NCT03145766

Immunogenicity and Safety of a Purified Vero Rabies Vaccine - Serum Free when administered according to a Simulated Rabies Post-exposure Regimen in Healthy Adults

Multicenter, observer-blind, controlled, randomized, Phase II study in 320 subjects aged 18 to <65 years. Each subject will receive one of the 2 formulations of the purified Vero Rabies - Serum Free vaccine (VRVg) or the Human Dipoid Cell Vaccine Imovax® Rabies. Vaccination will be according to the ESSEN post-exposure regimen and human rabies immunoglobulins (HRIG) will be administered at D0.

Clinical Trial Protocol Amendment 1

Health Authority File Number(s):	[redacted]
WHO Universal Trial Number (UTN):	U1111-1174-4976
Trial Code:	VRV11
Development Phase:	Phase II
Sponsor:	Sanofi Pasteur SA 2, avenue Pont Pasteur, F-69367 Lyon cedex 07, France Represented by: Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
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:	[redacted]
Clinical Team Leader	[redacted]
Global Safety Officer::	[redacted]

Clinical Trial Manager: [redacted]

Version and Date of the Protocol: Version 2.0 dated 20 January 2017

This protocol version 2.0 is the first amendment to the initial trial protocol version 1.0, dated 17 November 2016

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(s):	Rabies virus - Wistar rabies virus strain PMWI 38 - 1503 3M - grown on continuous Vero-SF cell cultures, inactivated by betapropiolactone

Title of the Trial:	Immunogenicity and Safety of the Purified Vero Rabies Vaccine - Serum Free when administered according to a Simulated Rabies Post-exposure Regimen in Healthy Adults
Development Phase:	Phase II
Coordinating Investigator:	[redacted]
Trial Centers:	The study will be conducted in 5 centers in the United States
Planned Trial Period:	Q2 2017 (FVFS) to Q1 2018 (LVLS)
Trial Design and Methodology:	Multicenter, observer-blind, controlled, randomized, Phase II study. Qualified staff member(s) administrating Purified Vero Rabies Vaccine - Serum Free (VRVg), i.e., Groups 1-4 described below, will additionally be blinded. A total of 320 subjects aged 18 to < 65 years will be included in the study and randomized to the following 5 groups:

	Vaccine	Formulation	Dosage	Number of subjects
Group 1	VRVg	VRVg-2*	Low	80
Group 2			Medium	80
Group 3			High	80
Group 4		VRVg-1*		40
Group 5	Imovax® Rabies			40

** VRVg-2, modified formulation ; VRVg-1, initial formulation*

A total of 8 visits (V01-V08) are planned.

All subjects will receive one vaccine injection on each of the following days: Day 0 (D0), D3, D7, D14 and D28 (ESSEN regimen). In addition, human rabies immunoglobulins (HRIG) will be concomitantly administered to all subjects on D0.

All subjects will provide blood samples for immunogenicity assessment at D0 (pre-vaccination), at D14, D28, D42 (corresponding to 7 days after the third injection, 14 days after the fourth injection and 14 days after the last injection, respectively) and at the last visit, i.e., 6 months after the last injection (M7).

Safety data will be collected after each vaccine injection.

Early Safety Data Review	This trial will not include an early review of safety data. However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in the country where the trial is taking place. If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the trial subjects and should assure appropriate therapy and follow-up.
Objectives:	***Immunogenicity*** To describe the immune response induced by VRVg-2 (low, medium and high dosage) versus VRVg-1 and Imovax Rabies, at D14 (7 days after the third injection), at D28 (14 days after the fourth injection), at D42 (14 days after the last injection), and at M7 (6 months after the last injection). ***Safety*** To describe the clinical safety profile of VRVg-2 (low, medium and high dosage) versus VRVg-1 and Imovax Rabies, after each vaccine injection.

Endpoints:	***Immunogenicity***
	• Titers (IU/mL) summarized at the subject/timepoint level.
	  • RVNA titers against rabies virus obtained by the rapid fluorescent focus inhibition test (RFFIT) at D0, D14, D28, D42 and M7 in all subjects
	  • Subject with an RVNA titer ≥ 0.5 IU/mL at D0, D14, D28, D42 and M7
	  • Subject with an RVNA titer ≥ LLOQ IU/mL, at D0, D14, D28, D42 and M7
	  • Individual titer ratio: D14/D0, D28/D0, D42/D0 and M7/D0
	• Virus neutralization: complete or incomplete, summarized at the subject/timepoint level.
	  • Subject with complete neutralization at the starting dilution (1/5) of the RFFIT assay at each timepoint
	Safety:
	• Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccine injection
	<u>*Collection of injection site reactions:*</u>
	• Occurrence of solicited (prelisted in the subject's diary card [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
	<u>*Collection of systemic reactions and AEs:*</u>
	• Occurrence of solicited (prelisted 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 serious adverse events (SAEs) throughout the trial

	Other endpoints recorded or derived will be described at the time of statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration, number of days of occurrence, grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.
Planned Sample Size:	A total of 320 subjects are to be enrolled: Group 1 (VRVg-2, low dosage): ..... n=80 Group 2 (VRVg-2, medium dosage): .... n=80 Group 3 (VRVg-2, high dosage): ..... n= 80 Group 4 (VRVg-1): ..... n= 40 Group 5 (Imovax Rabies, control): ..... n= 40
Schedule of Study Procedures:	Vaccination All subjects will receive a total of five vaccine injections, one at D0, at D3, at D7, at D14 and at D28. In addition, all subjects will receive HRIG at D0. Blood sampling All subjects will provide five blood samples: one at D0, one at D14, one at D28, one at D42 and one at M7. Blood sampling will be done prior to each vaccine injection (and prior to both, vaccine injection and HRIG injection at D0). Collection of safety data 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 AEs will be recorded between each injection, and during the 28 days following the last injection. Solicited injection site reactions will be recorded in the 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 safety information in a Memory Aid (MA) from D56 (28 days following the last injection) until the end of the trial (M7). Information about SAEs will be recorded throughout the trial.
Duration of Participation in the Trial:	The duration of each subject's participation in the trial will be approximately 7 months (28 days- vaccination period followed by 6 months -follow up period) except for prematurely discontinued subjects.
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 modified formulation. VRVg-1 is the initial formulation.
Form:	Freeze-dried

Composition:	Each 0.5 mL dose of either VRVg-2 or VRVg-1 contains Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain: ≥ 2.5 IU (potency; NIH) and the components specified in the following table: [redacted]
Route:	Intramuscular (IM)
Batch Number:	Batch numbers are to be determined
Control Product:	Imovax Rabies: 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 ≤ 100mg Diluent: Water for injection: qs 1 mL
Route:	IM
Batch Number:	Batch number is to be determined
Other Product:	Human Rabies Immunoglobulins (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; batch number to be determined

Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) Aged 18 to <65 years on the day of inclusion[a] 2) Informed consent form has been signed and dated 3) Able to attend all scheduled visits and to comply with all trial procedures 4) Body Mass Index (BMI): 18.5 $Kg/m^2 \leq BMI \leq 30$ Kg/m^2
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial 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) Receipt of any vaccine in the 4 weeks (28 days) preceding the first trial vaccination or planned receipt of any vaccine prior to Visit 6 4) Previous vaccination against rabies (in pre- or post-exposure regimen) with either the trial vaccine or another vaccine 5) Receipt of immune globulins, blood or blood-derived products in the past 3 months 6) 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) 7) At high risk for rabies infection during the trial[b] 8) 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[c] 9) Self-reported thrombocytopenia, contraindicating IM vaccination 10) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding

[a] "18 to <65 years" means from the day of the 18th birthday to the day before the 65th birthday. In states where the age of majority to consent to research is >18, inclusion criteria will be from the birthday acquiring the age of majority to the day before the 65th birthday.

