NCT03965962

Immunogenicity and Safety of a Purified Vero Rabies Vaccine – Serum Free in Comparison with Verorab® and Imovax® Rabies, in a Simulated Rabies Post-exposure Regimen in Healthy Adults in France

Multi-center, modified double-blind (Groups 1 to 3)/open (Group 4), controlled, randomized, Phase III study in 636 subjects aged ≥ 18 years. Subjects will receive 5 vaccine injections of either VRVg-2 (Groups 1 and 4), Verorab vaccine (Group 2), or Imovax Rabies vaccine (Group 3), at day [D] 0, D3, D7, D14, and D28 (ESSEN regimen). All groups with the exception of Group 4 will additionally receive human rabies immunoglobulin (HRIG) at D0.

Clinical Study Protocol, Amendment 2

Health Authority File Number(s):	BB-IND #: 015026 EudraCT #: 2018-004055-20
WHO Universal Trial Number (UTN):	U1111-1216-6151
Study Code:	VRV13
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur SA 14 Espace Henry Vallée, 69007 Lyon, France
Investigational Product(s):	Purified Vero Rabies Vaccine - Serum Free (VRVg): Purified inactivated rabies vaccine prepared on Vero cell line
Form / Route:	Liquid/Intramuscular
Indication For This Study:	Simulated treatment of rabies after potential exposure treatment
Manufacturer:	Same as Sponsor
Coordinating Investigator	[redacted]
Sponsor's Responsible Medical Officer and Clinical Team Leader	
Global Safety Officer:	

Regional Trial Manager: [redacted]

Version and Date of the Protocol: Version 6.0 dated 27 April 2020

History of Protocol Versions

Version	Date	Comments
1.0	07 December 2018	Submitted but not reviewed*
2.0	10 January 2019	IEC/IRB- and HAs- submitted version version not used in the study
3.0	22 March 2019	IEC/IRB- and HAs- approved version used in the study
4.0	25 September 2019	Superseded by Version 5.0 dated 27 September 2019 due to an administrative change during the development of Amendment 1 Version not submitted and not used in the study
5.0	27 September 2019	IEC/IRB- and HAs- approved version used in the study

Abbreviations: IEC, Independent Ethics Committee; IRB, Institutional Review Board; HAs, Health Authorities
*Technically submitted to US HA, but not reviewed

Table of Contents

List of Tables

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 - 1503 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 Simulated Rabies Post-exposure Regimen in Healthy Adults in France
Development Phase:	Phase III
Coordinating Investigator	[redacted]
Study Sites:	The study will be conducted in 2 centers in France Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Q3 2019 first visit, first subject (FVFS) to Q2 2021 last contact, last subject (LCLS, consisting of a phone call [PC] and not a visit)
Study Design, Schedule of Study Procedures, and Methodology:	Modified double-blind (Groups 1 to 3) and open for Group 4, controlled, randomized, multi-center study. A total of 636 healthy adults (≥ 18 years) are planned to be enrolled. Randomization will be 3:1:1:1 (VRVg-2 + HRIG: Verorab vaccine + HRIG: Imovax Rabies vaccine + HRIG: VRVg-2). Adults: n=636 Group 1: VRVg-2 + HRIG at D0: n=318 Group 2: Verorab vaccine + HRIG at D0: n=106 Group 3: Imovax Rabies vaccine + HRIG at D0: n=106 Group 4: VRVg-2 n=106 <u>Visits (V) and Phone calls (PC)</u> A total of 7 visits (V01-V07) and 1 PC are planned. <u>Vaccination</u> All subjects will receive a total of 5 injections: at D0, D3, D7, D14 and D28 through intramuscular (IM) route. In addition, human rabies immunoglobulins (HRIG) will be concomitantly administered at D0 to subjects randomized to Groups 1 to 3. <u>Blood sampling</u> All subjects will provide 4 blood samples: at D0, prior to the first vaccine injection, at D14 (7 days after the third vaccine injection), at D28 (14 days after the fourth vaccine injection), and at D42 (14 days after the last vaccine injection).

	Collection of safety data Solicited injection site reactions will be recorded in the diary card (DC) in the 7 days after each injection, and unsolicited injection site reactions will be recorded during the 28 days after each injection. Subjects will record information about solicited systemic reactions in a DC between the first and the second injections, between the second and the third injections, and during the 7 days following the remaining injections. Information about unsolicited systemic adverse events (AEs) will be recorded between each injection, and during the 28 days following the last injection. Subjects will record safety information in a memory aid (MA) from D56 (28 days following the last injection) until the end of the trial (month [M] 7). Information about serious adverse events (SAEs), adverse events of special interest (AESIs) and cases of pregnancy will be recorded throughout the trial. Study personnel will contact subjects by telephone at 6 months (+14 days) after the last vaccine injection 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) 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 and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	***Immunogenicity*** To demonstrate that VRVg-2 is non-inferior to Verorab and Imovax Rabies vaccines when co-administered with HRIG, in terms of proportion of subjects achieving a rabies virus neutralizing antibody (RVNA) titer ≥ 0.5 international units/milliliter (IU/mL) at D28, ie, 14 days after the fourth vaccine injection.
Primary Endpoints:	• RVNA titers (IU/mL) measured by the Rapid Fluorescent Focus Inhibition test (RFFIT) at D28: • Subject with an RVNA titer ≥ 0.5 IU/mL at D28
Secondary Objectives:	***Safety*** To describe the safety profile of VRVg-2 versus Verorab and Imovax Rabies vaccines when co-administered with HRIG, as well as that of VRVg-2, after each vaccine injection. ***Immunogenicity*** 1) To demonstrate that the proportion of subjects in the VRVg-2 + HRIG group achieving an RVNA titer ≥ 0.5 IU/mL at D28 is at least 95% 2) To describe the immune response induced by VRVg-2 versus Verorab and Imovax Rabies vaccines when co-administered with HRIG, as well as that induced by VRVg-2, at D14 (7 days after the third injection), at D28 (14 days after the fourth injection), and at D42 (14 days after the last injection).
Secondary Endpoints:	***Safety:*** • Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccine injection

	Collection of injection site reactions:
	• Occurrence of solicited (pre-listed in the subject's DC and electronic case report form [CRF]) injection site reactions occurring within 7 days after each injection
	• Occurrence of unsolicited (spontaneously reported) injection site reactions occurring within 28 days after each injection
	Collection of systemic reactions and AEs:
	• Occurrence of solicited (pre-listed in the subject's DC and CRF) systemic reactions between the first and the second injections as well as between the second and the third injections, and up to 7 days after the remaining injections
	• Occurrence of unsolicited (spontaneously reported) systemic AEs between each injection and up to 28 days after the last injection
	• Occurrence of SAEs and AESIs throughout the trial (until 6 months after last vaccination)
	
	Depending on the item, endpoints could include: 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.
	
	Immunogenicity
	
	• RVNA titers (IU/mL) measured by RFFIT, summarized at the subject/ time point level:
	  • RVNA titers at D0, D14, D28, and D42
	  • Subject with an RVNA titer ≥ 0.5 IU/mL at D0, D14, D28, and D42
	  • Subject with an RVNA titer ≥ LLOQ IU/mL at D0, D14, D28, and D42
	  • Individual RVNA titer ratio: D14/D0, D28/D0, and D42/D0
	• Subject with complete or incomplete neutralization at the starting dilution (1/5) of the RFFIT assay at D0, D14, D28, and D42

Planned Sample Size:	Originally, it was planned to enroll 504 subjects in this study. Following a clinical hold between Friday, 06 September 2019 and Tuesday, 10 September 2019, for the evaluation of a serious adverse event (SAE) as required by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), the sample size of the study had been modified to replace subjects who were to be excluded from the per protocol analysis set (PPAS) due to vaccination outside of the recommended time window and to increase the attrition rate of the study. Consequently 606 subjects were planned to be enrolled. As a consequence of the COVID-19 pandemic lockdown established by the French government, the study was put on hold. Enrollment was paused from the 12th of March 2020 and vaccinations were stopped on the 16th March 2020 for twenty-nine subjects who are expected to be withdrawn and excluded from the PPAS as they will be unable to complete their vaccination schedule as planned in the protocol. The sample size of the study will then be modified to replace these subjects. Now, a minimum of 636 subjects are planned to be enrolled: 318 in the VRVg-2 + HRIG group, and 106 in each of the remaining groups (Verorab vaccine + HRIG, Imovax Rabies vaccine + HRIG, and VRVg-2). One hundred subjects who will be excluded from the PPAS (71 from the first hold, 29 in the COVID-19 context) will be replaced and 1 additional subject will be added to keep the randomization ratio. A maximum dropout rate of 20% is anticipated. In case of any new study hold, withdrawn or out of vaccination time windows subjects might be replaced and sample size might be increased accordingly.
Duration of Participation in the Study:	The duration of each subject's participation in the trial will be approximately 7 months (28 day-vaccination period followed by 6-month safety follow-up period).
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*: quantity sufficient (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:	To be determined

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 1503-3M 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 ≤ 100 mg
	• Diluent:
	  • Water for injection: qs 1 mL

Route:	IM
Batch Number:	To be determined
Other Product:	IMOGAM® Rabies-HT: HRIG
Form:	Liquid/Solution in 2 mL vials
Composition:	• Human rabies immunoglobulins 150 IU/mL The recommended dose in a post-exposure regimen is 20 IU/kg of body weight
Route:	IM in the anterolateral thigh.
Batch Number:	Commercialized product: Imogam Rabies-HT HRIG; batch number to be determined
Inclusion Criteria:	An individual must fulfill all of the following criteria to be eligible for study enrollment: 1) Aged ≥ 18 years on the day of inclusion[a] 2) Informed consent form has been signed and dated by the subject 3) Able to attend all scheduled visits and to comply with all trial procedures 4) Body Mass Index (BMI): 18.5 Kg/m^2 ≤ BMI ≤ 30 Kg/m^2 5) Covered by health insurance

[a] " ≥ 18 years" means from the day of the 18th birthday onwards, with no upper age limit."

