohort 2 (V06) are collected.
- The 3rd statistical analysis will be carried out once all the immunogenicity and safety data up to 28 days after the booster vaccination in Cohort 2 (V10) are collected.
- The 4th statistical analysis will be carried out once the 6-month safety follow-up data post the booster vaccination in Cohort 2 (M30 up to M42) are collected.

No statistical adjustment is necessary because there are no repeat analyses of the same parameter.

12.5 Determination of Sample Size and Power Calculation

12.5.1 Primary Series

Original Plan for Cohort 1:

An alpha level of 2.5% (one-sided hypothesis), has been chosen to calculate the sample size.

Originally, assuming a proportion of subjects with an RVNA titer ≥ 0.5 IU/mL of 99% for both VRVg-2 and control vaccines in each age group at D42, a clinical acceptable difference of -5% for the difference of proportions at D42 betweenVRVg-2 and the control vaccines, and a power of

at least 95% for each of the NI testing in the primary objective, with and an unbalanced randomization ratio of 3:1:1 (VRVg-2: Verorab vaccine: Imovax Rabies vaccine), 258 evaluable subjects in the VRVg-2 group, and 86 evaluable subjects in each of the Verorab and Imovax Rabies vaccine groups who are planned to receive 3 vaccinations (at D0, D7 and D28) in primary series in each age group, will be necessary to provide a global power of 81.8% for the primary NI objective, using the Farrington and Manning (FM) method.

If the primary objective is met at D42, a total of 516 subjects evaluable in the VRVg-2 group will ensure 85.0% of power for the 1st secondary immunogenicity objective of superiority at D42. If the 1st secondary immunogenicity objective is met, overall power for the 2nd secondary immunogenicity NI objective of 2-dose VRVg-2 at D28 versus 2-dose comparator vaccines at D28 will be higher than 80%.

Under the assumption that 15% of subjects will not be evaluable in the PPAS, 303 subjects in the VRVg-2 group and 101 subjects in each of the Verorab and Imovax Rabies vaccine groups must be enrolled in each age group of the study per the original plan, as Primary Series Cohort 1.

Updated Plan for Cohort 1 and Cohort 2 (Protocol Amendments 2, 3, and 4):

According to the latest results from the VAJ00001 study and to be conservative, the estimation of proportion of adult subjects with an RVNA titer ≥ 0.5 IU/mL at D28 was adjusted from 99% to 96.5% for both VRVg-2 and control vaccines. With the aim to secure the study power for the 2nd secondary immunogenicity NI objective at D28 and maintain the randomization ratio, 609 evaluable adults in the VRVg-2 group, and 203 evaluable adults in each of the control vaccine group (Verorab and Imovax Rabies) will be necessary to provide a power of 81.7% to demonstrate the 2nd secondary immunogenicity objective at D28, using the FM method.

If the 2nd secondary immunogenicity objective is met at D28, a total of 867 subjects evaluable in the VRVg-2 group will ensure 99.2% of power for the secondary objective of superiority for VRVg-2 at D28 in the overall subjects (pooled pediatric and adult subjects).

Therefore, under the attrition rate of 15%, 690 additional adults (414 in VRVg-2; 138 in Verorab; 138 in Imovax Rabies) were planned to be enrolled in the study as Cohort 2 to receive 2 vaccinations at D0 and D7 in the primary series. Those 690 additional adults in Cohort 2 were planned to be pooled with the 505 adults enrolled in Cohort 1, for testing the 2nd secondary NI objective at D28. The 414 additional adults in VRVg-2 group in Cohort 2 were planned to be pooled with the 303 pediatric subjects and 303 adult subjects in VRVg-2 group in Cohort 1, for testing the secondary superiority objective for VRVg-2 at D28.

Therefore, a total of 1700 subjects (505 pediatric subjects and 1195 adult subjects) were planned to be enrolled in total by 2 Cohorts, including 505 pediatric subjects and 505 adult subjects in Cohort 1 who are planned to receive 3 doses of vaccinations in the primary series, and 690 adult subjects in Cohort 2 who were planned to receive 2 doses of vaccinations in the primary series.

As a consequence, a total of 1708 subjects (505 pediatric subjects and 1203 adult subjects) were actually enrolled, including 505 pediatric subjects and 505 adult subjects in Primary Series Cohort 1 and 698 adult subjects (including 8 replacements) in Cohort 2.

The 3:1:1 design is chosen to optimize the NI testing for immunogenicity and to increase the size of the safety database.