[b] 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

[c] The components of VRVg-1 and VRVg-2 are listed under Investigational Product and in the Investigator's Brochure Section 3.2.

	inclusion, contraindicating intramuscular vaccination 11) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily 12) Current alcohol abuse or drug addiction 13) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion[a] 14) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F [≥ 38.0°C]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided 15) 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 (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study 16) History of Guillain-Barré syndrome
Statistical Methods:	A first statistical analysis will be done once all safety and immunogenicity data collected up to D56, i.e., up to 28 days after the last vaccine injection, is obtained. A final statistical analysis will be done after completion of the trial. No hypothesis will be tested. The proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at each timepoint and the 95% Confidence Interval (CI) using the exact binomial method (Clopper-Person method, quoted by Newcombe) will be calculated by vaccine group. Antibody titers will also be described in terms of GMT and GMTR with their 95% CI in each vaccine group. All the safety parameters will be described in each vaccine group. Proportions and 95% CI will be calculated for each endpoint. *Sample size calculation* An arbitrary number of 80 subjects per VRVg-2 group and 40 subjects in both, VRVg-1 and control group (Imovax Rabies) will be included. [redacted]

[a] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders or chronic infection

In terms of safety, according to the occurrence rate of the observed AEs, 80 subjects will allow for the following 95% CI:

Observed numbers	Observed %	95% CI
8/80	10.0	(4.4; 18.8)
12/80	15.0	(8.0; 24.7)
16/80	20.0	(11.9; 30.4)
20/80	25.0	(16.0; 35.9)
24/80	30.0	(20.3; 41.3)

Table of Study Procedures

Phase II Trial, 8 Visits, 5 Vaccinations, 5 Blood Samples, 7 Months Period per Subject

Visit	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**
Visit interval	**VAC1**	**VAC2= VAC1+3D**	**VAC3 = VAC1+7D**	**VAC4 = VAC1+14D**	**VAC5= VAC1+28D**	**VAC5+14D**	**VAC5+28D**	**VAC5+6M**
Indicative Days (D)	**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 (5 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 MA
Injection site reactions and Systemic Event Assessment	√	√	√	√	√	√	√	
Temporary contraindications		√	√	√	√			
Reportable concomitant medication	√	√	√	√	√	√	√	
Termination Record								√
Definitive contraindications	Collected throughout the trial or up to V05							
Pregnancy cases	Collected throughout the trial							
Serious adverse events	Collected throughout the trial							

* For subjects of childbearing potential

List of Abbreviations

ACIP	Advisory Committee on Immunization Practice
AE	adverse event
Ag	antigen
AR	adverse reaction
AESI	adverse event of special interest
CDM	Clinical Data Management
CIF	complementary information form
CQA	Clinical Quality Assessment Department
CRA	Clinical Research Associate
CRF	electronic case report form
CTA	clinical trial agreement
CTL	Clinical Team Leader
DCF	data clarification form
EDC	electronic data capture
FAS	full analysis set
FBP	final bulk product
FDA	Food and Drug Administration
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPE	Global Pharmacovigilance and Epidemiology (Department)
GPV database	Global Pharmacovigilance database
GSO	Global Safety Officer
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug (application)
IRB	Institutional Review Board
IRT	interactive response technology
LCLS	last contact, last subject
LLT	lowest level term
LLOQ	lower limit of quantification

MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MTL	Medical Team Leader
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
UAR	unexpected adverse reaction
RMO	Responsible Medical Officer
SAE	serious adverse event
SafAS	safety analysis set
TMF	trial master file
ULOQ	upper limit of quantification
WHO	World Health Organization

1 Introduction

1.1 Background

Rabies is a viral zoonosis that occurs in >100 countries and territories. Although a number of carnivores and bat species serve as natural reservoirs, rabies in dogs is the source of 99% of human infections and poses a potential threat to >3.3 billion people. In humans, rabies is almost invariably fatal once clinical symptoms have developed. In a number of countries, human deaths from rabies are likely to be grossly underreported, particularly in the youngest age groups. The vast majority of the estimated 55 000 deaths caused by rabies each year occur in rural areas of Africa and Asia (1) (2).

1.1.1 Rabies Virus

Rabies is caused by Rabies virus, the first genotype in the genus *Lyssavirus*, from the *Rhabdoviridae* family. It has two 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 (3).

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 (3). The virus will then spread from the brain to highly innervated areas, including the salivary glands causing hydrophobia, hypersalivation, 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).

During 2014, 50 states and Puerto Rico reported 6033 cases of rabies in animals and 1 human case to Centers for Disease Control and Prevention (CDC). The total number of reported cases increased by 2.83% compared with 2013 (5,865 rabid animals and 3 human cases of rabies). Wild animals accounted for 92.6% of reported cases of rabies in 2014. Raccoons continued to be the most frequently reported rabid wildlife species (30.2% of all animal cases during 2014), followed by bats (29.1%), skunks (26.3%), and foxes (5.2%) (8). In 2014, a man from Missouri died following infection with a bat rabies virus variant (9). This is the second case of human rabies in Missouri in 6 years (a man died in 2008 due to rabies infection following a bat bite). Two human cases of rabies were reported in the United States in 2015. The first was detected in August 2015 when a 65-year-old man who had recently returned to Massachusetts following a trip to the Philippines; the second case was detected in September 2015 in a 77-year-old female admitted to a hospital in Wyoming (she had contacted with a bite in August 2015, without any medical care for rabies post-exposure prophylaxis).

Human death from rabies can be effectively prevented either by post-exposure treatment after rabies exposure, or by pre-exposure prophylaxis 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) (2).

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 (12) (13) (14) .

1.2 Background of the Investigational Product

Currently, Sanofi Pasteur has two rabies vaccines on the market: Imovax® Rabies and Verorab®. Imovax Rabies, a human diploid cell vaccine (HDCV), was first licensed in1975. It is registered and marketed, in the US, Canada, Australia and 14 European countries. On the other hand, Verorab, a purified Vero rabies vaccine (PVRV), was licensed in France in 1985 and is extensively registered worldwide including 10 EU countries (but not in the US, Canada and Australia). Both vaccines have well-defined safety and immunogenicity profiles (14) (15).

In addition to Imovax Rabies and Verorab, 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 [redacted] in the 1990's. This vaccine was never commercialized due to industrial constraints.

[redacted] VRVg is compliant with standards set by the European Union Pharmacopoeia (16), the World Health Organization (WHO), and the FDA (17). VRVg is issued from the Wistar Rabies Pitman Moore/WI 38 1503-3M strain. The development of VRVg manufacturing process takes advantage of the experience from rabies vaccines development acquired in-house.

VRVg has been, or is being, evaluated in 5 clinical trials to date: VRV01, VRV08, VRV04 and VRV02 completed (CSR of this last one ongoing), and VRV06 (ongoing). Table 1.1 summarizes the design and objectives of each of these trials.

Table 1.1: Description of design and objectives of VRVg trials performed to date

Trial Code	Trial Phase - Title	Country; Period ; Number of subjects (age); vaccination	Primary Objective(s)*
VRV01	Phase II – Immunogenicity of the Purified Vero Rabies Vaccine – Serum Free in Comparison with the Reference Purified Vero Rabies Vaccine in Pre-exposure Use in Healthy Adults	France; 2009-2011; 384 adults (18-60 years old); pre-exposure† + Booster	-Demonstrate the non-inferiority of VRVg to Verorab Criterion: the proportion of subjects showing RVNA titers ≥0.5 IU/mL§ at D42 (14 days after the 3rd vaccination)
VRV08	Phase III – Immunogenicity and Safety of the Purified Vero Rabies Vaccine - Serum Free in Comparison with the Reference Purified Vero Rabies Vaccine in Post-exposure Use in Healthy Subjects in China	China; 2011-2012; 816 subjects (408, 10 -17 years old to and 408, over the age of 18); post-exposure‡	-Demonstrate the non-inferiority of VRVg to Verorab Criterion: the proportion of subjects showing RVNA titters ≥0.5 IU/mL§ at D14 (7 days after the third vaccine injection)
VRV02	Phase II - Immunogenicity of the Purified Vero Rabies Vaccine – Serum Free in Comparison with the Human Diploid Cell Vaccine, Imovax Rabies™ in Pre-exposure Use in Healthy Adults	USA; 2013-2015; 408 adults (18 <65 years old); pre-exposure† + Booster	-Demonstrate the non- inferiority of VRVg to Imovax Rabies Criterion: the proportion of subjects showing RVNA titters ≥0.5 IU/mL§ at D42 (14 days after the 3rd vaccination) -Demonstrate that the observed proportion of subjects achieving an RVNA titer ≥ 0.5 IU/m§L at D42 is at least 99%, with a lower limit of the 95% confidence interval (CI) of at least 97%
VRV04	Phase II - Immunogenicity and Safety of the Purified Vero Rabies Vaccine - Serum Free in Comparison with the Rabies Human Diploid Cell Vaccine Administered in a Simulated Rabies Post-exposure Regimen in Healthy Adults	USA; 2013-2014; 342 adults (18 <65 years old); post-exposure‡ + HRIG	-Demonstrate the non-inferiority of VRVg to Imovax Rabies Criterion: the proportion of subjects showing RVNA titters ≥ 0.5 IU/mL§ at D14 (7 days after the third vaccine injection). -Demonstrate that the observed proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D14 is at least 99%, with a lower limit of the 95% confidence interval (CI) of at least 97%
VRV06	Phase II - - Immunogenicity and Safety of the Purified Vero Rabies Vaccine – Serum Free (VRVg) in Comparison with the Human Diploid Cell Vaccine, Imovax® Rabies in Pre-exposure Prophylaxis Regimen in Healthy Children and Adolescents Aged 2 to 17 Years	Philippines; 2014; 342 children and adolescents (2-17 years old); pre-exposure†	-Demonstrate the non- inferiority of VRVg to Imovax Rabies Criterion: the proportion of subjects showing RVNA titters ≥0.5 IU/mL§ at D14 (7 days after the third vaccine injection) -Demonstrate that the observed proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D14 is at least 99%, with a lower limit of the 95% confidence interval (CI) of at least 97%

*Secondary objectives in all trials consisted of Clinical safety and Immunological response description

†Pre-exposure regimen: All subjects were to receive 3 injections at Day 0 (D0), D7 and D28.

