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

Summary

EudraCT number	2018-004055-20
Trial protocol	FR
Global end of trial date	01 July 2021

Results information

Result version number	v1 (current)
This version publication date	15 July 2022
First version publication date	15 July 2022

Trial information

Trial identification

Sponsor protocol code	VRV13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03965962
WHO universal trial number (UTN)	U1111-1216-6151

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur
Sponsor organisation address	14 Espace Henry Vallée, Lyon, France, 69007
Public contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that Purified Vero Rabies Vaccine - Serum Free Vaccine generation 2 (VRVg-2) was non-inferior to Verorab and Imovax Rabies vaccines when co-administered with human rabies immunoglobulin (HRIG), in terms of proportion of subjects achieving a rabies virus neutralising antibody (RVNA) titer greater than or equal to (>=) 0.5 international units per millilitre (IU/mL) at Day 28, i.e., 14 days after the fourth vaccine injection.

Protection of trial subjects:

Subjects were informed of the risks of participating in the trial in accordance with international guidelines and applicable regulations. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment were also available on site in case of any immediate allergic reactions. Subjects were followed up for safety according to the endpoints of the trial. The safety follow-up for serious adverse events and adverse events of special interest lasted 6 months after the last vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 640
Worldwide total number of subjects	640
EEA total number of subjects	640

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	552
From 65 to 84 years	88
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 active centres in France.

Pre-assignment

Screening details:

A total of 640 subjects were enrolled in the study. Data presented in the disposition table (all milestones) is based on randomised group, except for safety analysis set (SafAS) milestone which is presented based on the actual vaccination group.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Modified double-blind (for Groups 1 to 3): the subject (or legally acceptable representative), and the Investigator remained unaware of the treatment assignments throughout the study. An unblinded qualified trial staff member administered the appropriate vaccine but was not involved in the immunogenicity and safety evaluations. Group 4 was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 VRVg-2+HRIG

Arm description:

Subjects received 0.5 millilitres (mL) intramuscular (IM) injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.

Arm type	Experimental
Investigational medicinal product name	VRVg-2: Purified Vero Rabies Vaccine- Serum Free Vaccine generation 2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM dose at Days 0, 3, 7, 14 and 28.

Investigational medicinal product name	IMOGAM® Rabies-HT Licensed HRIGs
Investigational medicinal product code	
Other name	Rabies immune globulin (human)
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

As per body weight, IM injections in the anterolateral thigh at Day 0.

Arm title	Group 2 Verorab+HRIG

Arm description:

Subjects received 0.5 mL IM injection of Verorab on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.

Arm type	Active comparator

Investigational medicinal product name	Verorab®: purified inactivated rabies vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM dose at Days 0, 3, 7, 14 and 28.

Investigational medicinal product name	IMOGAM® Rabies-HT Licensed HRIGs
Investigational medicinal product code	
Other name	Rabies immune globulin (human)
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

As per body weight, IM injections in the anterolateral thigh at Day 0.

Arm title	Group 3 Imovax Rabies+HRIG

Arm description:

Subjects received 1 mL IM injection of Imovax Rabies on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.

Arm type	Active comparator
Investigational medicinal product name	Imovax® Rabies
Investigational medicinal product code	
Other name	Human Diploid Cell Vaccine (HDCV)
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 mL, IM dose at Days 0, 3, 7, 14 and 28.

Investigational medicinal product name	IMOGAM® Rabies-HT Licensed HRIGs
Investigational medicinal product code	
Other name	Rabies immune globulin (human)
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

As per body weight, IM injections in the anterolateral thigh at Day 0.

Arm title	Group 4 VRVg-2

Arm description:

Subjects received 0.5 mL IM injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28.

Arm type	Experimental
Investigational medicinal product name	VRVg-2: Purified Vero Rabies Vaccine- Serum Free Vaccine generation 2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM dose at Days 0, 3, 7, 14 and 28.