Updated power estimations with additional objectives (Protocol Amendment 5):

Based on live blinded data observed from Cohort 1, the estimated attrition rate of Cohort 1 was adjusted from 15% to about 13.5% at both D28 and D42 for pediatric subjects, and adjusted to about 21.0% at D28 and 19.8% at D42 for adult subjects, respectively. Assuming the actual attrition rate of adult subjects in Cohort 2 is similar to Cohort 1, the adjusted estimations for evaluable number of subjects in the PPAS in each age group are as below:

- Pediatric subjects (Cohort 1 only): at both D28 and D42, there will be about 261 and 88 evaluable subjects in VRVg-2 group and each of the comparator vaccine groups, respectively.
- Adult subjects: at D28, there will be about 570 and 190 evaluable subjects in VRVg-2 group and each of the comparator vaccine groups, respectively (pooled Cohort 1 and Cohort 2); at D42, there will be about 243 and 81 evaluable subjects in VRVg-2 group and each of the comparator vaccine groups, respectively (Cohort 1 only).

Moreover, 2 new secondary immunogenicity objectives were added, both with a NI margin of 10%:

- To demonstrate the NI of 2-dose VRVg-2 at D28 versus 3-dose Imovax Rabies at D42 in each age group
- To demonstrate the NI of 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42 in the overall subjects (pooled pediatric and adult subjects) in Cohort 1

Finally, the primary objective and all 5 key secondary immunogenicity objectives will be evaluated sequentially. Each of the key immunogenicity objective will be tested only if the previous objective is achieved.

Based on the updated study objectives and the adjusted number of evaluable subjects in the PPAS, the power to demonstrate each of the key immunogenicity objectives is presented Table 12.1.

Table 12.1: Sample size and power estimation for primary and key secondary immunogenicity objectives.

Key Immunogenicity Objective	Age group	Evaluable N in the PPAS	Estimation/Margin	Power (%)
Primary Objective	Pediatric Subjects (Cohort[C] 1)	VRVg-2: 261 Verorab: 88	Seroconversion (SC) rate at D42: 99.0% NI margin: -5%	95.4[a]
		VRVg-2: 261 Imovax Rabies: 88	Same as above	95.4 [a]
	Adult Subjects (C1)	VRVg-2: 243 Verorab: 81	Same as above	93.8 [a]
		VRVg-2: 243 Imovax Rabies: 81	Same as above	93.8 [a]
				Overall: 80.0 [a]
Key Secondary Objectives				
#1	Overall (Pooled Pediatric and Adult Subjects in C1)	VRVg-2: 504	Sufficiency threshold: SC rate at D42 ≥99.0%, with lower limit (LL) of 95%CI ≥97.0%	**86.3 [b]**
#2	Pediatric Subjects (C1)	VRVg-2: 261 Verorab: 88	SC rate at D28: 99.0% NI margin: -5%	95.4 [a]
		VRVg-2: 261 Imovax Rabies: 88	Same as above	95.4 [a]
	Adult Subjects (Pooled C1+C2)	VRVg-2: 570 Verorab: 190	SC rate at D28: 96.5% NI margin: -5%	93.8 [a]
		VRVg-2: 570 Imovax Rabies: 190	Same as above	93.8 [a]
				Overall: 80.1 [a]
#3	Pediatric Subjects (C1)	VRVg-2 at D28: 261 Imovax Rabies at D42: 88	SC rate at D28: 99.0% SC rate at D42: 99.0% NI margin: -10%	>99.9 [a]
	Adult Subjects (D28 from Pooled C1+C2, D42 from C1)	VRVg-2 at D28 (Pooled Cohort 1+ Cohort 2): 570 Imovax Rabies at D42: 81	SC rate at D28: 96.5% SC rate at D42: 99.0%NI margin: -10%	>99.9 [a]
				Overall: >99.9 [a]
#4	Overall (Pooled Pediatric and Adult Subjects in Pooled C1 and C2)	VRVg-2: 831	Sufficiency threshold: SC rate at D42 ≥99.0%, with LL of 95%CI ≥97.0%	**98.9 [b]**
#5	Overall (Pooled Pediatric and Adult Subjects in C1 only)	Imovax Rabies at D28: 168 Imovax Rabies at D42: 168	SC rate at D28: 96.5% SC rate at D42: 99.0% NI margin: -10%	**90.0 [c]**

a Power calculated using Farrington and Manning (FM) method.

b Power calculated using Binomial Exact method.

c Power calculated using simulation (10000 times, assuming correction coefficient [Rho]=0.5), based on general linear model (GLM) for repeated measured data with categorical response under binomial distribution (link function=identify).