‡Post-exposure regimen: All subjects were to receive 5 injections at D0, D03, D07, D14 and D28 (Essen regimen).

§ Rabies Virus Neutralizing Antibody (RVNA) titer threshold ≥ 0.5 IU/mL by Rapid Fluorescent Focus Inhibition Test (RFFIT), was based on the fact that this antibody titer is an indicator of an adequate adaptive immune response according to the WHO.

The primary objectives for VRV01 and VRV08 were met, demonstrating the non-inferiority of VRVg to Verorab in both pre-and post-exposure regimens in the addressed populations. A booster dose of VRVg administered 1 year after the first dose in VRV01 induced a strong immune response irrespective of which of the two vaccines had been given for the primary series. VRVg was shown to be safe after each vaccination and its safety profile was similar to Verorab in terms of unsolicited adverse events and solicited systemic reactions (including booster vaccination in VRV01) (18) (19).

[redacted] Sanofi Pasteur made the decision to modify the VRVg initial formulation (referred to as VRVg-1) [redacted]. The modified formulation, referred to as VRVg-2, [redacted]

A phase II study (VRV11) using the most stringent settings is proposed to secure the selection of the final dosage before embarking in larger phase III non inferiority studies covering both pre-exposure and a post-exposure with HRIG administration schemes.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

Vaccination is the most effective preventive measure against rabies. Imovax Rabies vaccine is currently available and recommended for rabies prophylaxis by the WHO and the Advisory Committee on Immunization Practice (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 require additional vaccination in the event of exposure to the virus, regardless of the vaccine received in the context of this study.

[a] D42, 14 days after the 3rd vaccine injection, i.e., 2 weeks after the completion of the pre-exposure regimen.

[b] D14, 7 days after the 3rd vaccine injection, i.e., 2 weeks after initiation of the post-exposure regimen.

1.3.2 Potential Risks to Subjects

VRVg-1 and VRVg-2

[redacted] Results from repeat dose toxicity study conducted in rabbits based on rabies post-exposure regimen and consisting of 6 intramuscular injections with the highest VRVg-2 dosage as a worse case, indicated that this formulation is well tolerated (report available before the start of VRV11).

Based on the above, the potential risks of administration of VRVg-2 can be assimilated to those of VRVg-1.

During clinical studies conducted with VRVg-1 in pre-and post-exposure regimen the following suspected adverse reactions were reported (frequencies are based on safety data from VRV01, VRV08, VRV02 and VRV04):

- Very common (>10%): injection site pain, malaise, headache, and myalgia
- Common (>1% and <10%): Pyrexia
- Uncommon (≥ 0.1% and < 1%): lymphadenopathy, abdominal pain, diarrhoea, 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, erythema, hematoma, haemorhagea, induration, pruritus and swelling.
- Rare (< 1%): vertigo, abdominal rigidity, hypoaesthesia oral, vomiting, injection site warmth, pain, oral herpes, sinusitis, musculoskeletal pain, cough, cold sweat, hyperhidrosis, rash and rash generalized.

The comparability exercise done according to ICH Q5E (20) demonstrated that VRVg (i.e.,VRVg-1) and Verorab were comparable on the basis of pharmaceutical characterization, release testing, stability results and immunogenicity data. Thus, all suspected adverse reactions observed with Verorab (see below) are considered as possible risks for VRVg-1 and VRVg-2.

During clinical studies conducted with Verorab (pre- and post-exposure regimens), the following suspected adverse reactions were reported:

- 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, 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.

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

It is to note that the prefilled diluent syringe tip caps used for both VRVg-1 and VRVg-2 may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Imovax Rabies

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, injection site pain, erythema, and induration (swelling/hardness), hematoma, malaise
- 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 (<1/100000) 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 adverse reactions have been identified with the use of HRIGs, Imogam® rabies, as currently reported in the Company Core Data Sheet. They have been identified during postapproval use of Imogam® Rabies – HT. 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.

Cardiac Disorders
Hypotension, tachycardia
Gastrointestinal Disorders
Nausea, vomiting
General Disorders and Administration Site Conditions
Fever, chills
Immune System Disorders
Anaphylaxis, allergic reaction
Skin and Subcutaneous System Disorders
Rash, pruritus

In rare cases, HRIGs can induce a drop in blood pressure associated with an anaphylactic reaction, even in patients who had well tolerated previous treatment with human rabies immunoglobulin. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

1.4 Rationale for the Trial

The main objective of VRV11 is to define the VRVg-2 vaccine dosage [redacted], before embarking in large phase III non-inferiority studies including pre- and post-exposure regimens. This study involves the testing of a modified formulation of VRVg vaccine (VRVg-2) [redacted]

Briefly, three dosages of a reformulated VRVg vaccine (VRVg-2) [redacted] will be tested in parallel to the initial VRVg formulation (named VRVg-1) and Imovax Rabies. The three VRVg-2 dosages chosen (low, medium and high), will provide higher Ag amounts per dose than that of VRVg-1 tested in previous trials (VRV01, VRV08, VRV02, VRV04, VRV06) (Section 5.1.2; Table 5.2). Imovax Rabies, has been chosen as control, since it is the Sanofi Pasteur commercial rabies vaccine in the US. The choice will be carried out through the descriptive analysis of the immune response (in particular, the proportion of subjects with RVNA titers ≥0.5 international units (IU)/mL), the titers distribution and the GMTs, and the safety profile that results from administrating the different dosages/formulations tested. The immunogenicity objectives are descriptive and therefore the study is not powered to detect statistically significant differences in antibody responses or to assess non-inferiority to the control.

2 Trial Objectives

Immunogenicity

To describe the immune response induced by VRVg-2 (low, medium and high dosage) versus VRVg-1 and Imovax Rabies, at D14 (7 days after the third injection), at D28 (14 days after the fourth injection), at D42 (14 days after the last injection), and at M7 (6 months after the last injection).

Safety

To describe the clinical safety profile of VRVg-2 (low, medium and high dosage) versus VRVg-1 and Imovax Rabies after each vaccine injection.

The endpoints for the objectives are presented in Section 9.1.1 (Immunogenicity) and Section 9.2.2 (Safety).

3 Investigators and Trial Organization

This trial will be conducted in 5 centers in the US. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by one Coordinating Investigator. Details of the trial centers, the Investigators at each center, and the Coordinating Investigator(s) are provided in the "Involved Personnel List" 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 previous clinical studies (i.e., VRVg-1). The modifications introduced in VRVg-2 formulation are not expected to induce major safety issues based on the sponsor's experience with rabies vaccines.

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

The Sponsor’s Responsible Medical Officer (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, the present 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 trial. 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 trial to the IEC / IRB annually, or more frequently if requested. All serious adverse events (SAEs) occurring during the trial that are related to vaccination will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Trial Design and Plan

5.1.1 Trial Design

This will be a multicenter, observer-blind, controlled, randomized, Phase II study. A total of 320 subjects aged 18 to <65 years will be included. Each subject will receive one of the 2 formulations of the Purified Vero Rabies Vaccine - Serum Free (VRVg) or the Rabies Human Dipoid Cell Vaccine Imovax Rabies. Vaccination will be according to the ESSEN post-exposure schedule (i.e., a total of 5 injections [1 injection per day] administered at D0, D03, D07, D14 and D28) and human rabies immunoglobulins (HRIG) will be administered at D0.

Subjects will be assigned to the VRVg-1 group, VRVg-2 groups or Imovax Rabies group as presented in the table below.