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 first vaccination until at least 4 weeks after the last vaccination. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, or surgically sterile. 2) Participation at the time of study enrollment or, planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure 3) Subject who would receive more than 4500 euros as indemnities for his/her participation in biomedical research within the 12 last months, including the indemnities for the present study 4) Subject in the exclusion period of a previous study or subject who refuses to be on the national registry of subjects that participate in biomedical research (ie, "Fichier National des Volontaires pour la Recherche Biomédicale VRB") 5) Receipt of any vaccine in the 4 weeks (28 days) preceding the first trial vaccination or planned receipt of any vaccine prior to Visit 7 6) Previous vaccination against rabies (in pre- or post-exposure regimen) with either the trial vaccines or another vaccine 7) Receipt of immune globulins, blood or blood-derived products in the past 3 months 8) 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) 9) At high risk for rabies exposure during the trial[a] 10) Known systemic hypersensitivity to any of the vaccine or human rabies immunoglobulin components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[b] 11) Self-reported thrombocytopenia, contraindicating intramuscular vaccination 12) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination 13) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily 14) Current alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct of completion.

[a] Such as veterinarians and their staff, animal handlers, rabies researchers, and certain laboratory workers, persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies, people travelling where rabies is enzootic.

[b] The components of VRVg-2 are listed under Investigational Product and in the Investigator's Brochure Section 3.2. The components of Verorab and Imovax Rabies vaccines are listed under Control Products.

	15) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[a] 16) 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 17) Personal history of Guillain-Barré syndrome 18) 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 2 steps. A first statistical analysis will be done once all safety and immunogenicity data collected up to D56, ie, up to 28 days after the last vaccine injection, will be obtained and locked. Then an addendum will be done after the 6-month safety follow-up. The immunogenicity of VRVg-2 + HRIG will be compared to that of Verorab vaccine + HRIG and Imovax Rabies vaccine + HRIG at D28, ie, 14 days after the fourth vaccine injection, using a non-inferiority testing. For each comparison, the primary parameter will be the difference of the proportions 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 (%). VRVg-2 will be considered as non-inferior to the tested control if the hypothesis H_0 is rejected. For the non-inferiority hypotheses, the statistical methodology will be based on the use of the two-sided 95% confidence interval (CI) of the difference of proportions of subjects with an RVNA titer ≥ 0.5 IU/mL at D28. The 95% CI for differences will be calculated using Wilson score method without continuity correction. Each non-inferiority 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%. Overall, non-inferiority will be demonstrated if each of the non-inferiority between VRVg-2 + HRIG and both Verorab vaccine + HRIG and Imovax Rabies vaccine + HRIG is demonstrated. Both the PPAS (as the main analysis for non-inferiority) and the Full Analysis Set for Immunogenicity (FASI) excluding subjects with a D0 titer missing or a titer ≥ 0.5 IU/mL) will be used in the primary analysis. If the primary objective is reached, the following hypotheses will be tested at D28, as part of the secondary objectives:

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

	H_0: $P_{VRVg\text{-}2+HRIG} < 95\%$ H_1: $P_{VRVg\text{-}2+HRIG} \geq 95\%$ This will be demonstrated if 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 95%. All other secondary endpoints will be described by vaccine group using descriptive statistical methods. **Calculation of sample size:** An alpha level of 2.5% (one-sided hypothesis), a maximum acceptable difference of 5% for the proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28, and a power of at least 90% for each of the non-inferiority testing have been chosen to calculate the sample size, in order to ensure an overall power of at least 80% to reach the primary objective. Assuming a proportion of subjects with an RVNA titer ≥ 0.5 IU/mL of 99% for the 3 vaccine groups, and an unbalanced randomization 3:1:1 (VRVg-2 +HRIG: Verorab vaccine + HRIG: Imovax Rabies vaccine + HRIG), 213 subjects in the VRVg-2 + HRIG group and 71 subjects in each of the Verorab vaccine + HRIG and Imovax Rabies vaccine + HRIG groups will be necessary, to provide a power of 80% to test the global null hypothesis, using the Farrington and Manning method. Under the assumption that 20% of subjects will not be evaluable, 267 subjects in the VRVg-2 + HRIG group and 89 subjects in each, the Verorab vaccine + HRIG and the Imovax Rabies vaccine + HRIG groups should be enrolled. As a consequence of the first clinical hold of the study, 71 subjects from the 4 vaccine groups (assumed to be distributed with a distribution close to 36:12:12:12) were identified as to be excluded from the PPAS. With the aim to secure the study power, 60 additional subjects were to be enrolled among the 3 vaccine groups involved in the primary objective assessment, ie, a total of 606 subjects were to be enrolled as follows: 303 in the VRVg-2 + HRIG group and 101 in each of the Verorab vaccine + HRIG and Imovax Rabies vaccine + HRIG groups. As a consequence of the COVID-19 hold, 29 ongoing subjects were identified to be excluded from the PPAS as they were not able to complete their vaccination schedule as planned in the protocol. To maintain the planned study power and the randomization ratio, 30 additional subjects are planned to be enrolled, with a planned final distribution of 318:106:106:106. Assuming a proportion of subjects with an RVNA titer ≥ 0.5 IU/mL of 99% in the VRVg-2 group, this sample size will give more than 93% of power to demonstrate the superiority of this rate to 95%. In order to maintain 3:1:1:1 ratio, the additional arm of subjects receiving VRVg-2 as standalone will include 106 subjects; the results will be descriptive, mainly versus the VRVg-2 + HRIG group. The number of subjects is the same as the 2 controls to facilitate group allocation, and will allow good precision of the results. In case of any new study hold, total sample size might be increased to replace withdrawn or out of vaccination time windows subjects.

Table of Study Procedures

Phase III Trial, 7 Visits, 1 Phone call, 5 Vaccinations, 4 Blood Samples, 7 Months Period per Subject

Visit	V01	V02	V03	V04	V05	V06	V07	Phone Call
Visit interval	VAC1	VAC2= VAC1+3D	VAC3= VAC1+7D	VAC4= VAC1+14D	VAC5= VAC1+28D	VAC5+14D	VAC5+28D	VAC5*+6M
Indicative days (D)/Months (M)	D0	D3	D7 +1D	D14 ±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	√							
Blood sampling for serology (6 mL)	√			√	√	√		
Vaccine injection	√	√	√	√	√			
HRIG administration§	√							
30-minute observation period	√	√	√	√	√			
Diary card (DC) Memory aid (MA) Provided Checked Collected	DC1	DC1	DC1	DC2 DC1 DC1	DC3 DC2 DC2	DC3	MA DC3 DC3	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							

*VAC5 or last vaccine injection in the event of early terminated subject, contacted for the 6 months follow-up period through a phone call
†For female subjects of childbearing potential
‡Complete physical examination at V01 and medically-driven physical examination for remaining visits
§With the exception of subjects from Group 4 (who will receive VRVg-2 only)
Abbreviations: AESI: adverse event of special interest; D: day; DC: diary card; HRIG: human rabies immunoglobulin; MA: memory aid; SAE: serious adverse event; V: visit; VAC: vaccination.

List of Abbreviations

ACIP	Advisory Committee on Immunization Practice
AE	adverse event
AESI	adverse event of special interest
Ag	antigen
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
AR	adverse reaction
BMI	body mass index
CDM	Clinical Data Management
CI	confidence interval
CPRV	chromatographically purified rabies vaccine
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CRO	Contract Research Organization
CTA	clinical trial agreement
CTL	Clinical Team Leader
COVID-19	Coronavirus Disease 2019
DC	diary card
DNA	deoxyribonucleic acid
EDC	electronic data capture
FAS	Full Analysis Set
FASI	Full Analysis Set for Immunogenicity
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practices
GMT	Geometric Mean of Titers
GPV	Global Pharmacovigilance
GSO	Global Safety Officer
HRIG	human rabies immunoglobulin

IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
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
LCLS	last contact, last subject
LLOQ	lower limit of quantification
LLT	lowest level term
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MTL	Medical Team Leader
NSAID	non-steroidal anti-inflammatory drug
PEP	post-exposure prophylaxis
PI	Principal Investigator
PPAS	Per-Protocol Analysis Set
PVRV	purified vero rabies vaccine
qs	quantity sufficient
RFFIT	Rapid Fluorescent Focus Inhibition test
rHA	recombinant human albumin
RMO	Responsible Medical Officer
RVNA	rabies virus neutralizing antibody
SAE	serious adverse event
SafAS	safety analysis set
SF	serum free
SMT	Safety Management Team
SOP	standard operating procedure
TMF	trial master file
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 vector 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 (1) (3). 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 first 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 first, 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 (4). 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 first clinical symptoms (5) (6).