Number of subjects in period 1	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG
Started	320	107	107
Vaccination 1 (Day 0)	318	107	107
Vaccination 2 (Day 3)	317	104	107
Vaccination 3 (Day 7)	311	103	105
Vaccination 4 (Day 14)	301	101 [1]	101
Vaccination 5 (Day 28)	294 [2]	98 [3]	97
Safety analysis set (SafAS)	320	107	107
Completed	295	102	97
Not completed	25	5	10
Consent withdrawn by subject	3	-	-
Adverse event, non-fatal	1	-	-
Lost to follow-up	-	1	-
Protocol deviation	21	4	10

Number of subjects in period 1	Group 4 VRVg-2
Started	106
Vaccination 1 (Day 0)	106
Vaccination 2 (Day 3)	106
Vaccination 3 (Day 7)	105
Vaccination 4 (Day 14)	103
Vaccination 5 (Day 28)	98 [4]
Safety analysis set (SafAS)	104
Completed	100
Not completed	6
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Lost to follow-up	-
Protocol deviation	5

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The vaccinated number of subjects in each visit is less than the number of randomised subjects as not all randomised subjects received vaccination at each visit or not all randomised subjects presented at each visit.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The vaccinated number of subjects in each visit is less than the number of randomised subjects as not all randomised subjects received vaccination at each visit or not all randomised subjects presented at each visit.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: The vaccinated number of subjects in each visit is less than the number of randomised subjects as not all randomised subjects received vaccination at each visit or not all randomised subjects presented at each visit.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The vaccinated number of subjects in each visit is less than the number of randomised subjects as not all randomised subjects received vaccination at each visit or not all randomised subjects presented at each visit.

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 VRVg-2+HRIG
Reporting group description:	
Subjects received 0.5 millilitres (mL) intramuscular (IM) injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.	
Reporting group title	Group 2 Verorab+HRIG
Reporting group description:	
Subjects received 0.5 mL IM injection of Verorab on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.	
Reporting group title	Group 3 Imovax Rabies+HRIG
Reporting group description:	
Subjects received 1 mL IM injection of Imovax Rabies on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.	
Reporting group title	Group 4 VRVg-2
Reporting group description:	
Subjects received 0.5 mL IM injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28.	

Reporting group values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG
Number of subjects	320	107	107
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46.0	46.2	46.3
standard deviation	± 14.7	± 14.8	± 15.6
Gender categorical Units: Subjects			
Female	196	61	65
Male	124	46	42
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	2	0
Asian	4	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	1	0
White	301	102	104
More than one race	1	1	0
Unknown or Not Reported	3	0	0

Reporting group values	Group 4 VRVg-2	Total	
Number of subjects	106	640	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	46.4		
standard deviation	± 15.0	-	
Gender categorical Units: Subjects			
Female	60	382	
Male	46	258	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	4	
Asian	0	8	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	11	
White	105	612	
More than one race	0	2	
Unknown or Not Reported	0	3	

End points

End points reporting groups

Reporting group title	Group 1 VRVg-2+HRIG
Reporting group description:	
Subjects received 0.5 millilitres (mL) intramuscular (IM) injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.	
Reporting group title	Group 2 Verorab+HRIG
Reporting group description:	
Subjects received 0.5 mL IM injection of Verorab on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.	
Reporting group title	Group 3 Imovax Rabies+HRIG
Reporting group description:	
Subjects received 1 mL IM injection of Imovax Rabies on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.	
Reporting group title	Group 4 VRVg-2
Reporting group description:	
Subjects received 0.5 mL IM injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28.	

Primary: Percentage of Subjects With Rabies Virus Neutralising Antibody (RVNA) Titers Greater Than or Equal to (>=) 0.5 International Units per Millilitre (IU/mL)-Non-Inferiority Analysis

End point title	Percentage of Subjects With Rabies Virus Neutralising Antibody (RVNA) Titers Greater Than or Equal to (>=) 0.5 International Units per Millilitre (IU/mL)-Non-Inferiority Analysis[1]
End point description:	
RVNA titer against rabies virus was assessed using the Rapid Fluorescent Focus Inhibition test (RFFIT) assay method. Analysis was performed on the per-protocol analysis set (PPAS) that included all subjects who received at least 1 dose of the study vaccines. The subjects who presented protocol deviations, met PPAS exclusion criteria were excluded from PPAS. Data for this endpoint was planned to be collected and analysed only for Groups 1, 2, and 3.	
End point type	Primary
End point timeframe:	
Day 28	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was planned to be collected and analysed only for Groups 1, 2, and 3.