Table 5.1 Distribution of Subjects According to Vaccination Group

	Vaccine	**Formulation**	**Dosage**	**Number of subjects**
Group 1	VRVg	VRVg-2	Low	80
Group 2			Medium	80
Group 3			High	80
Group 4		VRVg-1		40
Group 5	Imovax® Rabies			40

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 vaccine at D14, D28, D42 and at M7.

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 Trial Design

In order to overcome uncertainty around the dose that would provide the expected robust seroconversion, VRV11 will compare three dosages of a reformulated VRVg vaccine (named VRVg-2) to previous VRVg formulation (named VRVg-1) and to Imovax Rabies (control).

[redacted]

VRV11 will use the simulated post exposure Essen regimen, i.e. in five injections, on D0, D3, D7, D14 and D28, based on the WHO recommendations (21). Co-administration of HRIG at D0, will be also carried out. Thus, VRVg-2 will be tested through the most stringent settings safety and immunogenicity wise.

Table 5.2: [redacted]

[redacted]

VRV11 study samples will be tested at Sanofi Pasteur Global Clinical Immunology department (GCI).

Since Imovax Rabies can be distinguished from VRVg-1 and VRVg-2, in order to avoid bias in safety data collection, the person who will assess the safety will be different from the person who will administer the vaccine (blind observer). Thus, neither the investigator assessing safety nor the subjects will know which vaccine is administered. In addition, within the groups vaccinated with

VRVg-1 and VRVg-2 (low, medium and high dosages), the person who will administer the vaccine will be blind as to which VRVg formulation and dosage she/he will administer.

5.1.3 Trial 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).

Trial description:

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

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 post-exposure prophylaxis (PEP). HRIGs will be administered at D0 at the time of the first vaccine injection.

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, i.e., 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), 14 days after VAC5 (D42) and 6 months after VAC5 (M7). The RFFIT assay will be used for immunogenicity assessment.

Blood sampling:

All subjects will provide a total of five blood samples of 5-mL each, to assess the immune response induced by the rabies vaccines.

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

Table 5.3: Blood Sampling and Vaccination Schedule

	V01	V02	V03	V04	V05	V06	V07	V08
Visit interval	VAC1	VAC2= VAC1+3D	VAC3 = VAC1+7D	VAC4 = VAC1+14D	VAC5= VAC1+28D	VAC5+14D	VAC5+28D	VAC5+6M
Vaccine Injection	x	x	x	x	x			
HRIG (Imogam® Rabies)	x							
Blood sampling (5 mL)	x			x	x	x		x

Collection of safety data:

At each visit, study staff (different from the staff who administered the vaccine) 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 and collected at V08.

Management of Subjects in Case of Rabies Exposure

The management of subjects in case of rabies exposure will follow the post-exposure treatment according to ACIP recommendations (22) in the anti-rabies reference center:

- If subjects have no documented RVNA titer ≥ 0.5 IU/mL, i.e., before titration of blood samples, post-exposure antirabies vaccination will include administration of both passive antibody, i.e., administration of anti-rabies immunoglobulin, and vaccine
- If subjects have documented RVNA titer ≥ 0.5 IU/mL, i.e., after titration of blood samples, they will only receive the rabies vaccine.
- 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 subject nor the study staff in charge of CRF completion will know which vaccine was administered. Only the person who will perform the vaccine injection will know which vaccine will be administered.

Vaccine injections (VAC) will have to be performed on alternate sides, at least 3 cm apart from the previous injection site: 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 subject's information about the trial, obtain written informed consent, and give him/her a signed copy.

2) Obtain verbal medical history about the subject. For woman of child-bearing potential, check the use of effective methods of contraception (example of effective methods of contraception include hormonal implants, intrauterine devices [hormonal or non-hormonal], oral contraceptive pills, hormonal patch and condom used with spermicide [sponge, contraceptive foam or cream]).
3) Collect demographic data, including weight and high to determine the Body Mass Index (BMI).
4) Collect ongoing medications including other therapies in the source document and reportable concomitant medication in the CRF (see Section 6.8).
5) Urine pregnancy test, if applicable.
6) Conduct a physical examination, including temperature.
7) Check inclusion and exclusion criteria for eligibility.
8) Call the Interactive Response Technology (IRT) system (IV/WRS) for randomization, dose number assignment and allocation of subject number (see Section 6.6).
9) Obtain the first 5mL 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) Inject the appropriate study vaccine (VAC1) on the opposite side to that of the blood sampling.
11) Inject HRIG in the tight (see Section 6.3.2).
12) Keep the subject under observation for 30 minutes, and record any adverse reaction in the source document.
13) Give the subject the first diary card (DC1), a thermometer, and a ruler, and go over the instructions for their use.
14) Remind the subject to bring back the Diary card when they return for V02 at a specified date and time.
15) Remind the subject to notify the site in case of an SAE or pregnancy (for woman of childbearing potential).
16) 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 adverse events, 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) Call the Interactive Response Technology (IRT) system (IV/WRS) for randomization, dose number assignment and allocation of subject number (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 adverse reaction in the source document.
8) Remind the subject to bring back the Diary card when they return for V03 at a specified date and time.
9) Remind the subject to notify the site in case of an SAE or pregnancy (for woman of childbearing potential).
10) 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 adverse events, 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) Call the Interactive Response Technology (IRT) system (IV/WRS) for randomization, dose number assignment and allocation of subject number (see Section 6.6).
6) Inject the appropriate study vaccine (VAC3) in the opposite arm as compared to the VAC2.
7) Keep the subject under observation for 30 minutes, and record any adverse reaction in the source document.
8) Remind the subject to bring back the Diary card when they return for V04 at a specified date and time.
9) Remind the subject to notify the site in case of an SAE or pregnancy (for woman of childbearing potential).
10) 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 adverse events, 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 5mL blood sample (see Section 7.1for detailed instructions regarding the handling of blood samples).
5) Check contraindication for subsequent vaccinations (see Section 5.2.7).
6) Call the Interactive Response Technology (IRT) system (IV/WRS) for randomization, dose number assignment and allocation of subject number (see Section 6.6).
7) Inject the appropriate study vaccine (VAC4) in the opposite arm as compared to the VAC3.
8) Keep the subject under observation for 30 minutes, and record any adverse reaction in the source document.
9) Give the subject the second diary card (DC2).
10) Remind the subject to notify the site in case of an SAE or pregnancy (for woman of childbearing potential).
11) 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 adverse events, 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 5mL blood sample (see Section 7.1for detailed instructions regarding the handling of blood samples).
5) Check contraindication for subsequent vaccinations (Section 5.2.7).
6) Call the Interactive Response Technology (IRT) system (IV/WRS) for randomization, dose number assignment and allocation of subject number (see Section 6.6).
7) Inject the appropriate study vaccine (VAC5) in the opposite arm as compared to the VAC4.
8) Keep the subject under observation for 30 minutes, and record any adverse reaction in the source document.
9) Give the subject the third diary card (DC3).
10) Remind the subject to notify the site in case of an SAE or pregnancy (for woman of childbearing potential).
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 adverse events, medications, or therapy that occurred since vaccination by Investigator or delegate. The subject will continue using the DC1 to collect safety information until the next visit.
2) Conduct a physical examination.

3) Obtain the fourth 5mL 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 or pregnancy (for woman of childbearing potential).
5) Complete the relevant source document information and CRF pages for this visit.

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

1) Review and collect the DC3 with the subject, including any adverse events, medications, or therapy that occurred since vaccination by Investigator or delegate.
2) Conduct a physical examination.
3) Give the subject with the memory aid (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 an SAE or pregnancy (for woman of childbearing potential).
5) Complete the relevant source document information and CRF pages for this visit.

V08 (6 months [±14 days] after VAC5): Collection of Safety Information and Blood Sample

1) Review MA by Investigator or delegate.
2) Obtain the fifth 5 mL blood sample (see Section 7.1for detailed instructions regarding the handling of blood samples).
3) Complete the relevant source document information, complete the termination record of the CRF, and enter the subject's termination information in the IVRS / IWRS.

SAEs and AEs That Are Related to Vaccination or That Led to Discontinuation:

At any time during the study, a subject who experiences an SAE or an AE must be followed if *either* of the following is true:

- The SAE or AE is considered by the Investigator to be related to vaccination, and is not resolved by the end of the subject's participation in the trial
- The subject has been discontinued from the trial because of the SAE or AE

Any such subject must be followed until the condition resolves, becomes stable, or becomes chronic.