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 (7).

Since 2013, rabies cases in animals have decreased in Europe. No human cases were reported in 2015 and 2016, while 6 cases had been reported between 2012 and 2014, mostly exposed outside Europe. However, the risk is still present in Eastern Europe where rabies remains endemic.

No endemic human rabies cases have been reported in metropolitan France since 1924. Currently, the risk of exposition to a non-flying rabid mammal in metropolitan France is negligible. However, since 1970, still 24 patients have been reported to die in France after being infected abroad, with the exception of 1 patient who had received a corneal graft from an infected Egyptian donor, and another patient who was infected in Guyana (2008) by a hematophagous bat. The last patient who died due to rabies in France (10-year-old child) was diagnosed in October 2017 after an extended stay in Sri Lanka. It is to note the significant number of patients, overall 4223 in 2016 and 4676 in 2017, having received post-exposure prophylaxis (PEP) in France (8) (9).

Human death from rabies can be effectively prevented either by post-exposure treatment after rabies exposure, or by pre-exposure prophylaxis (PrEP) to subjects with high risk of exposure. More than 15 million people receive post-exposure treatments each year after being exposed to animals suspected of having rabies (10). 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 (11) (12).

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 first rabies vaccines prepared on animal nervous tissue, responsible for neurological disorders (13) (14) (15).

1.2 Background of the Investigational Product

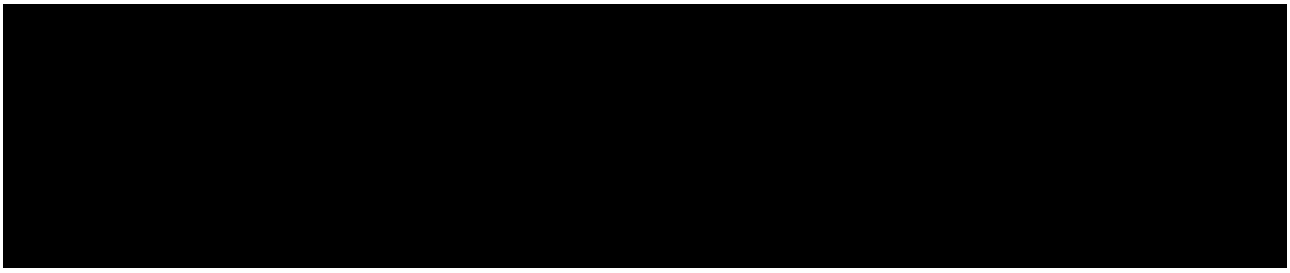
Currently, Sanofi Pasteur has 2 rabies vaccines registered worldwide and available on the market: Imovax® Rabies and Verorab®. Imovax Rabies, a human diploid cell vaccine, was first licensed in 1975. It is currently registered in 19 countries, including the US, Canada, Australia and 13 European countries. On the other hand, a purified Vero rabies vaccine (PVRV), was first licensed in France in 1985 under the commercial name of Verorab, and is extensively registered worldwide

in 84 countries including 10 European 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 6042) 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 Purified Vero rabies vaccine – serum free (SF), 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 deoxyribonucleic acid (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.



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 PEP of rabies), in order to provide the grounds for a 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

[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).

Verorab vaccine in VRV01 and VRV08 and to Imovax Rabies vaccine in VRV06, with the expected level of seroconversions (ie, > 99% subjects with RVNA titer ≥ 0.5 IU/mL). [redacted] Sanofi Pasteur made the decision 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 second 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 (ARs) 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. [redacted]

Next step in VRVg clinical development consists of 2 Phase III non-inferiority studies which will compare the selected dose in VRV11 [redacted] with the 2 rabies vaccines marketed by Sanofi Pasteur (Verorab and Imovax Rabies vaccines); ie, a simulated PEP regimen in adults (this study: VRV13), and a PrEP regimen comprising adult and pediatric populations. VRV13 will not include pediatric subjects since the risk-benefit of the administration of HRIG in simulated conditions in this population is not justified. Further, disease progression and vaccine response is similar in both adults and pediatric subjects, and the results obtained in VRV13 will be extrapolated to the pediatric population.

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[a] [redacted]

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

In detail, VRV13 will enroll adults aged ≥ 18 years, and the vaccination schedule will follow the ESSEN regimen, ie, 5 doses administered at D0, D3, D7, D14 and D28, with administration of HRIG at D0 in simulated conditions (healthy, non-exposed subjects). The duration of the safety follow-up is planned to be until 6 months after the last dose of vaccine. The selection of France as the country for VRV13 is because the population is rabies-naive and both Verorab and Imovax Rabies are licensed in France and can be used as controls. Previous experience and feasibility to conduct the study were also taken into account.

As per prior communications to the European Medicines Agency (EMA)[a] and the US FDA[b], the performance of VRVg-2 (+ HRIG) will be demonstrated through the non-inferiority to Verorab vaccine (+ HRIG) and Imovax Rabies vaccine (+ HRIG), in terms of proportion of subjects achieving a RVNA titer ≥ 0.5 IU/mL at D28 (ie, 14 days after the fourth vaccine injection [primary objective]), with an expected endpoint of at least 95% seroconversion rate at this time point (secondary objective). A VRVg-2 group without HRIG administration will be added to allow for the description of differences in the immunological response between VRVg-2 with, and without HRIG administration.

It should be noted that latest guidance from the WHO (April 2018) recommends a PEP regimen consisting of 4 IM doses instead of 5 (D0, D3, D7 and between D14 and D28) (21). This is in line with the current Advisory Committee on Immunization Practices (ACIP) guidance (dated 2010; ie, 4 IM dose schedule on D0, D3, D7, and D14) (22). The study design of VRV13 will enable the evaluation of the immune response after 4 doses according to these recommendations, as well as after 5 doses, consistent with previous WHO guidelines and VRVg trials.

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 specific safety concerns are therefore expected with VRVg-2. An internal ongoing safety review will be performed by the Safety Management Team (SMT), which includes safety signal detection.

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. Imovax Rabies is recommended by the ACIP.

Subjects receiving VRVg will be vaccinated against rabies, and are expected to be protected against infection in the event of contact with the virus. As a standard approach, subjects may

[a] CHMP scientific advice, May 2017 and Follow up Scientific advices, March 2018 and September 2018.

[b] CBER Type A meeting December 2017, CBER Type B meeting November 2018.

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 VRV13 has been evaluated in a clinical trial during the development of a CPRV vaccine with satisfactory safety profile. [redacted]

Results from precedent VRV11study 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 ARs 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 subjects (N=80) in VRV11, following a post-exposure regimen (5 injections within 28 days) with

HRIG administration on the first 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 ARs 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 Company Core Data Sheet:

The following AEs are derivated from several clinical studies where Verorab vaccine has been used in both pre-exposure and post-exposure schedule:

- Very common (> 10%): lymphadenopathy, myalgia, injection site pain, fever, and malaise
- Common (> 1% and < 10%): skin allergic reactions, rash, pruritus (itching), edema, headache, dizziness, somnolence, abdominal pain, nausea, arthralgia, chills (shivering), injection site erythema, injection site pruritus, injection site hematoma, injection site induration, asthenia, influenza-like symptoms
- Uncommon (> 0.1% and < 1%): urticaria, angioedema, dyspnea, diarrhea, injection site edema

In addition, the following AEs have been reported during the post-marketing surveillance of the Verorab vaccine. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship of exposure to Verorab:

- Immune system disorders
  - Anaphylactic reactions
  - Serum sickness type reactions
- Nervous system disorders
  - Encephalitis
  - Convulsions
- Ear and labyrinth disorders
  - Sudden sensorineural hearing loss
- Gastrointestinal disorders
  - Vomiting

Serious hypersensitivity reactions may occur after any vaccination, and they are considered important identified risks with Verorab. Other serious events listed above (encephalitis, convulsion, sudden sensorineural hearing loss) are considered important potential risks, because

although cases have been reported from post-marketing experience with Verorab, their causal association with the vaccine have not been established.

Imovax Rabies vaccine

The following risks have been identified with the use of Imovax Rabies as currently reported in the Company Core Data Sheet:

- Very common (> 10%): adenopathy, headache, nausea, myalgia, malaise, injection site pain, injection site erythema, injection site induration (swelling/hardness), and injection site hematoma
- Common (> 1% and < 10%): allergic reactions with skin disorders such as urticaria and rash, or respiratory manifestations such as dyspnea and wheezing, dizziness, abdominal pain, vomiting, diarrhea, arthralgia, injection site pruritus (itching), fever, chills (shivering)

In addition, the following AEs have been reported very rarely (< 0.01%) during the post-marketing surveillance of Imovax Rabies. Based on spontaneous reporting, their frequencies have been estimated using the number of reports and the estimated number of patients. However, the exact incidences cannot be precisely calculated.

- Immune system disorders
  Skin allergic reactions pruritus (itching), edema
  Anaphylactic reactions
  Serum sickness type reactions

These reactions have been associated with the presence of betapropiolactone-altered human albumin in Imovax Rabies.

Allergic reactions occurred less frequently among persons receiving primary vaccination.