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	239	77	78	
Units: percentage of subjects				
number (confidence interval 95%)	99.6 (97.7 to 100)	100 (95.3 to 100)	98.7 (93.1 to 100)	

Statistical analyses

Statistical analysis title	Group 1: VRVg-2+HRIG, Group 2: Verorab+HRIG
Comparison groups	Group 1 VRVg-2+HRIG v Group 2 Verorab+HRIG
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in Percentage
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.33
upper limit	4.35

Notes:

[2] - The two-sided 95 percent (%) confidence interval (CI) was calculated based on the Wilson score method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 95% CI of the difference of the percentages between the test group (Group 1) and control group (Group 2) was greater than (>) -5% at Day 28.

Statistical analysis title	Group 1: VRVg-2+HRIG, Group 3: Imovax Rabies+HRIG
Comparison groups	Group 1 VRVg-2+HRIG v Group 3 Imovax Rabies+HRIG
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in Percentage
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	6.5

Notes:

[3] - The two-sided 95 % CI was calculated based on the Wilson score method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 95% CI of the difference of the percentages between the test group (Group 1) and control group (Group 3) was > -5% at Day 28.

Secondary: Percentage of Subjects With Rabies Virus Neutralising Antibody Titers >=0.5 IU/mL

End point title	Percentage of Subjects With Rabies Virus Neutralising Antibody Titers >=0.5 IU/mL

End point description:

RVNA titer against rabies virus was assessed using the RFFIT assay method. Immune response of VRVg-2 was considered sufficient if the lower limit of the 95% CI for percentage of subjects in Group 1 with RVNA titers >=0.5 IU/mL was not less than 95% at Day 28, when the primary non-inferiority objective was achieved at Day 28. Analysis was performed on the PPAS. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 14, Day 28 and Day 42

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	239	77	78	77
Units: percentage of subjects				
number (confidence interval 95%)				
Day 0 (n=239,77,78,77)	0 (0 to 1.5)	0 (0 to 4.7)	0 (0 to 4.6)	0 (0 to 4.7)
Day 14 (n=213,75,68,69)	92.5 (88.1 to 95.6)	88.0 (78.4 to 94.4)	94.1 (85.6 to 98.4)	97.1 (89.9 to 99.6)
Day 28 (n=239,77,78,77)	99.6 (97.7 to 100)	100 (95.3 to 100)	98.7 (93.1 to 100)	100 (95.3 to 100)
Day 42 (n=226,74,76,76)	100 (98.4 to 100)	100 (95.1 to 100)	98.7 (92.9 to 100)	100 (95.3 to 100)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Rabies Virus Neutralising Antibody Titers >=0.2 IU/mL (Lower Limit of Quantification [LLOQ])

End point title	Percentage of Subjects With Rabies Virus Neutralising Antibody Titers >=0.2 IU/mL (Lower Limit of Quantification [LLOQ])

End point description:

RVNA titer against rabies virus was assessed using the RFFIT assay method. Lower limit of quantitation (LLOQ) for the RFFIT assay was 0.2 IU/mL. Analysis was performed on the PPAS. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 14, Day 28 and Day 42

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	239	77	78	77
Units: percentage of subjects				
number (confidence interval 95%)				
Day 0 (n=239,77,78,77)	0 (0 to 1.5)	0 (0 to 4.7)	0 (0 to 4.6)	0 (0 to 4.7)
Day 14 (n=213,75,68,69)	99.5 (97.4 to 100)	100 (95.2 to 100)	98.5 (92.1 to 100)	100 (94.8 to 100)
Day 28 (n=239,77,78,77)	100 (98.5 to 100)	100 (95.3 to 100)	98.7 (93.1 to 100)	100 (95.3 to 100)
Day 42 (n=226,74,76,76)	100 (98.4 to 100)	100 (95.1 to 100)	100 (95.3 to 100)	100 (95.3 to 100)

Statistical analyses

No statistical analyses for this end point

Secondary: Rabies Virus Neutralising Antibody (RVNA) Geometric Mean Titers (GMTs) Against Rabies Virus

End point title	Rabies Virus Neutralising Antibody (RVNA) Geometric Mean Titers (GMTs) Against Rabies Virus

End point description:

RVNA GMT against rabies virus was assessed using the RFFIT assay method. Analysis was performed on the PPAS. Here, 'n' = subjects with available data for each specified category and '99999' is used as space filler which signifies that upper and lower limits of 95% CI were not estimable because all the subjects had same value and no variability was observed.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 14, Day 28 and Day 42

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	239	77	78	77
Units: IU/mL				
geometric mean (confidence interval 95%)				
Day 0 (n=239,77,78,77)	0.100 (0.100 to 0.101)	0.100 (-99999 to 99999)	0.100 (-99999 to 99999)	0.101 (0.099 to 0.102)
Day 14 (n=213,75,68,69)	2.40 (2.09 to 2.76)	1.86 (1.44 to 2.41)	1.83 (1.46 to 2.28)	5.41 (4.24 to 6.90)
Day 28 (n=239,77,78,77)	6.49 (5.75 to 7.34)	5.03 (3.94 to 6.44)	5.51 (4.35 to 6.96)	12.4 (10.5 to 14.5)
Day 42 (n=226,74,76,76)	13.6 (12.3 to 15.0)	9.47 (7.96 to 11.3)	10.7 (8.97 to 12.7)	19.8 (17.5 to 22.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratio (GMTR) of Rabies Virus Neutralising Antibody Titers

End point title	Geometric Mean Titer Ratio (GMTR) of Rabies Virus Neutralising Antibody Titers

End point description:

RVNA titer against rabies virus was assessed using the RFFIT assay method. GMTRs were calculated as the ratio of GMTs post vaccination (i.e., on Day 14, 28 and Day 42) and pre-vaccination on Day 0. Analysis was performed on the PPAS. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 14, Day 28 and Day 42

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	239	77	78	77
Units: ratio				
geometric mean (confidence interval 95%)				
Day 14/Day 0 (n=213,75,68,69)	24.0 (20.8 to 27.6)	18.6 (14.4 to 24.1)	18.3 (14.6 to 22.8)	53.7 (42.1 to 68.4)
Day 28/Day 0 (n=239,77,78,77)	64.8 (57.3 to 73.2)	50.3 (39.4 to 64.4)	55.1 (43.5 to 69.6)	123 (105 to 144)
Day 42/Day 0 (n=226,74,76,76)	135 (122 to 149)	94.7 (79.6 to 113)	107 (89.7 to 127)	197 (173 to 224)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Determined Complete and Determined Incomplete Virus Neutralisation

End point title	Percentage of Subjects with Determined Complete and Determined Incomplete Virus Neutralisation

End point description:

Virus neutralisation was defined as complete (absence of fluorescent cells) and incomplete (presence of fluorescent cells) at the subject/timepoint level at the starting dilution (1/5) of RFFIT assay. Percentage of subjects with determined complete and determined incomplete virus neutralisation were reported. Analysis was performed on PPAS. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 14, Day 28 and Day 42

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	239	77	78	77
Units: percentage of subjects				
number (confidence interval 95%)				
Day 0: Complete Neutralisation (n=231,74,72,74)	0.4 (0 to 2.4)	0 (0 to 4.9)	0 (0 to 5.0)	1.4 (0 to 7.3)
Day 0: Incomplete Neutralisation (n=231,74,72,74)	99.6 (97.6 to 100)	100 (95.1 to 100)	100 (95.0 to 100)	98.6 (92.7 to 100)
Day 14: Complete Neutralisation (n=229,75,75,77)	98.7 (96.2 to 99.7)	100 (95.2 to 100)	98.7 (92.8 to 100)	98.7 (93.0 to 100)
Day 14: Incomplete Neutralisation (n=229,75,75,77)	1.3 (0.3 to 3.8)	0 (0 to 4.8)	1.3 (0 to 7.2)	1.3 (0 to 7.0)

Day 28: Complete Neutralisation (n=237,77,78,77)	100 (98.5 to 100)	100 (95.3 to 100)	98.7 (93.1 to 100)	100 (95.3 to 100)
Day 28: Incomplete Neutralisation (n=237,77,78,77)	0 (0 to 1.5)	0 (0 to 4.7)	1.3 (0 to 6.9)	0 (0 to 4.7)
Day 42: Complete Neutralisation (n=236,77,78,77)	100 (98.4 to 100)	100 (95.3 to 100)	100 (95.4 to 100)	100 (95.3 to 100)
Day 42: Incomplete Neutralisation (n=236,77,78,77)	0 (0 to 1.6)	0 (0 to 4.7)	0 (0 to 4.6)	0 (0 to 4.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Immediate Unsolicited Adverse Events (AEs)