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 Trial Calendar

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

Planned trial period - FVFS[a] to LVLS[a]:	April 2017 – February 2018
Planned inclusion period - FVFS[a] to FVLS[a]:	April 2017 – May 2017
Planned vaccination period:	April 2017 – June 2017
Planned follow-up period:	June 2017 – February 2018
Planned end of trial:	February 2018
Planned date of final clinical trial report:	July 2018

The expected trial duration is 7 months for all subjects included in the trial.

5.2 Enrollment and Retention of Trial 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 IRB for approval.

Recruitment procedures and materials will be submitted for 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 trial. 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 trial 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.

[a] FVFS: first visit first subject LVLS: last visit last subject FVLS: first visit last subject

If new information becomes available that may be relevant to the subject's willingness to continue participation in the trial, 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.

Informed consent forms will be provided in duplicate, or a photocopy 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 in order to be eligible for trial enrollment:

1) Aged 18 to <65 years on the day of inclusion[a]
2) Informed consent form has been signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures
4) BMI: 18.5 $Kg/m^2 \leq$ BMI $\leq$ 30 Kg/m^2

5.2.5 Exclusion Criteria

An individual fulfilling any of the following criteria is to be excluded from trial 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) Receipt of any vaccine in the 4 weeks (28 days) preceding the first trial vaccination or planned receipt of any vaccine prior to V06
4) Previous vaccination against rabies (in pre- or post-exposure regimen) with either the trial vaccine or another vaccine
5) Receipt of immune globulins, blood or blood-derived products in the past 3 months
6) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within

[a] "18 to <65 years" means from the day of the 18th birthday to the day before the 65th birthday. In states where the age of majority to consent to research is >18, inclusion criteria will be from the birthday acquiring the age of majority to the day before the 65th birthday.

the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

7) At high risk for rabies infection during the trial
8) 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
9) Self-reported thrombocytopenia, contraindicating IM vaccination
10) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination
11) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
12) Current alcohol abuse or drug addiction
13) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion
14) Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F [≥ 38.0°C]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided
15) 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 (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
16) History of Guillain-Barré syndrome

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 medical history (reported as diagnosis) including conditions for which the subject is or has been followed by a physician or conditions 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 CRF. The significant medical history section of the CRF contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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

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

The reporting of signs and symptoms 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 trial.

5.2.7 Contraindications for Subsequent Vaccinations

5.2.7.1 Temporary Contraindications

Should a subject experience the condition below, the Investigator will postpone further vaccination until the condition is resolved.

- Febrile illness (temperature ≥100.4°F) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment

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.

5.2.7.2 Definitive Contraindications

Should a subject experience one 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 V06 (VAC5+14D)
- 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 will not be withdrawn due to contraindication but will be followed up for safety and possibly immunogenicity assessment.

5.2.8 Conditions for Withdrawal

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

A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject's permission
- 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 on the CRF.

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

Withdrawn subjects will not 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 (i.e., at least 3 documented telephone calls on different days 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 CRF and in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Trial

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

- **Serious adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an SAE, as defined in Section 9.2.1
- O**ther adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an AE other than an SAE, as defined in Section 9.2.1
- N**on-compliance with protocol:** To be used when the Investigator withdraws a subject from the study because of failure to follow the protocol, including when it is retrospectively discovered that a subject did not fulfill the eligibility criteria. (e.g., not attending visits, not being available for telephone calls, not providing blood samples). The Investigator will provide a comment as to the specific cause of non-compliance.
- **Lost to follow-up:** To be used when the Investigator withdraws a subject from the study because of failure to establish contact, as outlined in Section 5.2.9. The Investigator will provide documentation that contact was attempted (i.e., return of unsigned certified letter receipt).
- **Voluntary withdrawal not due to an adverse event:** To be used when a subject drops out of the study for any reason other than those listed above.

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 trial because of an SAE, other type of AE, non-compliance with the protocol, or loss of eligibility, including definite contraindications.

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.

When early termination is due to an AE or SAE, loss of eligibility, non-compliance with the protocol including definite contraindications, the subject will be contacted.

For subjects where the reason for early termination is voluntary withdrawal, the site will attempt to contact them by V08 (6-month following the last planned vaccination), 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 one dose of the study vaccine(s) has been administered, the subject will not be discontinued from the trial and 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 an e- Pregnancy Reporting Form 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—i.e., details about the delivery and the newborn, or about pregnancy termination—and must update the Pregnancy Reporting Form, this time marking the “Follow-up” checkbox. This information should be provided to the Sponsor within 1 month of delivery.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, 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 and Epidemiology (GPE) Department regardless of when the SAE occurs (e.g., even after the end of the trial).

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's Responsible Medical Officer (RMO) for advice on trial 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 GPE (Please refer to Section 10).

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.5.

5.4 Modification of the Trial and Protocol

Any amendments to this trial 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 e.g., that affect the conduct of the trial 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 or logistical aspect of the trial but does not affect its design or objectives 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 trial, during the period for which IEC / IRB approval has already been given, are not initiated without IEC / IRB review and approval, except to eliminate apparent immediate hazards to subjects.

5.5 Interruption of the Trial

The trial may be discontinued if new data about the investigational product resulting from this or any other trials become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, and / or the IECs / IRBs. If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the regulatory authorities, and the IECs / IRBs of the reason for termination or suspension, as specified by the applicable regulatory requirements.

The Investigator shall promptly inform the trial subjects and assure appropriate therapy and / or follow-up for them.

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 occurrence of any related SAE or related death[a] at any time during the recruitment period will trigger a suspension of enrollment and subsequent vaccination for the enrolled subjects. The FDA will be notified within 48 hours of assessment of the causal relationship of the case.

The SMT will then perform a full evaluation of the case and an analysis of circumstances around the events, and if no increased safety risk is concluded, will provide advice on the appropriate strategy to continue enrollment. The FDA will be notified within 48 hours about the SMT decision.

[a] related cases as assessed by the Investigator and/or Sponsor medical monitor

6 Vaccines 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 modified formulation.
- VRVg-1 is the initial formulation.

Form: freeze-dried

Route: intramuscular (IM) injection into the deltoid muscle

6.1.1 Composition

VRVg-2

Each 0.5 mL dose of VRVg-2 reconstituted vaccine in each of its 3 dosages: low, medium and high, contains Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain fulfilling a potency≥ 2.5 IU (NIH) and the components specified in the following table (Table 6.1):

Table 6.1: [redacted]

[redacted]

Powder and diluent batch numbers are to be determined.

VRVg-1

Each 0.5 mL dose of VRVg-1 reconstituted vaccine contains Rabies Virus – Wistar Rabies Pitman Moore/WI 38 1503-3M strain fulfilling a potency ≥ 2.5 IU (NIH) and the components specified in the following table (Table 6.2)

Table 6.2: [redacted]

[redacted]

* [redacted]

Powder and diluent batch numbers are to be determined.

6.1.2 Preparation and Administration

The procedures for preparing and administering VRVg-2 and VRVg-1 are the same. They 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; e.g., the first injection in the left deltoid, the second in the right deltoid and so on.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.4.1), 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 or other immediate allergic reaction, under the responsibility of trained personnel.

6.1.3 Dose Selection and Timing

VRVg-2

[redacted]

VRVg-1

The dose selected for VRVg-1 formulation will be analogous to that used in previous VRVg trials (VRV01, VRV08, VRV02, VRV04 and VRV06) for comparative purposes.

As described in Section 5.1.2, the vaccination schedule is based on the ACIP and WHO recommendations.

6.2 Identity of Control Product

The control vaccine that will be used in the trial is Imovax® Rabies (licensed in the US)

6.2.1 Composition

Each dose contains:

Powder (batch to be determined):

- Rabies Virus – Wistar rabies PMWI 38 - 1503-3M strain: ≥ 2.5 IU (NIH)
- Human albumin: qs

Diluent (batch to be determined):

Water for injection: qs 1 mL

6.2.2 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.

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.

6.2.3 Dose Selection and Timing

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

6.3 Identity of Other Product

Licensed HRIGs (Imogam® Rabies) will be administered at D0 in all subjects included in the trial for simulated post-exposure treatment.

6.3.1 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.

6.3.2 Preparation and Administration

Imogam® Rabies 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 as presented 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).

6.3.3 Dose Selection and Timing

Imogam® Rabies 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.

6.4 Product Logistics

6.4.1 Labeling and Packaging

Each dose of the different rabies vaccines (i.e., VRVg-1, VRVg-2 and Imovax Rabies) 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 packed into one blister. 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 US and French requirements.