- Nervous system disorders
  Paresthesia
  Neuropathy
  Convulsion, encephalitis
- General disorders and administration site conditions
  Asthenia

HRIGs

The following AEs have been identified with the use of HRIGs (Imogam Rabies – HT) during post-marketing use, as currently reported in the Company Core Data Sheet. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Imogam Rabies – HT exposure. These are:

- Cardiac disorders
  Hypotension
  Tachycardia
- Gastrointestinal disorders

Nausea
Vomiting

- General disorders and administration site conditions
  Local reaction
  Fever, chills
- Immune system disorders
  Allergic type reaction
  Anaphylactic shock
- Skin and subcutaneous system disorders
  General pruritus
  Rash

When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally 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

Rabies vaccines would not cause immune suppression. Therefore, risk of the subjects to have 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 (e.g. commute to the site and at the site).

Risk mitigation:

- The study 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 trial and implement measures which prioritize subject safety (main criteria) and data validity in agreement with the investigators, IRB/EC, ANSM, FDA and EMA applicable recommendations (23) (24) (25). These assessments will be documented.

1.4 Rationale for the Study

Previous Phase II clinical study (VRV11) concluded that VRVg-2 (ie, VRVg-2 dose selected) 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 VRV13 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 adult population in a simulated PEP regimen. See Section 5.1.2 for further details.

2 Study Objectives

2.1 Primary Objective(s)

Immunogenicity

To demonstrate that VRVg-2 is non-inferior to Verorab and Imovax Rabies vaccines when co-administered with HRIG, in terms of proportion of subjects achieving a RVNA titer ≥ 0.5 IU/mL at D28, ie, 14 days after the fourth vaccine injection.

The endpoints for the primary objective are presented in Section 9.1.2.1.

2.2 Secondary Objective(s)

Safety

To describe the safety profile of VRVg-2 versus Verorab and Imovax Rabies vaccines when co-administered with HRIG, as well as that of VRVg-2, after each vaccine injection.

Immunogenicity

1) To demonstrate that the proportion of subjects in the VRVg-2 + HRIG group achieving an RVNA titer ≥ 0.5 IU/mL at D28 is at least 95%.
2) To describe the immune response induced by VRVg-2 versus Verorab and Imovax Rabies vaccines when co-administered with HRIG, as well as that induced by VRVg-2, at D14 (7 days after the third injection), at D28 (14 days after the fourth injection), and at D42 (14 days after the last injection).

The endpoints for the secondary objectives are presented in Section 9.2.1.2 (safety) and Section 9.2.2.1 (immunogenicity).

3 Investigators and Study Organization

This study will be conducted in 2 centers in France, with one Principal Investigator (PI) per center. One of the 2 PIs will be the Coordinating Investigator and will coordinate with the PI from the other site and any sub-investigators at the individual sites.

Details of the study centers, the Investigators at each center, and the Coordinating Investigator are provided in the "List of Investigators and Centers Involved in the Trial" 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 is planned to be set up for this trial 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, VRV08, VRV02, VRV04, VRV06, and VRV11). 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. The development of VRVg is being

[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 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 from the Clinical Department. Reviews will be performed in a blinded manner.

The SMT, led by the GSO and the Clinical Team Leader (CTL), will be responsible for the review, assessment and evaluation of safety data generated from this study. The SMT is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

The Sponsor's Responsible Medical Officer (RMO, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted].

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form (ICF), 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).

The Investigator or Sponsor 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 (see also Section 5.4).

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This will be a multi-center, modified double-blind (Groups 1 to 3)/open (Group 4), controlled, randomized, Phase III study in 636 subjects aged ≥ 18 years. Subjects will receive 5 vaccine injections of either VRVg-2 (Groups 1 and 4), Verorab vaccine (Group 2), or Imovax Rabies vaccine (Group 3), at day [D] 0, D3, D7, D14, and D28 (ESSEN regimen). All groups with the exception of Group 4 will additionally receive HRIG at D0.

Vaccination and HRIG will be administered through the IM route.

Subjects will be randomized 3:1:1:1 (Group 1, 2, 3, and 4, 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 subjects*
Group 1	VRVg-2 + HRIG	318
Group 2	Verorab® + HRIG	106
Group 3	Imovax® Rabies + HRIG	106
Group 4	VRVg-2	106

*Justification of the sample size is given in Section 12.5.

All subjects will provide blood samples before the first vaccination at D0 (baseline titer) and for the assessment of the immune response to the rabies vaccines at D14 (7 days after the third vaccine injection), D28 (14 days after the fourth vaccine injection), and D42 (14 days after the last 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.

5.1.2 Justification of the Study Design

VRV13 will use the simulated post-exposure ESSEN regimen, ie, in 5 injections, on D0, D3, D7, D14, and D28. In detail, the performance of VRVg-2 (+ HRIG) will be demonstrated through the non-inferiority to both Verorab vaccine (+ HRIG) and Imovax Rabies vaccine (+ HRIG), in terms

of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL[a] at D28 (ie, 14 days after the fourth vaccine injection [primary objective]), with an expected endpoint of at least 95% seroconversion rate at this time point (secondary objective).

The design and endpoints were agreed with the EMA[b] and the US FDA[c]. [redacted]

A VRVg-2 group without HRIG administration will be added to allow for the description of differences in the immunological response between VRVg-2 with, and without HRIG administration.

Overall the design of this study will be consistent with previous VRVg trials and WHO guidelines, and will also be in line with latest recommendations from the WHO (April 2018; ie, PEP regimen consisting of 4 IM doses D0, D3, D7 and between D14 and D28) (21), and current ACIP guidance (dated 2010; ie, 4 IM dose schedule on D0, D3, D7, and D14) (22), since timely assessment after the fourth vaccine injection at D28 is planned.

Other noteworthy design features of this study are:

- Verorab and Imovax Rabies vaccines are both current standard of care employed globally. Their inclusion as controls/comparators aims supporting VRVg licensure worldwide. However, demonstration of non-inferiority to Verorab is not required for study success to support licensure in the US.
- The choice of France as the country for conducting the study was driven by the local regulatory context and the feasibility for using both Verorab and Imovax Rabies as vaccine comparators in rabies-naive population.
- The choice to include adults aged ≥ 18 years without upper age limit aims at supporting a vaccine indication covering all age groups. It is to note that the results obtained in VRV13 will be extrapolated to the pediatric population since the risk-benefit of the administration of HRIG in simulated conditions in this population is not justified.
- Randomization of participants will be by IRT (stratified by center), in 3:1:1:1 ratio (Group 1 to Group 4), respectively.
- Since VRVg-2, Verorab, and Imovax Rabies vaccines can be distinguished, the study is conducted in modified double-blind for groups 1 to 3 (VRVg-2 + HRIG, Verorab vaccine + HRIG, and Imovax Rabies vaccine + HRIG); ie, the person who assesses the safety is different from the person who administers the vaccine. This avoids bias in safety data collection. Neither the Investigator assessing safety nor the subjects will know which vaccine is

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

[b] CHMP scientific advice, May 2017 and Follow up Scientific advice, March 2018.

[c] CBER Type A meeting, December 2017 and CBER EOP2 meeting, November 2018.

administered. Group 4 will receive only VRVg-2, and will be open-label (both the researchers and participants will know which treatment is being administered).

- VRV13 study samples will be tested at Sanofi Pasteur Global Clinical Immunology department (GCI) through the RFFIT assay, the gold standard of rabies virus neutralization assays.
- The French IEC / IRB will provide consent to perform the study before it starts.

5.1.3 Study Plan

The trial plan is summarized in the Table of Study Procedures

Recruitment and information of subjects:

Before inclusion in the trial, the Investigator will orally inform potentially eligible subjects about the trial. They will be given an oral description of the trial design, presenting the general benefits and risks related to the trial. 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.

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

Informed consent will be obtained before inclusion of the subject in the study (see Section 5.2.2). In case of any safety finding during the conduct of the study, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) can request to provide an addendum to the ICF. This ICF addendum should be signed additionally at any other visit before further procedures.

Trial description:

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

Eligible subjects will receive a total of 5 injections (1 injection at D0, D03, D07, D14 and D28) according to the ESSEN regimen for rabies PEP. HRIGs will be administered at D0 at the time of the first vaccine injection in groups 1 to 3 only.

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 fifth 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.

Immunogenicity will be assessed in all subjects included in the trial, before the first vaccine injection (VAC1) (D0), before VAC4 (D14), before VAC5 (D28) and 14 days after VAC5 (D42). The RFFIT assay will be used for immunogenicity assessment.

Blood sampling:

All subjects will provide a total of 4 blood samples of 6-mL each, to assess the immune response induced by the rabies vaccines.

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

Table 5.2: Blood sampling and vaccination schedule

	V01	V02	V03	V04	V05	V06	V07
Visit interval	VAC1	VAC2= VAC1+3D	VAC3= VAC1+7D	VAC4= VAC1+14D	VAC5= VAC1+28D	VAC5+14D	VAC5+28D
Vaccine injection	x	x	x	x	x		
HRIG Groups 1 to 3 Group 4	x						
Blood sampling (6 mL)	x			x	x	x	

Collection of safety data:

At each visit, study staff will either check and/or collect the safety DCs provided to subjects to report safety data. A memory aid (MA) will be provided to the subjects at V07 to collect SAEs and AESIs up to the end of the study. The MA will be checked at the Phone call at M7. Since the study is modified double-blind for Groups 1 to 3, study staff who will check and collect safety information will be different from the staff who administered the vaccine. This will apply to all groups (applied also to Group 4 [open-label] for simplicity).