End point title	Percentage of Subjects With Immediate Unsolicited Adverse Events (AEs)

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study vaccine and does not necessary had to have a causal relationship with treatment. An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the case report book (CRB) in terms of diagnosis and/or onset post-vaccination. All subjects were observed for 30 minutes after any vaccination, and any unsolicited AEs occurred during that time were recorded as immediate unsolicited AEs in the CRB. Immediate AEs considered as related to vaccination were recorded as immediate unsolicited adverse reactions (ARs). Analysis was performed on the safety analysis set (SafAS) that included subject who had received at least one dose of the study vaccine and were analysed according to the actual treatment received. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Within 30 minutes after any and each vaccination (Vaccinations 1, 2, 3, 4 and 5)

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	320	107	107	104
Units: percentage of subjects				
number (not applicable)				
Post-any vaccination (n=320, 107, 107, 104)	0.9	0	0	1.0
Post-vaccination 1 (n=320, 107, 107, 104)	0.9	0	0	1.0
Post-vaccination 2 (n=319, 104, 107, 104)	0	0	0	0
Post-vaccination 3 (n=313, 103, 105, 103)	0	0	0	0
Post-vaccination 4 (n=303, 101, 101, 101)	0	0	0	0
Post-vaccination 5 (n=296, 98, 97, 96)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Solicited Injection Site Reactions

End point title	Percentage of Subjects With Solicited Injection Site Reactions

End point description:

A solicited reaction (SR) was an expected AR observed and reported under conditions (nature and onset) prelisted (i.e., solicited) in the protocol and CRB and considered as related to vaccination. An AR was all noxious and unintended responses to a medicinal product related to any dose. Solicited injection site reactions included pain, erythema and swelling at and around the injection site. Analysis was performed on the SafAS. Here, 'n'= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Within 7 days after any and each vaccination (Vaccinations 1, 2, 3, 4 and 5)

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	320	107	107	104
Units: percentage of subjects				
number (not applicable)				
Pain Post-any vaccination (n=320,107,107,104)	44.4	34.6	45.8	42.3
Pain Post-vaccination 1 (n=320,107,107,104)	22.2	17.8	23.4	22.1
Pain Post-vaccination 2 (n=319,104,107,104)	26.3	16.3	15.9	19.2
Pain Post-vaccination 3 (n=312,103,105,103)	23.4	13.6	21.9	22.3
Pain Post-vaccination 4 (n=300,101,100,100)	23.0	11.9	29.0	27.0
Pain Post-vaccination 5 (n=295,98,97,96)	13.6	12.2	24.7	21.9
Erythema Post-any vaccination (n=320,107,107,104)	1.6	4.7	2.8	1.0
Erythema Post-vaccination 1 (n=320,107,107,104)	0	0.9	0.9	0
Erythema Post-vaccination 2 (n=319,104,107,104)	0	0	0	0
Erythema Post-vaccination 3 (n=312,103,105,103)	0	1.0	1.0	0
Erythema Post-vaccination 4 (n=300,101,100,100)	1.0	3.0	1.0	1.0
Erythema Post-vaccination 5 (n=295,98,97,96)	0.7	1.0	1.0	0
Swelling Post-any vaccination (n=320,107,107,104)	1.6	0.9	0.9	0
Swelling Post-vaccination 1 (n=320,107,107,104)	0.3	0	0	0
Swelling Post-vaccination 2 (n=319,104,106,104)	0	0	0	0
Swelling Post-vaccination 3 (n=312,103,105,103)	0.6	0	1.0	0

Swelling Post-vaccination 4 (n=300,101,100,100)	0.7	0	0	0
Swelling Post-vaccination 5 (n=295,98,97,96)	0.3	1.0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Solicited Systemic Reactions

End point title	Percentage of Subjects With Solicited Systemic Reactions

End point description:

SR was an expected AR observed and reported under conditions (nature and onset) prelisted (i.e., solicited) in the protocol and CRB and considered as related to vaccination. An AR was all noxious and unintended responses to a medicinal product related to any dose. Solicited systemic reactions included fever, headache, malaise and myalgia. Analysis was performed on the SafAS. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Up to 7 days after any and each vaccination (Vaccinations 1, 2, 3, 4 and 5)

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	320	107	107	104
Units: percentage of subjects				
number (not applicable)				
Fever Post-any vaccination (n=319,107,107,104)	1.3	1.9	3.7	1.0
Fever Post-vaccination 1 (n=319,107,107,104)	0	0	0.9	0
Fever Post-vaccination 2 (n=318,104,107,104)	0	0	0.9	0
Fever Post-vaccination 3 (n=311,103,105,103)	0.6	1.0	1.0	0
Fever Post-vaccination 4 (n=300,101,100,100)	0	0	2.0	1.0
Fever Post-vaccination 5 (n=295,97,97,95)	0.7	1.0	1.0	0
Headache Post-any vaccination (n=320,107,107,104)	33.4	32.7	35.5	34.6
Headache Post-vaccination 1 (n=320,107,107,104)	13.8	18.7	16.8	16.3
Headache Post-vaccination 2 (n=319,104,107,104)	8.2	9.6	9.3	5.8
Headache Post-vaccination 3 (n=312,103,105,103)	12.2	12.6	15.2	13.6
Headache Post-vaccination 4 (n=300,101,100,100)	9.7	9.9	5.0	14.0
Headache Post-vaccination 5 (n=295,98,97,96)	7.8	7.1	5.2	13.5

Malaise Post-any vaccination (n=320,107,107,104)	10.6	12.1	13.1	12.5
Malaise Post-vaccination 1 (n=320,107,107,104)	6.3	6.5	4.7	3.8
Malaise Post-vaccination 2 (n=319,104,107,104)	2.2	2.9	4.7	1.0
Malaise Post-vaccination 3 (n=312,103,105,103)	2.9	3.9	3.8	5.8
Malaise Post-vaccination 4 (n=300,101,100,100)	2.7	1.0	1.0	6.0
Malaise Post-vaccination 5 (n=295,98,97,96)	2.0	0	2.1	2.1
Myalgia Post-any vaccination (n=320,107,107,104)	36.9	34.6	35.5	31.7
Myalgia Post-vaccination 1 (n=320,107,107,104)	18.1	15.9	21.5	19.2
Myalgia Post-vaccination 2 (n=319,104,107,104)	15.7	10.6	8.4	13.5
Myalgia Post-vaccination 3 (n=312,103,105,103)	16.0	12.6	14.3	11.7
Myalgia Post-vaccination 4 (n=300,101,100,100)	11.7	7.9	14.0	17.0
Myalgia Post-vaccination 5 (n=295,98,97,96)	8.8	8.2	10.3	11.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Unsolicited Adverse Events

End point title	Percentage of Subjects With Unsolicited Adverse Events

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study vaccine and does not necessary had to have a causal relationship with treatment. An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset post-vaccination. Analysis was performed on the SafAS. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Up to 28 days after any and each vaccination (Vaccinations 1, 2, 3, 4 and 5)

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	320	107	107	104
Units: percentage of subjects				
number (not applicable)				
Post-any vaccination (n=320, 107, 107, 104)	45.3	43.0	36.4	40.4
Post-vaccination 1 (n=320, 107, 107, 104)	14.7	20.6	11.2	9.6

Post-vaccination 2 (n=319, 104, 107, 104)	8.5	4.8	10.3	4.8
Post-vaccination 3 (n=313, 103, 105, 103)	9.9	8.7	6.7	7.8
Post-vaccination 4 (n=303, 101, 101, 101)	12.2	8.9	13.9	10.9
Post-vaccination 5 (n=296, 98, 97, 96)	20.3	11.2	12.4	21.9

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)

End point title	Percentage of Subjects With Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study vaccine and does not necessary had to have a causal relationship with treatment. An SAE was any untoward medical occurrence that at any dose resulted in death, life-threatening, initial or prolonged inpatient hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect or a medically important event. An AESI was defined as one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor was appropriate. All SAEs and AESIs occurring during the study that were related to the product administered were reported by the Investigator to the Independent Ethics Committee/Institutional Review Board. Relatedness to study vaccine was based on Investigator's discretion. Analysis was performed on the SafAS.