12.5.2 Booster Phase

A subset of 170 adults in Primary Series Cohort 1 who received the 3-dose PrEP regimen in the primary series will be included in the booster phase in M12 of the study; having 102 subjects receiving the complete 3 doses regimen schedule with VRVg-2 (primary series + booster) and 170 subjects receiving VRVg-2 as a booster (regardless the vaccine received in the primary series) in the FASB will provide the following level of precision around the expected percentage of subjects with an RVNA titer ≥ 0.5 IU/mL at D14 after the booster vaccination at M12:

Number of subjects with RVNA titer ≥ 0.5 IU/mL on M12+D14	**FASB1 – VRVg-2 group (N=102)**		**Number of subjects with RVNA titer ≥ 0.5 IU/mL on M12+D14**	**FASB1 (N=170)**	
	% observed	**95% CI**		**% observed**	**95% CI**
102	100.0	(96.45 – 100)	**170**	100.0	(97.85 – 100)
101	99.0	(94.66 – 99.98)	**169**	99.4	(96.77 – 99.99)
100	98.0	(93.1 – 99.76)	**168**	98.8	(95.81 – 99.86)
99	97.1	(91.64 – 99.39)	**167**	98.2	(94.93 – 99.63)
98	96.1	(90.26 – 98.92)	**166**	97.6	(94.09 – 99.36)

Note: The 95% CI for the single proportion is calculated using the exact binomial method (Clopper Pearson method), quoted by Newcombe (70).

A subset of 230 adults who received the one week 2-dose PrEP regimen will be included in the Immunogenicity Persistence and Booster Phase Cohort 2. Assuming approximate 15% of subjects will not be evaluable in the FASB for booster evaluation at M24 up to M36, having 117 evaluable subjects receiving the complete 2 doses regimen schedule with VRVg-2 (primary series + booster) and 195 evaluable subjects receiving VRVg-2 as a booster (regardless the vaccine received in the primary series) will provide the following level of precision around the expected percentage of subjects with an RVNA titer ≥ 0.5 IU/mL at D14 after the booster vaccination at M24 up to M36:

Number of subjects with RVNA titer ≥ 0.5 IU/mL on M24 up to M36+D14	FASB2 – VRVg-2 group (N=117)		Number of subjects with RVNA titer ≥ 0.5 IU/mL on M24 up to M36+D14	FASB2 (N=195)	
	% observed	95% CI		% observed	95% CI
117	100.00	(96.90; 100)	**195**	100.00	(98.13; 100)
116	99.15	(95.33; 99.98)	**194**	99.49	(97.18; 99.99)
115	98.29	(93.96; 99.79)	**193**	98.97	(96.34; 99.88)
114	97.44	(92.69; 99.47)	**192**	98.46	(95.57; 99.68)
113	96.58	(91.48; 99.06)	**191**	97.95	(94.83; 99.44)

Note: The 95% CI for the single proportion is calculated using the exact binomial method (Clopper Pearson method), quoted by Newcombe (70).

13 Ethical and Legal Issues and Investigator/ Sponsor Responsibilities

13.1 Ethical Conduct of the Study/ Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and/ or national regulations and directives.

13.2 Source Data and Source Documents

“Source data” are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, DCs, medical and hospital records, informed consent/ AFs, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a DC, the blinded study coordinator will obtain verbal clarification from the subject, enter the response into the “Investigator’s comment” page of the DC, and transfer the information to the CRB.

The subject pre-screening log should list all individuals contacted by the Investigators to participate in the study, regardless of the outcome.

13.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a subject's medical records are not at the investigational site, it is the responsibility of the Investigator to obtain those records if needed.

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the Global Data Protection Regulation. Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subject's race and ethnicity will be collected in this study because these data are required by regulatory agencies (72) (see Section 12.1.3).

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the study (ie, before the inclusion of the 1st subject), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the site; and that the study Investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study Investigator team and the CRAs on these topics may be performed as necessary and should be documented.

The following instruction manuals will be provided: the CRF Completion Instructions for entering data into the CRB, and the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

After the start of the study, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits and must allow the Sponsor/delegate staff direct access to subject medical files and CRBs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold chain monitoring, archiving).
- Source-verify completed CRBs and any corresponding answered queries.
- Determine the number of complete or ongoing issues identified at monitoring visits (eg, protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the study, a close-out visit will be performed to ensure that:

- The center has all the documents necessary for archiving
- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical Quality Assessment department (CQA) or by independent auditors to verify that the study has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to study documents during these inspections and audits.

13.4.3 Archiving

The Investigator and the study site shall retain and preserve 1 copy of the Study File containing the essential documents related to the study and records generated during the study ("Study File") for the longer of the 2 following periods ("Retention Period"):

- 25 years after the signature of the final study report or
- Such longer period as required by applicable regulatory requirements

If during the Retention Period, the study site is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), the study site shall contact the Sponsor to organize the transfer of the Study File to the Sponsor's designee at the Sponsor's expense. Following the Retention Period, the Investigator and/or the study site are responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the study will be kept by the Sponsor in the TMF. Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A Clinical Study Agreement will be signed by all the parties involved in the study's performance, if relevant. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and/ or the study protocol.

13.6 Stipends for Participation

Expenses that are directly related to the subject's participation in the study (for example cost of transportation for attending visits) will be compensated. Subjects/parents/legal representatives will not receive any remuneration for participation in the study.

13.7 Publication Policy

Data derived from this study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

Sanofi Pasteur must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study at least 90 days prior to submission for publication / presentation. Any information identified by Sanofi Pasteur as confidential must be deleted prior to submission, it being understood that the results of this study are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

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