Management of Subjects in Case of Rabies Exposure

According to the national rabies epidemiology and the exclusion criteria of VRV13, the exposure to rabies will be unlikely during the trial. Nevertheless, the management of subjects in case of rabies exposure will follow the post-exposure treatment according to the French national recommendation for PEP (26).

- If subjects have no documented RVNA titer ≥ 0.5 IU/mL, ie, before titration of blood samples, post-exposure anti-rabies vaccination will include administration of vaccine (according to ESSEN or Zagreb regimen) and preferably co- administration of anti-rabies immunoglobulin, when recommended, according to the national recommendations.
- If subjects have documented RVNA titer ≥ 0.5 IU/mL, ie, after titration of blood samples, they will only receive the rabies vaccine (as per post-exposure schedule for previously immunized individuals).
- 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

Throughout the trial, neither the participants from Groups 1 to 3 nor the study staff in charge of CRB completion will know which vaccine is being administered. Only the person who will perform the vaccine injection will know which vaccine will be administered.

Participants from Group 4 and the study staff in charge of completion of their CRB will know which vaccine is being administered.

Vaccine injections (VAC) will have to be performed on alternate sides, at least 3 cm apart from the previous injection site: for example VAC1 on the right, VAC2 on the left, VAC3 on the right and so on.

V01 (D0): Inclusion, Randomization, Blood Sample and Vaccination

1) Give the subjects information about the trial, obtain written informed consent, and give him/her a signed copy[a].
2) Collect demographic data.
3) Obtain past and current medical history and check inclusion and exclusion criteria for eligibility.
4) 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]).
5) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.9).
6) Urine pregnancy test, if applicable.
7) Conduct a physical examination, including temperature, weight and height to determine the Body Mass Index (BMI).
8) Contact the Interactive Response Technology (IRT) system for randomization; dose number assignment and allocation of subject number (see Section 6.6).
9) Obtain the first 6 mL blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (3 attempts), then V01 can be rescheduled to a later date at which point informed consent and inclusion/exclusion criteria must be re-validated. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.
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) Inject HRIG in the thigh (see Section 6.4.2) if subject is randomized to Groups 1 to 3.
13) Keep the subject under observation for 30 minutes, and record any AR in the source document.

[a] In case of any safety finding after the start of the study, ANSM can request to provide an addendum to the ICF. This ICF addendum should be signed additionally at any other visit before further procedures.

14) Give the subject the first diary card (DC1), a thermometer, and a ruler, and go over the instructions for their use.
15) Remind the subject to bring back DC1 when they return for V02 at a specified date and time.
16) Remind the subject to notify the site in case of a SAE and AESI.
17) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
18) Complete the relevant source document information and CRF pages for this visit.

V02 (3 days after VAC1): Collection of Safety Information and Vaccination

1) Review the DC1 with the subject, including any AEs, SAEs, AESIs, medications, or therapy that occurred since vaccination by Investigator or delegate. The subject will continue using the DC1 to collect safety information until the V04.
2) Urine pregnancy test, if applicable.
3) Conduct a physical examination, including temperature.
4) Check contraindication for subsequent vaccinations (see Section 5.2.7).
5) Contact the IRT system for dose number assignment (see Section 6.6).
6) Inject the appropriate study vaccine (VAC2) in the opposite arm as compared to the VAC1.
7) Keep the subject under observation for 30 minutes, and record any AR in the source document.
8) Remind the subject to bring back DC1 when they return for V03 at a specified date and time.
9) Remind the subject to notify the site in case of a SAE, and AESI.
10) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
11) Complete the relevant source document information and CRF pages for this visit.

V03 (7 [+1] days after VAC1): Collection of Safety Information and Vaccination

1) Review the DC1 with the subject, including any AEs, SAE, AESIs, medications, or therapy that occurred since vaccination by Investigator or delegate. The subject will continue using the DC1 to collect safety information until V04.
2) Urine pregnancy test, if applicable.
3) Conduct a physical examination, including temperature.
4) Check contraindication for subsequent vaccinations (see Section 5.2.7).
5) Contact the IRT system for dose number assignment (see Section 6.6).
6) Inject the appropriate study vaccine (VAC3) in the opposite arm as compared to the VAC2 at least 3 cm apart from the first injection site.

7) Keep the subject under observation for 30 minutes, and record any AR in the source document.
8) Remind the subject to bring back DC1 when they return for V04 at a specified date and time.
9) Remind the subject to notify the site in case of a SAE and AESI.
10) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
11) Complete the relevant source document information and CRF pages for this visit.

V04 (14 [±1] days after VAC1): Collection of Safety Information, Blood Sample and Vaccination

1) Review and collect the DC1 with the subject, including any AEs, SAE, AESI, medications, or therapy that occurred since vaccination by Investigator or delegate.
2) Urine pregnancy test, if applicable.
3) Conduct a physical examination, including temperature.
4) Obtain the second 6 mL blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
5) Check contraindication for subsequent vaccinations (see Section 5.2.7)
6) Contact the IRT system for dose number assignment, see Section 6.6).
7) Inject the appropriate study vaccine (VAC4) in the opposite arm to that of VAC3 and at least 3 cm apart from the previous injection site.
8) Keep the subject under observation for 30 minutes, and record any AR in the source document.
9) Give the subject the second diary card (DC2).
10) Remind the subject to notify the site in case of a SAE and AESI.
11) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
12) Complete the relevant source document information and CRF pages for this visit.

V05 (28 [±3] days after VAC1): Collection of Safety Information, Blood Sample and Vaccination

1) Review and collect the DC2 with the subject, including any AEs, SAEs, AESIs, medications, or therapy that occurred since vaccination by Investigator or delegate.
2) Urine pregnancy test, if applicable.
3) Conduct a physical examination, including temperature
4) Obtain the third 6 mL blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
5) Contact the IRT system for dose number assignment (see Section 6.6).

6) Inject the appropriate study vaccine (VAC5) in the opposite arm to that of VAC4 and at least 3 cm apart from the previous injection site.
7) Keep the subject under observation for 30 minutes, and record any AR in the source document.
8) Give the subject the third diary card (DC3).
9) Remind the subject to notify the site in case of a SAE and AESI.
10) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
11) Complete the relevant source document information and CRF pages for this visit.

V06 (14 [±3] days after VAC5): Collection of Safety Information and Blood Sample

1) Review the DC3 with the subject, including any AEs, SAEs, AESIs, medications, or therapy that occurred since vaccination by Investigator or delegate. The subject will continue using the DC3 to collect safety information until the next visit.
2) Conduct a physical examination.
3) Obtain the fourth 6 mL blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
4) Remind the subject to notify the site in case of an SAE and AESI.
5) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
6) Complete the relevant source document information and CRFs for this visit.

V07 (28 [±3] days after VAC5): Collection of Safety Information

1) Review and collect the DC3 with the subject, including any AEs, SAEs, AESIs, medications, or therapy that occurred since vaccination by Investigator or delegate.
2) Conduct a physical examination.
3) Give the subject with the MA to record any SAEs or AESIs that may occur during the 6-month safety follow-up.
4) Remind the subject to notify the site in case of a SAE, and AESI.
5) For woman of childbearing potential: remind the subject to notify the site in case of pregnancy.
6) Complete the relevant source document information and CRF pages for this visit.
7) Complete the trial termination record.

Contact Telephone Call (6 months [+14 days] after VAC5; ie, D180 to D194 after VAC5): Collection of Safety Information

1) Review MA by a qualified person Investigator or delegate, including any AEs, SAE, AESIs, medications or therapy, and pregnancy for woman of childbearing potential that occurred since last visit.
2) Complete the relevant source document information and appropriate CRF.

Follow-up of subjects with Related AEs or with AEs That Led to Study/Vaccination Discontinuation:

Unless a subject 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 from vaccination.

Pregnancy cases

At any time during the study, a subject who discovers that she is pregnant must be followed until the delivery (see Section 5.2.12).

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.

Planned study periods/dates:

(FVFS [first visit, first subject] to LCLS [last contact, last subject]:	Q3 2019 ~ Q2 2021
Inclusion period (FVFS to FVLS [first visit, last subject]:	Q3 2019 ~ Q3 2020
Vaccination period:	Q3 2019 ~ Q3 2020
Date of final clinical study report:	Q3 2021

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Before the start of the trial, the Investigator or delegate will contact an appropriate pool 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 voluntarily confirms his or her willingness to 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.

In accordance with GCP, prior to signing and dating the consent form, the subject 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 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 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.

ICFs 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

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

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 ≥ 18 years on the day of inclusion[a]
2) ICF has been signed and dated by the subject
3) Able to attend all scheduled visits and to comply with all trial procedures
4) Body Mass Index (BMI): 18.5 Kg/m^2 ≤ BMI ≤ 30 Kg/m^2
5) Covered by health insurance

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 first vaccination until at least 4 weeks after the last vaccination. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, or surgically sterile.

[a] " ≥ 18 years" means from the day of the 18th birthday onwards, with no upper age limit."