Imogam® Rabies doses will have standard commercial labels.

6.4.2 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.

6.4.2.1 Product Shipment

The Clinical Logistics Coordinator or designee will contact the Investigator or a designee in order 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 (i.e., 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.

6.4.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a qualified staff member to assume this responsibility (e.g. 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. 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 trial site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the authorized person should contact the Sanofi Pasteur representative for further instructions.

6.4.2.3 Product Accountability

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

The necessary information on the product labels is to be entered into the source document.

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

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

6.4.3 Replacement Doses

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

For Imogam® Rabies, if a dose is broken another one will be used.

6.4.4 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 trial period.

6.4.5 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.

6.5 Blinding and Code-breaking Procedures

The study will be conducted in an observer-blind manner for all vaccinations:

- Unblinded qualified study staff member(s), independent of the safety evaluation and other trial evaluations, will prepare and administer the vaccine.
- The blinded staff member(s), including the Investigator, in charge of safety assessment will not know which vaccine is administered.
- The subject will remain blinded 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 (e.g., anaphylactic shock).

The IRT system vendor will be responsible for providing the vaccine dose identification number to be received by the enrolled subject.

The code may be broken by the Investigator only in the event of an SAE and if identification of the vaccine received could influence the treatment of the SAE. Code-breaking should be limited, to the extent possible, to the subject experiencing the SAE.

The blind can be broken by the Investigator or a sub-investigator (medical doctor only[a]), by contacting 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 must notify the Sanofi Pasteur Responsible Medical Officer if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents.

A request for the code to be broken may be made by GPV Department for reporting to Health authorities in the case of an SAE as described in the International Conference on Harmonisation (ICH E2A). In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (i.e., the subject's vaccine dose/ group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPE representative.

In all cases, 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 - D56), but the randomization list will not be provided to Investigators and will be kept internally without access to GCI staff.

6.6 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 call the IRT system to assign a subject number. The subject number will consist of eight digits, the first three digits corresponding to the number of the center followed by five digits corresponding to a chronological order of enrollment. The IRT system will define which product (dose number) will be administered for each vaccination.

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 R&D Quality Assurance Department at Sanofi Pasteur will hold the randomization codes of doses in a secured location.

6.7 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:

[a] according to local regulations

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

6.8 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications including other therapies e.g., blood products, should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during trial participation.

Documentation in the CRF of concomitant medication will be limited to specific categories of medication of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRF from the day of vaccination to the end of the solicited and unsolicited follow-up period (e.g., 28 day safety follow-up) as they may impact the response to the vaccination and impact the consistency of the information collected on concomitant medications at any vaccination.

The "reportable" medications are classified according to 2 categories. These are:

- Category 1 antipyretics, analgesics, non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immune modulators.

Note: inhaled and topical steroids should not be captured.

- Category 2: pertaining to definitive contraindication, as specified below.
  - 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)
  - Thrombocytopenia, bleeding disorder or receipt of anticoagulants contraindicating IM vaccination
  - Administration of a vaccine other than the study vaccine between D0 and V06 (VAC5+ 14D)

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

- Trade name
- Given as treatment or as prophylaxis
- Medication category
- Start and stop dates

Dosage and administration route will not be recorded. Homeopathic medication will not be recorded. Topical medication will not be recorded.

Medication given in response to an AE will be captured in the "Action Taken" column of the AE only. No details will be recorded in the concomitant medication module of the CRF unless the medication 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, V06 and V08. See the Table of Study Procedures and 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At V01, V04, V05, V06 and V08, 5 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; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 Sample Preparation

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

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

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

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

The subject's number and the date of sampling, the number of aliquots obtained, and the subject's parent's/guardian'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 during the entire trial. 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 International Air Transport Association (IATA) 602 regulations.

Samples will be shipped to Global Clinical Immunology (GCI) at Sanofi Pasteur. The address is provided in the Operating Guidelines. Testing will be performed by the GCI laboratory or its designee.

7.4 Future Use of Stored Serum Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 5 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

Subjects will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. 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 laboratory methods. Human genetic tests will never be performed on these samples without individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the trial sites with protocols, ICFs, eCRF, diary cards, as well as with the following trial materials: all study vaccines, HRIGs, pregnancy tests, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders (which will be retrieved at the end of the trial), shipping containers, rulers, and digital thermometers.

The means for performing Electronic Data Capture (EDC) will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the trial.

The Investigator will supply all phlebotomy (with the exception of blood collection tubes, which are provided by the Sponsor), and centrifugation equipment, and biohazard and / or safety supplies. The biohazard and safety supplies include 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. They must allow approximately 1 week for an order to be filled and to have the supplies sent to their site.

9 Endpoints and Assessment Methods

9.1 Immunogenicity

The objective is to describe the immune response induced by VRVg-2 (low, medium and high dosage) versus VRVg-1 and Imovax Rabies, at D14 (7 days after the third injection), at D28 (14 days after the fourth injection) at D42 (14 days after the last injection), and at M7 (6 months after the last injection).

9.1.1 Immunogenicity Endpoints

- Titers (IU/mL) summarized at the subject/timepoint level.
  - RVNA titers against rabies virus obtained by the rapid fluorescent focus inhibition test (RFFIT) at D0, D14, D28, D42 and M7 in all subjects
  - Subject with an RVNA titer ≥ 0.5 IU/mL at D0, D14, D28, D42 and M7
  - Subject with an RVNA titer ≥ LLOQ IU/mL, at D0, D14, D28, D42 and M7
  - Individual titer ratio: D14/D0, D28/D0, D42/D0 and M7/D0

- Virus neutralization: complete or incomplete, summarized at the subject/timepoint level.
  - Subject with complete neutralization at the starting dilution (1/5) of the RFFIT assay at each timepoint

9.1.2 Immunogenicity Assessment Methods

The assay method to quantify neutralizing antibodies against rabies virus in human serum samples is the rapid fluorescent focus inhibition test (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 are 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 either the 1st or 2nd WHO international standard for anti-rabies immunoglobulin or 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 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/timepoint 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 undefined, if duplicates give different results.

9.2 Safety

The objective is to describe the clinical safety profile of VRVg-2 (low, medium and high dosage) versus VRVg-1 and Imovax Rabies, after each vaccine injection.

9.2.1 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 clinical investigation subject administered a pharmaceutical product and which does not necessarily have to 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 concomitant illness
- 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 action taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the trial 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 condition worsens in frequency or intensity, or if in the assessment of the treating physician 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 (e.g., 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. This is not the same as *serious* which is based on patient / event outcome or action criteria usually associated with events that pose a threat to a patient'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 (including overdose):

- 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[d]

Adverse Reaction:

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

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

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 (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

---

[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 Serious Adverse Events, with the exception of: hospitalization planned before inclusion into the study or out-patient 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.

[d] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events 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 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.

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the CRF**.** The assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of:

- Symptom and
- Onset post-vaccination

e.g., injection site pain between D0 and D03 post-vaccination, or headache between D0 and D07 after the last vaccination.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and / or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D7 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE.

An unsolicited non-serious AE is an unsolicited AE excluding SAEs.

Injection Site Reaction:

An injection site reaction[a] is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions.

Systemic AE:

Systemic AEs are all AEs that are not injection 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 site, e.g., erythema that is localized but that is not at the injection site.

In addition, reactions reported at the site(s) of HRIGs administration will be reported as systemic AEs.

[a] All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

Adverse Events of Special Interest (AESIs):

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.

9.2.2 Safety Endpoints

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

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

Collection of injection site reactions:

- Occurrence of solicited (prelisted in the subject's diary card [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 (prelisted 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 serious adverse events (SAEs) throughout the trial.

Other endpoints recorded or derived will be described at the time of statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration, number of days of occurrence, grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

9.2.3 Safety Assessment Methods

9.2.3.1 Immediate Post-vaccination Surveillance Period

Subjects will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination surveillance 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 CRF, as follows:

- Any unsolicited systemic AE occurring during the first 30 minutes post-vaccination will be recorded on the CRF as immediate unsolicited systemic AE.

- Solicited and unsolicited injection site reactions and solicited systemic reactions will not be actively solicited during the 30-minute period. If they occur within 30 minutes of vaccination, they will be recorded and analyzed as starting on the day of vaccination.
- Any SAE occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10.

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

After each vaccination, subjects will be provided with a safety diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days[a] (i.e., D0 to D7) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event, if any (e.g., 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 taken by the subject to treat any **solicited reactions** will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

4: Hospitalization (inpatient)

Table 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRF, together with the intensity scales.