End point type	Secondary

End point timeframe:

From Baseline (Day 0) up to 6 months after last vaccination (i.e., up to Month 7)

End point values	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG	Group 4 VRVg-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	320	107	107	104
Units: percentage of subjects				
number (not applicable)				
SAE	1.3	3.7	0	2.9
SAE related to study vaccine	0	1.9	0	0
AESI	0	0	0	0
AESI related to study vaccine	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited AE data collected from Day 0 (post-vaccination 1) up to 28 days post any vaccination. SR data collected within 7 days post any vaccination. SAE were collected from Baseline (Day 0) up to 6 months after last vaccination (i.e., up to Month 7)

Adverse event reporting additional description:

Analysis performed on SafAS. SR: an expected AR observed and reported under conditions (nature and onset) prelisted (i.e., solicited) in protocol and CRB and considered as related to vaccination. An unsolicited AE: an observed AE that did not fulfill conditions prelisted (i.e., solicited) in CRB in terms of diagnosis and/or onset post-vaccination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Group 1 VRVg-2+HRIG

Reporting group description:

Subjects received 0.5 millilitres (mL) intramuscular (IM) injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.

Reporting group title	Group 2 Verorab+HRIG

Reporting group description:

Subjects received 0.5 mL IM injection of Verorab on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.

Reporting group title	Group 3 Imovax Rabies+HRIG

Reporting group description:

Subjects received 1 mL IM injection of Imovax Rabies on Days 0, 3, 7, 14 and 28 along with HRIG injection at Day 0.

Reporting group title	Group 4 VRVg-2

Reporting group description:

Subjects received 0.5 mL IM injection of VRVg-2 formulation on Days 0, 3, 7, 14 and 28.

Serious adverse events	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 320 (1.25%)	4 / 107 (3.74%)	0 / 107 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma Benign			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	0 / 107 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Ligament Injury			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 320 (0.31%)	0 / 107 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cervical Radiculopathy			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 320 (0.31%)	0 / 107 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	1 / 107 (0.93%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	0 / 107 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	1 / 107 (0.93%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	1 / 107 (0.93%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
General Physical Health Deterioration			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	1 / 107 (0.93%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	0 / 107 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 320 (0.31%)	0 / 107 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Eating Disorder			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 320 (0.31%)	0 / 107 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 320 (0.00%)	1 / 107 (0.93%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 4 VRVg-2		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 104 (2.88%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma Benign			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ligament Injury			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical Radiculopathy			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyskinesia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic Stroke			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General Physical Health Deterioration			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Eating Disorder			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Erysipelas			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1 VRVg-2+HRIG	Group 2 Verorab+HRIG	Group 3 Imovax Rabies+HRIG
Total subjects affected by non-serious adverse events			
subjects affected / exposed	204 / 320 (63.75%)	59 / 107 (55.14%)	66 / 107 (61.68%)
Nervous system disorders			
Headache	Additional description: Headache events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	113 / 320 (35.31%)	35 / 107 (32.71%)	41 / 107 (38.32%)
occurrences (all)	173	62	59
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 320 (0.94%)	6 / 107 (5.61%)	1 / 107 (0.93%)
occurrences (all)	3	6	1
Injection Site Pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	142 / 320 (44.38%)	37 / 107 (34.58%)	49 / 107 (45.79%)
occurrences (all)	337	74	118
Malaise			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	34 / 320 (10.63%)	13 / 107 (12.15%)	14 / 107 (13.08%)
occurrences (all)	50	15	17
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Myalgia events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	118 / 320 (36.88%)	37 / 107 (34.58%)	38 / 107 (35.51%)
occurrences (all)	221	58	71