2) Participation at the time of study enrollment or, planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.
3) Subject who would receive more than 4 500 euros as indemnities for his/her participation in biomedical research within the 12 last months, including the indemnities for the present study.
4) Subject in the exclusion period of a previous study or subject who refuses to be on the national registry of subjects that participate in biomedical research (ie," Fichier National des Volontaires pour la Recherche Biomédicale VRB")
5) Receipt of any vaccine in the 4 weeks (28 days) preceding the first trial vaccination or planned receipt of any vaccine prior to Visit 7.
6) Previous vaccination against rabies (in pre- or post-exposure regimen) with either the trial vaccines or another vaccine
7) Receipt of immune globulins, blood or blood-derived products in the past 3 months
8) 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)
9) At high risk for rabies exposure during the trial[a]
10) Known systemic hypersensitivity to any of the vaccine or HRIG components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[b]
11) Self-reported thrombocytopenia, contraindicating IM vaccination
12) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination
13) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
14) Current alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct of completion.

[a] Such as veterinarians and their staff, animal handlers, rabies researchers, and certain laboratory workers, persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies, people travelling where rabies is enzootic.

[b] The components of VRVg-2 are listed under Investigational Product and in the Investigator's Brochure Section 3.2. The components of Verorab and Imovax Rabies vaccines are listed under Control Products, and the components of HRIG, under Other Product. (See Section 6.1 to Section 6.4)

15) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[a]
16) 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
17) Personal history of Guillain-Barré syndrome
18) 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, the site may contact this physician with the subject's consent, to inform him / her of the subject's participation in the study.

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 at least:

- 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, dates, treatments received and dosages. The use of medications (prescribed or out-of-the-counter) such as chloroquine and hydroxychloroquine within at least 2 months before enrollment should be recorded, given their interference with rabies vaccines (22) (27).

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

5.2.7 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 or until the clinical hold is lifted. Postponement must still be within the timeframe for vaccination indicated in the Table of Study Procedures. If any dose is delayed, the subsequent doses should be delayed according to the original time interval.

1) Moderate or severe acute illness/infection (according to Investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C)
2) Clinical hold as instructed by the Sponsor, ANSM, or other regulatory authority

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)
- HIV seropositivity
- Thrombocytopenia, bleeding disorder or receipt of anticoagulants contraindicating IM vaccination
- Administration of a vaccine other than the study vaccine between D0 and V07 (VAC5+28D)
- An SAE related to the trial 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 possibly immunogenicity assessments, as applicable.

5.2.8 Conditions for Withdrawal

Subjects will be informed that they have the right to withdraw from the study at any time.

A subject may be withdrawn from the study:

- 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 AE) or for another reason.

Withdrawn subjects may be replaced.

5.2.9 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.

5.2.10 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 5.2.9. The certified letter was sent by the Investigator and returned unsigned, and the subject 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, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration including when it is retrospectively discovered that a subject did not fulfill the eligibility criteria • If the subject experiences a definitive contraindication that is not an SAE or AE. • The subject 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	To be used: When the subject indicated unwillingness to continue in the study • When the subject 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.)

5.2.11 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 (including subjects from a clinical hold).

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", the site will attempt to contact the subject 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.

5.2.12 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 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). However, no additional vaccination will be administered.

All pregnancy cases should be reported if they occurred during the study. 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. The study staff should instruct the patient to report any congenital anomalies of the newborn, even if diagnosed after the follow-up done at the time 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 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.

In the event that a change in the protocol is necessary to eliminate an immediate hazard to the subjects, the health authorities (competent regulatory authority) and the IEC / IRB should be informed as soon as possible. They should also be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator Brochure or labeling information will be sent to the IEC / IRB and to health authorities (competent regulatory authority), as required by local regulation.

5.4.1 VRV13 Amendments Justification

Amendment 1

Any study conducted in healthy volunteers could be put on hold by the ANSM due to any SAE. Consequently, the SAE "multiple crises of abnormal movements in both arms and legs" led to the clinical hold of the study between Friday, 06 September 2019 and Tuesday, 10 September 2019.

The following SAEs have been identified during the conduct of the VRV13 study so far:

- One SAE of "impaired general condition" in a 72-year-old woman after she received the 5th dose of vaccination in one of the blinded arms. The subject developed diarrhea, nausea, and asthenia with loss of weight and was hospitalized after her visit at D42. During hospitalization, isolated hyponatremia was found. After treatment and resolution of diarrhea, she was discharged. The subject continued with refractory hyponatremia and loss of weight. Studies are ongoing to define her diagnosis. The event did not cause termination of the subject from the study. The SAE was considered related by the Investigator and unrelated by the Sponsor.
- One SAE of "multiple crises of abnormal movements in both arms and legs" without fever or loss of consciousness in a 45 year old man approximately 5 weeks after his 5th vaccination in one of the blinded arms. The subject was hospitalized but no other crises were observed; magnetic resonance imaging, electroencephalogram, electrolytes and hematology were normal. Relevant medical history included benign positional paroxysmal vertigo since mid-August and history of tick bite in July. The subject was discharged 2 days later. No other episodes of abnormal movements were observed. Studies are ongoing to define his diagnosis. The event did not cause termination of the subject from the study. The SAE was considered related by the Investigator and unrelated by the Sponsor.

  As per the recommendations of the ANSM, all subjects who are participating in the study will be/or have been informed about the 2 SAEs in the ICF or through an addendum to the ICF. The subjects will also be informed about the clinical hold and increase in sample size. The Investigators have been notified and the Investigator Brochure will include this information.

The available information supports the conclusion that the risk/benefit ratio of the vaccines used in this trial is favorable. Therefore, the Sponsor increased the sample size of the study (see Section 12.5) and increased the attrition rate to ensure the adequate power to fulfil the endpoints (see Section 9).

Amendment 2

Due to the COVID-19 pandemic, the enrollment of subjects was put on hold on the 12th of March 2020 due to the increase number of cases in France. The ongoing vaccinations were stopped on the 16th of March 2020 due to the confinement established in the country and the consequent impossibility to follow study visits within requested time window. As the study vaccine is being administered in healthy individuals in a simulated schedule, there is no safety issue in case of incomplete vaccination.

Different measures were taken according to the stage of the vaccination:

- For subjects who have finished their vaccination scheme (3 subjects): the follow-up of the subject was monitored by phone. The 2 due visits V6 (D42), and V7 (D56) were replaced by phone call to monitor the safety (no blood sample was taken).
- For the subjects who have not finished their vaccination scheme (29 subjects): Subjects were withdrawn from the study due to protocol deviation (ie, inability to attend vaccination visit within allowed time windows), but they continue to be followed for safety (see Section 5.2.11). The follow-up of the subject will be monitored by phone.
- The 6-month follow-up will be done by phone as planned in the protocol.

These measures were taken by the Sponsor to ensure well-being of subjects (ie, to limit exposure to COVID-19) and were implemented without IRB/EC approval, as per national and international guidances. However, IRB/EC and health authorities were informed promptly about the measures reported in the current amendment.

The enrollment will resume as soon as subject's safety is ensured, and national health authorities approves. Therefore, in the current amendment, to replace withdrawn subjects, the Sponsor will increase the sample size of the study (see Section 12.5) to ensure the adequate power to fulfill the endpoints (see Section 9).

5.4.2 Measures implemented due to COVID-19 pandemic

The Sponsor will implement alternative processes consistent with the protocol to ensure trial participant safety and trial data quality and integrity according to IRB/EC, ANSM, FDA and EMA applicable recommendations (23) (24) (25).

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 advice of the Sponsor, the Investigators, the IECs / IRBs, or the governing regulatory authorities in the country where the study is taking place (see also Section 3).

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 and should assure appropriate subject therapy and/or follow-up.

6 Products Administered

6.1 Identity of the Investigational Product

The investigational product is VRVg: Purified Vero Rabies Vaccine - 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

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 in 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, 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 first injection in the left deltoid, the second in the right deltoid and so on.

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 each vaccination to ensure their safety, and any reactions during this period will be documented in the CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction, under the responsibility of trained personnel.

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

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, 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 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

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 ≤ 100 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 trial product in Section 6.1.2, with the exception that the diluent volume is approximately 1ml 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

Imogam Rabies-HT Licensed HRIGs will be administered at D0 in all subjects from arms 1 to 3 included in the trial.

Form: Liquid/Solution in 2-mL vials

Route: IM injection in the anterolateral thigh

6.4.1 Composition

- Human rabies immunoglobulins 150 IU/mL (commercial batch to be determined)

The recommended dose is 20 IU/kg (or 9 IU/lb) of body weight.

6.4.2 Preparation and Administration

Imogam Rabies-HT is a ready-to-use, colorless to light opalescent solution for injection. The volume to be injected per subject is to be calculated based on the body weight (20 IU/kg) as presented as example in the table below.

Weight (kg)	Quantity of HRIG (IU)	Volume (mL)	Number of injections
60	1200	8	2
80	1600	10.67	3
100	2000	13.33	3
120	2400	16	4

A 5-mL syringe will be used and will be filled using several vials as necessary. The content of the syringe should be injected by the IM route at a body site distant from the rabies vaccine injection site (anterolateral thigh). A maximum of 5 mL is to be administered by injection; the total volume will be divided and administered at separate sites (sites should be at least 3 cm apart).