[a] As applicable

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

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card (DC) term	Pain	Redness	Swelling
Definition		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: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	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 DC. 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

CRF 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 ≥ 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 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

* 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.

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 CRF. The preferred route for this trial is oral. Pre-vaccination temperature is also systematically collected on the source document. Tympanic thermometers must not be used.

9.2.3.3 Unsolicited Non-serious Adverse Events From Day 0 to Day 28 After Each Vaccination

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 diary card for this purpose.

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

- Start and stop dates[a]
- Intensity of the event:
  - For measurable unsolicited non-serious 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)
  - Other unsolicited non-serious AEs will be classified according to the following intensity scale:
    - Grade 1: No interference with activity
    - Grade 2: Some interference with activity
    - Grade 3: Significant; prevents daily activity
- Action taken for each AE, if any (e.g., medication)

  The action taken by the subject to treat any **unsolicited AEs** will be classified in the CRF using the following scale:

  0: None

  1: Medication (self-medication with an existing prescription or over-the-counter medication)

  2: Health care provider contact (no new medication prescribed)

[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 trial will be considered as ongoing at the end of the trial.

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

- Whether the AE led to study discontinuation
- Whether the AE was related to vaccination (for unsolicited systemic AEs)

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

  0: Not related – The AE is clearly / most probably caused by other etiologies such as subject's 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 first vaccination

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

  Note: By convention, all injection site AEs (solicited and unsolicited) and all solicited systemic reactions are considered to be related to vaccination and referred to as reactions, and therefore 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 trial 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.

9.2.3.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from inclusion until 6 months after the last vaccination.

Any SAE occurring at any time during the trial will be reported by the Investigator through the EDC system and according to the completion guidelines provided by the Sponsor. 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 (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). The Investigator will assess the causal relationship of the SAE with the investigational product as either "Not related" or "Related", as described in previous section and specifically, in Section 10.4.

See Section 10 for further details on SAE reporting.

9.2.3.5 Adverse Events of Special Interest

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

[a] ICH Guidelines, Clinical Safety Data Management E2A

- 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(23) (24) (25).

9.3 Efficacy

No clinical efficacy data will be obtained in the trial.

10 Reporting of Serious Adverse Events

In order 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 products. It is the responsibility of the Investigator to request all necessary documentation (e.g., 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 into the eSAE Form.

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the trial or experiment must be reported within 24 hours to the Sponsor's GPE Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The SAE form must be signed by a licensed physician (M.D. or D.O.) for whom the task is listed on the Study Task Delegation and Signature List after each update to the Form.

The Investigator must complete the "eSAE Form" in the EDC application. After validation, an e-mail alert will automatically be sent to the GPE mailbox, the CRA and the Clinical Team Leader (CTL). This message will include the country, the study code, the subject number, whether the report is initial or a follow-up, the diagnosis and / or symptoms, the seriousness criteria, the relationship, if related, and the outcome, if fatal.

If the EDC system is unavailable, the site must notify the Sponsor using the paper version of the SAE Reporting Form, as follows:

The Investigator must complete the SAE Reporting Form, check off the "Initial Reporting Form" box, and send it 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: SanofiPasteurPharmaco@sanofipasteur.com

When the system becomes available, the Investigator must transcribe the information from the paper version of the eSAE Form into the EDC system.

If there is need for urgent consultation, the Investigator is to contact a designated Sponsor representative. The contact information is provided in the "List of Investigators and Centers Involved in the Trial" document.

10.2 Follow-up Reporting by the Investigator

The eSAE Form completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). After validation, an e-mail alert will be sent automatically to the GPE Department and to the CRA. All relevant information must be included directly in the eSAE Form. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the GPE 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 product 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 will first be evaluated by the Investigator, using the following definitions:

> **0 - 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 SAE is incompatible with a causal relationship; or the SAE started before the first vaccination.
>
> **1 - Related**: There is a "reasonable possibility" that the SAE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship.
>
> *(ICH Guidelines, Clinical Safety Data Management E2A)*

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

The decision to modify or discontinue the trial may be made after mutual agreement between the Sponsor and the Investigators.

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 [redacted], or the CTL will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the trial protocol.

11 Data Collection and Management

11.1 Data Collection and CRF Completion

Individual safety diary cards, specifically designed for this trial 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 9.2.3. 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.

A memory aid will be provided to the subjects at V07 to help them record information on events occurring between this visit and the V08 (6-month post last vaccination).

Relevant information will be transcribed into the CRF. Any SAE (including AESI) and any pregnancy captured during this 6-month follow-up period will be reported and followed-up as per the normal process for reporting SAEs and pregnancies, respectively.

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 trial information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRF. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRF has been designed specifically for this trial 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 CRFs, 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 guidelines will be provided to assist with data entry during the course of the trial.

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 trial 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 trial 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 in order to track all modifications and to ensure database integrity.

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

11.2 Data Management

Management of Clinical Data

Data generated during the trial will be managed following two different processes:

- Clinical data, defined as all data reported in the CRF, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.
- Data pertaining to SAEs, which are reported by the Investigator on the eSAE Forms or SAE Reporting Forms, and to pregnancies which are reported by the Investigator on the ePregnancy Forms or Pregnancy Reporting Forms, will be handled by the Sponsor's GPE Department.

During the trial, clinical data reported in the CRFs 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 in order to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the trial. 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 database.

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

SAE Data Management

During the trial, data pertaining to SAEs reported on eSAE (or paper SAE) Forms will be integrated into the Sponsor's centralized GPV database.

Upon receipt of an eSAE Form (or paper SAE form), the data will be entered into the GPV database after a duplicate check. Each SAE case will be assigned a case identification number. Each case will be entered in the GPV database and assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. Assessment of related cases will be done in collaboration with the PSO 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 pertaining to SAEs in the GPV database will be reconciled with that in the clinical database.

Pregnancy Data Management

During the trial, data pertaining to pregnancies reported on ePregnancy (or paper Pregnancy) Form will be integrated into the Sponsor's centralized GPV database.

Upon receipt of an ePregnancy Form (or paper Pregnancy Form), the data will be entered into the GPV database after a duplicate check. Each pregnancy case will be assigned a case identification number. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

If pregnancy is associated with a SAE (e.g. abortion, fetal death), this SAE will be reported and followed-up as per the normal process for reporting SAEs (both Pregnancy and SAE forms have to be filled).

The information pertaining to the presence of pregnancies will be reconciled between the GPV and clinical databases.

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

The statistical analysis will be performed in two steps:

A first statistical analysis will be performed when results on all immunogenicity and safety data collected up to D56, i.e. up to 28 days after the primary vaccination series will be obtained and locked.

A final statistical analysis will be performed when immunogenicity and safety results from D56 to M7 will be obtained and locked.

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

The dose for further clinical development will be based on the safety and immunogenicity profiles of the 3 VRVg-2 dosages evaluated in this study in particular the proportion of subjects with RVNA titers ≥ 0.5 international units (IU)/mL, the Geometric Mean Titers and the titer

distribution at all time-points. The study is descriptive and no statistical testing between the groups is planned.

12.1 Statistical Methods

12.1.1 Hypotheses and Statistical Methods for Immunological Objective

12.1.1.1 Hypotheses

No hypothesis will be tested.

12.1.1.2 Statistical Methods

Analysis of RVNA titers after vaccination series will be done per vaccine group using:

- GMTs at D0, D14, D42 and M7 in all subjects
- GM of individual titer ratio (GMTR): on D14/D0, D42/D0 and M7/D0 in all subjects
- The proportion of subjects with RVNA titer ≥0.5 IU/mL at D0, D42 and M7 in all subjects
- The proportion of seropositive subjects at D0, D14, D42 and M7 in all subjects (i.e., subject with an RVNA titer ≥ LLOQ)
- The proportion of subjects with Complete or Incomplete results at the 1/5 starting dilution at D0, D14, D42 and M7 in all subjects.

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

12.1.2 Hypotheses and Statistical Methods for Safety Objective

12.1.2.1 Hypotheses

No hypothesis will be tested.

12.1.2.2 Statistical Methods

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 (26) .

12.2 Analysis Sets

12.2.1 Full Analysis Set

The FAS is defined as the subset of randomized subjects who received at least one dose of the study vaccines.

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 PP analysis set (PPAS) is a subset of the FAS.
The PPAS will be defined for D14 timepoint (in healthy individuals who are vaccinated, the 0.5 IU/mL threshold considered to be protective should be achieved in most individuals by day 14 after the first injection of a post-exposure regimen, with or without simultaneous administration of rabies) (2).