Non-serious adverse events	Group 4 VRVg-2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 104 (64.42%)		
Nervous system disorders			
Headache	Additional description: Headache events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	40 / 104 (38.46%)		
occurrences (all)	73		
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Injection Site Pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	44 / 104 (42.31%)		
occurrences (all)	115		
Malaise			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	13 / 104 (12.50%)		
occurrences (all)	19		
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Myalgia events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	34 / 104 (32.69%)		
occurrences (all)	75		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2019	Following changes were made: Any study conducted in healthy volunteers could be put on hold by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) due to any SAE. Consequently, the SAE "multiple crises of abnormal movements in both arms and legs" led to the temporary halt of the study from 06 September 2019 to 10 September 2019. That SAE was considered as related to the vaccine by the Investigator and unrelated by the Sponsor. As per the recommendations of the ANSM, all subjects who were participating in the study had to be informed about the related SAEs in the informed consent form (ICF) or through an addendum to the ICF. The subjects were also informed about the temporary halt and the increase in sample size. The Investigators were notified and the Investigator's Brochure was updated with this information. Due to the temporary halt, the Sponsor increased the sample size to replace subjects who were to be excluded from the PPAS due to inability to perform the vaccination within allowed time windows for the first 4 dose and adjusted the attrition rate of the study from 15% to 20% to ensure the adequate power to fulfill the primary and key secondary objectives.
27 April 2020	Following changes were made: Due to coronavirus disease 2019 (COVID 19) pandemic, enrollment of subjects was paused on 12 March 2020 due to increased number of cases in France. Ongoing vaccinations were stopped on 16 March 2020 due to the confinement established in the country and consequent impossibility to follow study visits within requested time window. As the study vaccine was administered in healthy individuals in simulated schedule, there was no safety issue in case of incomplete vaccination. Different measures were taken according to the stage of vaccination:• For 3 subjects who had finished their vaccination scheme, follow-up was monitored by phone. The 2 due visits (Visit [V] 06 [Day 42] and V07 [Day 56]) were replaced by phone call to monitor safety (no blood sample was taken). • For 29 subjects who had not finished their vaccination scheme, they were withdrawn from the study due to protocol deviation (ie, inability to attend vaccination visit within allowed time windows), but they continued to be followed for safety. The follow-up of these subjects was monitored by phone. •The 6-month follow-up was done by phone as planned in protocol. These measures were taken by Sponsor to ensure the well-being of subjects (ie, to limit exposure to COVID-19) and were implemented without IRB/IEC approval, as per national and international guidance's. However, IRB/IEC and health authorities were informed promptly about measures reported in the amendment. The enrollment resumed as soon as subjects' safety was ensured, and national health authorities and Ethic Committee approved. The Sponsor increased sample size of the study to replace subjects who were to be excluded from PPAS due to inability to attend vaccination visit within allowed time windows for the first 4 dose or inability to take blood samples during the confinement and to ensure adequate statistical power to fulfill the primary and key secondary objectives and allowed further replacement of withdrawn subjects.
09 March 2021	Following changes were made: Most of the subjects were expected to have reached RVNA titers >= 0.5 IU/mL after 4 or 5 doses of any rabies vaccine. If this did not occurred (i.e., RVNA titers < 0.5 IU/mL at Day 42) or occurred lately (i.e., RVNA titers < 0.5 IU/mL up to Day 28 and RVNA titers >= 0.5 IU/mL from Day 42), the absence or delayed immune response to the rabies vaccination might suggested an undiagnosed comorbidity that causes immunosuppression. Therefore, any subject in this situation was to be offered additional blood tests to evaluate a potential immunosuppression, the assessment of the RVNA titer in case of non-response to the rabies vaccine before and after a vaccination with a licensed vaccine in the country might be offered, as applicable and according to the pre-exposure prophylaxis recommendations in national guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 September 2019	The SAE "multiple crises of abnormal movements in both arms and legs" led to the temporary halt of the study from 06 September 2019 to 10 September 2019 as precautionary measurement. That SAE was considered as related to the vaccine by the Investigator and unrelated by the Sponsor. As per the recommendations of the ANSM, all subjects who were participating in the study had to be informed about the related SAEs in the ICF or through an addendum to the ICF. The subjects were also informed about the temporary halt and the increase in sample size. The Investigators were notified and the Investigator's Brochure was updated with this information.	11 September 2019
12 March 2020	Due to the coronavirus disease 2019 (COVID 19) pandemic, the enrollment of subjects was paused on 12 March 2020 due to the increased number of cases in France. The ongoing vaccinations were stopped on 16 March 2020 due to the confinement established in the country and the consequent impossibility to follow study visits within requested time window. As the study vaccine was administered in healthy individuals in a simulated schedule, there was no safety issue in case of incomplete vaccination.	-

Notes:

Limitations and caveats

None reported