6.4.3 Dose Selection and Timing

Imogam Rabies -HT will be injected as recommended in the package insert and as approved in the marketing authorization of the product. As this study is performed in a simulated post-exposure condition, the entire volume will be administered by intramuscular route.

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 French regulation requirements.

Imogam Rabies-HT doses will be in an individual box that will be identified by a dose number.

6.5.2 Product Shipment, Storage, and Accountability

Products must be kept in a secure place with restricted access. All products will be stored at a temperature ranging from 2°C to 8°C. The temperature must be monitored and documented (see the Operating Guidelines) for the entire duration of the trial. In case of disruption of the cold

chain, vaccines must not be administered. In that case, the unblinded staff should contact the Clinical Logistics Coordinator for further instructions.

6.5.2.1 Product Shipment

The Clinical Logistics Coordinator 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.

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 (eg, unblinded staff member).

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 vaccine is 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 dose number 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 vaccine replacement dose is required (eg, because the syringe broke or particulate matter was observed in the syringe), the site personnel must contact the IRT to receive the new dose allocation.

For Imogam Rabies-HT (HRIG), if a dose is broken another one will be used.

6.5.4 Disposal of Unused Products

Unused or wasted products will be 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 has a modified double-blind part for Groups 1 to 3 and an open-label part for Group 4.

The study will be conducted as follows:

- Unblinded (open for Group 4) qualified study staff member(s), independent of the safety evaluation and other trial evaluations, will prepare and administer the vaccine.
- The blinded (open for Group 4) staff member(s), including the Investigator, in charge of safety assessment will not know which vaccine is administered (except for Group 4).
- The subject will remain blinded (except for Group 4) and will not know which vaccine is administered: the product will not be prepared in the subject's presence.

The blinded staff members, including the Investigator responsible for safety assessment, will not attend the vaccination session, but will remain on site in case of emergency (eg, anaphylactic shock).

The IRT system vendor will be responsible for providing the vaccine dose number to be received by the enrolled subject and the HRIG administration (HRIG may be administered or not). The subject, the Investigator, and study staff members who collect the safety data and laboratory personnel who analyze the blood samples will all be blinded to the group assignment. The study staff member who prepares or administers the vaccine will not be authorized to collect any safety / serology data.

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 (medical doctor only[a]), 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 is to be completed in the CRF.

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[b]. 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.

In any case, the code will be broken for the statistical analysis of the primary analysis (D0 to D56), but the randomization list will not be provided to Investigators and will be kept until the end of the study (Clinical Study Report finalization).

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.
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). [redacted] is the fifth subject enrolled in Center [redacted]).
The IRT system will define which product (dose number) will be administered for each vaccination and if HRIG must be administrated or not.

Randomization, managed by IRT system, will be performed using the permuted block method with stratification on centers. This guarantees, at any time and in each center, the right number of subjects with respect to the randomization scheme that has been defined for the trial.

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.

[a] according to local regulations

[b] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

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 the first 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 (ie, from V01 to V07) as they may impact the response to the vaccination and impact the consistency of the information collected on concomitant medications at any vaccination.

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 immune modulators.
- 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 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)

Medications should be collected as concomitant if there is a reasonable possibility that they may still impact on safety and/or immune assessment, even when the treatment was stopped before collection (e.g. medications characterized by long half-live, dose accumulation, or which might cause delayed adverse reactions).

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 (22, 27). Exceptionally, dosage may be collected for these medications.

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[a] 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 prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at V01, V04, V05, and V06. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At V01, V04, V05, and V06, 6 mL of blood will be collected in tubes provided 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, 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.

[a]As previously mentioned, dosage of medications such as chloroquine or hydroxychloroquine may be collected.

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 on the appropriate form during the entire study. If it rises above -10°C for any period of time, the Clinical Logistics Coordinator 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 Logistics Coordinator. 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.

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 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, CRBs, SAE reporting forms, DCs, MA and other study documents, as well as with the following study materials: all study vaccines, , HRIGs, pregnancy tests, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, , 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 (with the exception of blood collection tubes, which are provided by the Sponsor), 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 for 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 D28:
  - Subject with an RVNA titer ≥ 0.5 IU/mL at D28

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 (DFA) 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) may be obtained in duplicates for each tested sample, and the individual geometric mean of duplicates calculated as needed (to be confirmed with the applicable version of the standard operating procedure [SOP] at the time of testing).

Lower limit of quantitation (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/time point level at the starting dilution (1/5) of the RFFIT assay. Samples may be assessed in duplicates (to be confirmed with the applicable version of the SOP at the time of testing), 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).Planned and scheduled surgery is not considered as an SAE and should be recorded at the time of inclusion in the trial.

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)

[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.

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 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)

Unexpected Adverse Reaction (UAR):
An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational medicinal product). Depending of the severity of the AR, rapid communication by the Investigator to the Sponsor can be appropriate.

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 first 30 minutes after vaccination.

Solicited Reaction:

A solicited reaction is an "expected" AR (sign or symptom) observed and reported under the conditions (nature and onset) prelisted 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.

The assessment of these reactions by the Investigator is mandatory.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted 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, prelisted 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).

It is to note that the concomitant administration of vaccine and HRIG at D0 will not allow differentiation between systemic AEs related to the vaccine or to HRIG.

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 primary endpoints for the evaluation of safety are:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccine injection

Collection of injection site reactions:

- Occurrence of solicited (pre-listed in the in the subject's DC and CRB) injection site reactions occurring within 7 days after each injection
- Occurrence of unsolicited (spontaneously reported) injection site reactions occurring within 28 days after each injection

Collection of systemic reactions and AEs:

- Occurrence of solicited (pre-listed in the subject's DC and CRB) systemic reactions between the first and the second injections as well as between the second and the third injections, and up to 7 days after the remaining injections
- Occurrence of unsolicited (spontaneously reported) systemic AEs between each injection and up to 28 days after the last injection
- Occurrence of SAEs and AESIs throughout the trial (until 6 months after last vaccination)

Depending on the item, endpoints could include: 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.

9.2.1.3 Safety Assessment Methods

At each visit, the Investigator or a delegate will perform a clinical or medically-driven physical examination and will ask the subject about any solicited reactions and unsolicited AEs recorded in the DC, as well as about any other AEs, SAEs, AESIs 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 the first vaccination, subjects will be provided with a digital thermometer and a flexible ruler, and after each vaccination, subjects will be provided with a DC. Subjects 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, as applicable (ie, solicited injection site reactions from Day 0 through Day 7; solicited systemic reactions between the first and the second injections, between the second and the third injections, and up to 7 days after the remaining injections), until resolution:

- Daily temperature, with the route by which it was taken, preferably oral route
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event (eg, medication)

For solicited reactions still ongoing after the solicited period, daily intensity will be recorded in the DC until resolution of the reaction.

The action(s) taken by the subject 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 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the DCs and CRB, together with the intensity scales.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	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 adverse event 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 adverse event 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 participant. Grade 3: A type of adverse event 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

* For the subjective reaction of pain, subjects 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 systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	**Fever**	**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 adverse event 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 adverse event 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 adverse event 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: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of adverse event 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 participant.	Grade 2: A type of adverse event 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 participant.	Grade 2: A type of adverse event 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 participant.
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

* For all reactions but fever, subjects 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 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 oral. 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 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. 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 (including, but not limited to, start and stop dates, diagnosis, seriousness), 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)

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 and Table 9.2).

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

  - Grade 1: A type of AE 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.

[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 2: A type of AE 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 participant.
- Grade 3: A type of AE 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 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 (AESI)

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

- 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 trial 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 (important identified or potential risks) of other rabies vaccines. For each AESI, the standard case definitions from the Brighton Collaboration will be used (28) (29) (30).

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/ time point level:
- RVNA titers at D0, D14, D28, and D42
- Subject with an RVNA titer ≥ 0.5 IU/mL at D0, D14, D28, and D42
- Subject with an RVNA titer ≥ LLOQ IU/mL, at D0, D14, D28, and D42
- Individual RVNA titer ratio: D14/D0, D28/D0, and D42/D0
- Subject with complete or incomplete neutralization at the starting dilution (1/5) of the RFFIT assay at D0, D14, D28, and D42.

9.2.2.2 Immunogenicity Assessment Methods

The methodology employed is shown in Section 9.1.2.2.

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 (including diagnosis, symptoms and their evolution, relevant personal and family medical history, concomitant treatments at the time of SAE onset, details of etiological investigations including all clinical and laboratory results, etc…) 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 D.O.]) 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 CTL 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:

- By fax, to the following number: 1-570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com

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

If there is 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 to 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 participants for the recording of daily safety information as described in Section 9.2.1.3. These DCs will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant

details. Subjects 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 on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects over the telephone using a questionnaire to capture SAEs and AESIs, if applicable. A MA aid may be provided to the subjects 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.

At specified intervals, the Investigator or an authorized designee will interview the subjects 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 first 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 trail will be initiated in the EDC system at the time of the first 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, US).

The statistical analysis will be performed in 2 steps. A first statistical analysis will be carried out once all the safety and immunogenicity data collected up to D56, ie, up to 28 days after the last vaccine injection, will be obtained and locked. Then an addendum will be performed after the 6-month safety follow-up.

12.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

12.1.1.1 Hypotheses

The immunogenicity of VRVg-2 + HRIG will be compared to that of both Verorab + HRIG and Imovax Rabies vaccine + HRIG at D28, ie, 14 days after the fourth vaccine injection, using a non-inferiority testing.