The subjects presenting with at least one of the following relevant protocol deviations before D14 (i.e., 7 days after the third vaccine injection) will be excluded from the PPAS:

- Subject did not meet all inclusion protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive the correct number of the first three doses of vaccine
- Subject received a vaccine other than the one that he/she was randomized to receive
- Preparation and/or administration of vaccine was not done as per protocol for the first three vaccinations

- Subject did not receive vaccine in the proper time window from D0, as follows:
  - Vac2 in [D03-D05]
  - Vac3 in [D07-D09]
- Subject did not provide a post-dose 3 serology sample in the proper time window [D13-D15] from D00
- Subject received a protocol-restricted therapy/medication/vaccine (belonging to category 2)
- Subject's serology sample is missing or did not produce valid test results at both D0 and D14
- Seropositive subject at D0, i.e., 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 Imogam Rabies at D0

Adherence to the definition of the PP analysis set may also be decided during the blind review of data, i.e., before breaking the code.

12.2.4 Other Analysis Set(s)

Not applicable.

12.2.5 Populations Used in Analyses

Immunogenicity analyses will be performed on the FAS, according to the randomized vaccine group. The main immunogenicity analyses will also be performed on the PPAS, according to the injected group.

Safety analyses will be performed on the SafAS, according to the injected 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.

12.4 Interim / Preliminary Analysis

No formal interim analyses are planned; the statistical analysis will be performed in 2 steps as presented in the beginning of this Section 12.

12.5 Determination of Sample Size and Power Calculation

An arbitrary number of 80 subjects per VRVg-2 group and 40 subjects in both, VRVg-1 and control group (Imovax Rabies) will be included.

[redacted]

Table 12.1: [redacted]

[redacted]

In terms of safety, according to the occurrence rate of the observed AEs, 80 subjects will allow for the following 95% CI (Table 12.2):

95% CI calculations corresponding to anticipated AEs rates in VRVg-2 groups of 80 subjects

Table 12.2: 95% CI calculations corresponding to anticipated AEs rates in VRVg-2 groups of 80 subjects

Observed numbers	Observed %	95% CI
8/80	10.0	(4.4; 18.8)
12/80	15.0	(8.0; 24.7)
16/80	20.0	(11.9; 30.4)
20/80	25.0	(16.0; 35.9)
24/80	30.0	(20.3; 41.3)

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Trial / Good Clinical Practice

The conduct of this trial will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for good clinical practice (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, diary cards, medical and hospital records, screening logs, ICFs, telephone contact logs, and worksheets. The purpose of trial source documents is to document the existence of subjects and to substantiate the integrity of the trial 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 diary card, the study coordinator will obtain verbal clarification from the subject, enter the response into the "investigator’s comment" page of the diary card, and transfer the information to the CRF.

The subject pre-screening log should list all individuals contacted by the Investigators to participate in the trial, 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 later 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.

13.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the trial, 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.

[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.

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 trial (i.e., before the inclusion of the first subject in the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the trial protocol and the detailed trial procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRF 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 trial has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the trial, 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 Guidelines for entering data into the CRF, and the Operating Guidelines for detailed trial procedures such as the product management and sample-handling procedures.

After the start of the trial, 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 CRFs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the trial 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 CRFs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., 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 CRF, 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 trial, 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 trial 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 trial documents during these inspections and audits.

13.4.3 Archiving

The Investigator must keep all trial documents after the completion or discontinuation of the trial, whatever the nature of the investigational center (private practice, hospital, or institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, trial documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any trial documents upon less than 90 days advance written notification to the Sponsor. In addition, trial documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the trial documents.

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 trial, including certificates attesting that satisfactory audit and inspection procedures have been carried out, 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 CTA will be signed by all the parties involved in the trial'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 the time and travel required for study visits and procedures.

13.7 Publication Policy

Data derived from this trial are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the trial must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the trial, any participating center may publish or otherwise use its own data provided that any publication of data from the trial gives recognition

to the trial 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 trial 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 trial are not to be considered confidential.

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

14 References List

1 WHO Expert Consultation on rabies. Second Report. WHO Technical Report Series 982. Geneva, Switzerland. 2013.

2 Rabies Vaccines: WHO Position Paper; Weekly Epidemiological Record, No 32, 2010, 85, 309-320.

3 Plotkin SA. Rabies. Clin Infect Dis 2000;30:4-12.

4 Hankins DG, Rosekrans JA. Overview, prevention, and treatment of rabies. Mayo Clin Proc 2004; 79:671-76.

5 Dietzschold B, Schnell M, Koprowski H. Pathogenesis of rabies. Curr Top Microbiol Immunol 2005;292:45-56.

6 Rupprecht CE, Gibbons RV. Prophylaxis against rabies. New Engl J Med 2004;351:2626-35.

7 WHO Expert Committee on Rabies. Eighth report. WHO Technical Report Series 824. Geneva, Switzerland. 1992.

8 Centers for Disease Control and Prevention. Rabies Surveillance Data in the United States available at https://www.cdc.gov/rabies/location/usa/surveillance/index.html. Accessed on 17 January 2017

9 CDC. Human Rabies - Missouri, 2014. MMWR March 18, 2016/65(10);253-6.

10 World Health Organization. Rabies: fact sheet 99, updated March 2016. http://www.who.int/mediacentre/factsheets/fs099/en. Accessed on 17 January 2017.

11 CDC - Recommendation and Reports, Human Rabies Prevention - United States 1999, Recommendation of the ACIP MMWR January 8, 1999/Vol.48/No.RR-1.

12 Dreesen DW. A global review of rabies vaccines for human use. Vaccine 1997; Vol; 15, Suppl., pp S2-S6.

13 Fayaz A. 20 years of rabies post-exposure treatment with cell culture rabies vaccines in Iran (1975-1995).

14 Toovey S; Preventing Rabies with the Verorab Vaccine: 1985-2005 Twenty Years of Clinical Experience. Travel Med Infect Dis. 2007 Nov;5(6):327-48. Epub 2007 Sep 17. Review.

15 Plotkin S.A. State-of-the-art Clinical Article: Rabies. Clinical Infectious Diseases 2000; 30:4-12.

16 European Pharmacopoeia 5.0. Rabies vaccine for Human use prepared in cell cultures. 01/2005:0216.

17 United States Pharmacopeia. Vaccine for Human Use. General Consideration. USP 33 Chapter 1235.

18 Pichon S, Guinet-Morlot F, Minutello M, Donazzolo Y, Rouzier R, Chassard D, et al., A serum-free, purified vero cell rabies vaccine is safe and as immunogenic as the reference vaccine Verorab™ for pre-exposure use in healthy adults: Results from a randomized controlled phase-II trial. Vaccine. 2013 Apr 26;31(18):2295-301.

19 Li R, Huang L, Li J, Mo Z, He B, Wang Y, et al., A next-generation, serum-free, highly purified Vero cell rabies vaccine is safe and as immunogenic as the reference vaccine Verorab® when administered according to a post-exposure regimen in healthy children and adults in China. Vaccine 2013 Oct 19 (31) 5940- 5947

20 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use. ICH Harmonised Tripartite Guideline. Comparability of Biotechnological/Biological Product Subject to Changes in their Manufacturing Process. Q5E. Current Step 4 version dated 18 November 2004.

21 WHO recommendations on Rabies Post-exposure treatment and the correct technique of intradermal immunization against Rabies. WHO/EMC/ZOO/96.

22 Human Rabies Prevention - United States of America 2008. Recommendation of the Advisory Committee on Immunization Practices.

23 Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis and presentation of immunization data. Vaccine (25);2007: 5675-84.

24 Bonhoeffer J, Menkes J, Gold MS, et al. Generalized convulsive seizure as an AE following immunization: case definition and guidelines for data collection, analysis and presentation. Vaccine (22);2004: 557-62.

25 Sejvar JJ, Kohl KS, Bilynsky R, et al. Encephalitis, myelitis and acute disseminated encephalomyelitis (ADEM): Case definitions, guidelines for collection, analysis and presentation of immunization safety data. Vaccine (25);2007: 5771-92.

26 Newcombe R.G., Two-sided confidence intervals for the single proportion: comparison of seven methods, Statistics in Medicine, (1998) 17, 857-72

15 Signature Pages

Document Number	Version Number
CLI_1715279	2.0
Project Code VRVg	
Document Name Protocol body	

	Approver Name	Date (Universal Time)	Reason for Signature
Approval	[redacted]		
Approval			