For each comparison, the primary parameter will be the difference of 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 (%).

VRVg-2 will be considered as non-inferior to the tested control if the hypothesis H0 is rejected.

12.1.1.2 Statistical Methods

For the non-inferiority hypothesis 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 D28 between the VRVg-2 vaccine group and the comparator. The 95% CI for differences will be calculated using Wilson score method without continuity correction (31).

Each non-inferiority 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%.

Overall non-inferiority will be reached if each of the non-inferiority between VRVg-2 + HRIG and both Verorab vaccine + HRIG and Imovax Rabies vaccine + HRIG will be demonstrated.

12.1.2 Hypotheses and Statistical Methods for Secondary Objective(s)

12.1.2.1 Hypotheses

If the primary objective is reached, the following hypotheses will be tested at D28, as part of the secondary objectives:

H0: $P_{VRVg-2+HRIG} < 95\%$

H1: $P_{VRVg-2+HRIG} \geq 95\%$

The proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28 after receiving VRVg-2 will be considered as equal to or higher than 95% if the hypothesis H0 is rejected.

12.1.2.2 Statistical Methods

The superiority testing will be demonstrated if the lower limit of the 95% CI of the proportion, calculated using the exact binomial distribution (32), is equal to or higher than 95%.

All other secondary endpoints will be described by vaccine group using descriptive statistical methods, as follows.

Immunogenicity endpoints

Analysis of RVNA titers after vaccination series will be done per vaccine group, in all subjects, using:

- GMTs at D0, D14, D28 and D42
- GM of individual titer ratio (GMTR): on D14/D0, D28/D0 and D42/D0
- The proportion of seropositive subjects at D0, D14, D28 and D42 (ie, subject with an RVNA titer ⩾ LLOQ)
- The proportion of subjects with RVNA titer ⩾0.5 IU/mL at D0, D14, D28 and D42
- The proportion of subjects with Complete or Incomplete results at the 1/5 starting dilution at D0, D14, D28 and D42

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 (32)) will be used for the single proportions.

Reverse Cumulative Distribution Curves (RCDC) will be plotted in all vaccine groups at D0, D14, D28 and D42.

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 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 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 (32).

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 (33), 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, 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 (33).

The possible impact of the COVID-19 pandemic on the immunogenicity and safety results will be assessed and corresponding exploratory analyses will be detailed in the Statistical Analysis Plan.

12.2 Analysis Sets

12.2.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as the subset of randomized subjects who received at least 1 dose of the study vaccines.

The Full Analysis Set for Immunogenicity (FASI) is defined as a subset of the FAS, defined as all subjects from FAS 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 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 first dose received that corresponds to a protocol group.

12.2.3 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPAS) is a subset of the FAS.

As D28 is the time point used for primary objective assessment, the PPAS will be defined at D28 (V05). The subjects presenting with at least one of the following relevant protocol deviations before D28 (ie, 14 days after the fourth vaccine injection) will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive the first 4 doses of the vaccination schedule
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine (including HRIG for groups 1 to 3) was not done as per-protocol for the first 4 vaccinations
- Subject did not receive the first 4 vaccine injections in the proper time window
    - Vac2 in [D03-D05]
    - Vac3 in [D07-D09]
    - Vac4 in [D13-D16]

- Subject did not provide the post-dose 4 serology sample at V05 in the proper time window [D25-D31] from D0
- Subject received a protocol-prohibited therapy/medication/vaccine (belonging to categories 2 and 3) before V05
- Subject's serology sample is missing or did not produce valid test results at both D0 and D28
- Seropositive subject at D0, ie, RVNA titer ⩾ LLOQ
- Subject developed a protocol-specified withdrawal criterion during the study but was not withdrawn
- Subject did not receive the correct amount of HRIG at D0

  Adherence to the definition of the PPAS analysis set may also be decided during the blinded data review, ie, before breaking the code and locking the data base.

12.2.4 Other Analysis Set(s)

Not applicable.

12.2.5 Populations Used in Analyses

The following table (Table 12.1) presents populations used in the statistical analysis.

Table 12.1: Populations used in the analyses

		Analysis sets	Analysis by
Primary Objective	**D28 Non-inferiority testing**	PPAS (main analysis), FAS/FASI	Received vaccine group Randomized vaccine group
Secondary Objectives	**D28 Superiority testing**	PPAS, FAS/FASI	Received vaccine group Randomized vaccine group
	Immunogenicity description	PPAS, FAS/FASI	Received vaccine group Randomized vaccine group
	Safety description	SafAS	Received vaccine group

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

No formal interim analyses are planned; the statistical analysis will be performed in 2 steps as follows:

A limited statistical analysis of the safety and immunogenicity data obtained up to D56 will be conducted once data are available and an interim database lock will be conducted. A final analysis will be conducted once the 6-month safety data have been collected and the final database lock has occurred. No statistical adjustment is necessary because there are no repeat analyses of the same parameter.

12.5 Determination of Sample Size and Power Calculation

The sample size calculation is driven by the non-inferiority testing.

An alpha level of 2.5% (one-sided hypothesis), a maximum acceptable difference of 5% for the proportion of subjects with an RVNA titer ≥ 0.5 IU/mL at D28, and a power of at least 90% for each of the non-inferiority testing have been chosen to calculate the sample size, in order to ensure an overall power of at least 80% to reach the primary objective. Assuming a proportion of subjects with an RVNA titer ≥ 0.5 IU/mL of 99% for the 3 vaccine groups, and an unbalanced randomization 3:1:1 (VRVg-2 + HRIG : Verorab vaccine + HRIG : Imovax Rabies vaccine + HRIG), 213 subjects in the VRVg-2 + HRIG group and 71 subjects in each of the Verorab vaccine + HRIG and Imovax Rabies vaccine + HRIG groups will be necessary, to provide a power of 80% to test the global null hypothesis, using the Farrington and Manning method (34).

Originally, it was planned to enroll 504 subjects in this study. Following a clinical hold between Friday, 06 September 2019 and Tuesday, 10 September 2019, for the evaluation of an SAE as required by the ANSM, the sample size of the study had been modified to replace subjects who were to be excluded from the PPAS due to vaccination outside of the recommended time window and to increase the attrition rate of the study.

Under the assumption that 20% of subjects will not be evaluable, 267 subjects in the VRVg-2 + HRIG group and 89 subjects in each, the Verorab vaccine + HRIG and the Imovax Rabies vaccine + HRIG groups should be enrolled.

As a consequence of the first clinical hold of the study, 71 subjects from the 4 vaccine groups (assumed to be distributed with a distribution close to 36:12:12:12) were identified as to be excluded from the PPAS. With the aim to secure the study power, 60 additional subjects were to be enrolled among the 3 vaccine groups involved in the primary objective assessment, ie, a total

of 606 subjects were to be enrolled as follows: 303 in the VRVg-2 + HRIG group and 101 in each of the Verorab vaccine + HRIG and Imovax Rabies vaccine + HRIG groups.

Then, in the context of the COVID-19 crisis, enrollment was paused from the 12th of March 2020 and ongoing vaccination were stopped on the 16th of March 2020. Twenty-nine ongoing subjects (from all the 4 groups) are expected to be withdrawn and excluded from the PPAS as they are unable to complete their vaccination schedule as planned in the protocol due to national confinement measures. Still with the aim to secure the study power and maintain the randomization ratio, 30 additional subjects will be enrolled in the study. Finally, 636 subjects are planned to be enrolled, with a planned overall distribution of 318:106:106:106 among the 4 vaccine groups. Assuming a proportion of subjects with an RVNA titer ≥ 0.5 IU/mL of 99% in the VRVg-2 + HRIG group, this sample size will give more than 93% of power to demonstrate the superiority of this rate to 95% on the PPAS. In order to maintain the 3:1:1:1 ratio, the additional arm of subjects receiving VRVg-2 as standalone will include 106 subjects; the results will be descriptive, mainly versus the VRVg-2 + HRIG group. The number of subjects is the same as the 2 controls to facilitate group allocation and will allow good precision of the results.

The 3:1:1 design is chosen to optimize the non-inferiority testing for immunogenicity with 2 comparators and to increase the size of the safety database of VRVg-2 vaccine.

In case of any new study hold, withdrawn or out of vaccination time windows subjects might be replaced and sample size might be increased accordingly.

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, screening logs, informed consent / assent forms, 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 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.

The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

Good Documentation Practice should be followed by the Investigator and the site staff managing source documents.

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.

Sanofi Pasteur personnel (or designates), the IECs / IRBs, and regulatory agencies, including the FDA, require direct access to all study records, and will treat these documents in a confidential manner.

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.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Since monitoring tasks may be carried out by a subcontractor who is not determined at the time of protocol writing, note that, activities performed "by" the Sponsor, can be read as "under the responsibility of" the Sponsor.

Before the start of the study (ie, before the inclusion of the first 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.

[a] Unless the electronic medical records are managed by validated computerized systems that are compliant with US 21 CFR Part 11, in which case they are acceptable on their own.

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 Trial Master File (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 Trial 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

Subjects may be provided with a stipend according to local practice to compensate for their participation the study (eg, dedicated time and travel required for study visits and procedures).

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.

14 Reference List

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15 Signature Page