



## Clinical trial results:

### 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

#### Summary

EudraCT number	2015-005194-20
Trial protocol	Outside EU/EEA
Global end of trial date	10 March 2012

#### Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	20 April 2016

#### Trial information

##### Trial identification

Sponsor protocol code	VRV08
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01339312
WHO universal trial number (UTN)	U1111-1117-7193

Notes:

#### Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, F-69367
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 33 4 37 37 54 76, ada-maria.minutello@sanofipasteur.com
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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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 March 2012
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

•To demonstrate that VRVg is at least as immunogenic as the reference vaccine, Verorab vaccine, in terms of proportion of subjects with a rabies virus neutralizing antibody (RVNA) titer  $\geq 0.5$  international units (IU)/mL at Day 14, i.e. before the fourth injection, in subjects aged 10 to 17 years and in subjects aged 18 years and over.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. 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 was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	17 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	China: 816
Worldwide total number of subjects	816
EEA total number of subjects	0

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)	176
Adolescents (12-17 years)	232

Adults (18-64 years)	408
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study subjects were enrolled from 17 April 2011 to 07 August 2011 at 1 clinic center in China.

### Pre-assignment

Screening details:

A total of 816 subjects who met all of the inclusion and none of the exclusion criteria were randomized and vaccinated in this study. Two subjects randomized to receive VRVg received Verorab for the 1st injection and were therefore included in the Verorab group for safety analysis.

### Period 1

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

Blinding implementation details:

This was an observer-blind study. Subjects were blinded to which vaccine was administered. Only the person who prepared and administered the vaccine remained unblinded. To maintain the blind, the person who administered the vaccine was different from the person who assessed safety to avoid bias in safety collection. In the event of an emergency (i.e., serious adverse event) the code could be broken as explained in the code-breaking procedures by the Investigator.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	VRVg

Arm description:

Subjects received a total of 5 Purified Vero Rabies Vaccine - Serum Free (VRVg) vaccine injections.

Arm type	Experimental
Investigational medicinal product name	Purified Vero Rabies Vaccine - Serum Free (VRVg)
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, intramuscular (alternating between the left and right deltoid for each injection, starting with the left deltoid for the first injection), 1 injection each on Day 0, 3, 7, 14, and 28 (for a total of 5 injections)

<b>Arm title</b>	Verorab
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Arm description:

Subjects received a total of 5 Purified Vero Rabies Vaccine (Verorab) vaccine injections.

Arm type	Active comparator
Investigational medicinal product name	Purified Vero Rabies Vaccine (Verorab 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, intramuscular (alternating between the left and right deltoid for each injection, starting with the left deltoid for the first injection), 1 injection each on Day 0, 3, 7, 14, and 28 (for a total of 5 injections)

<b>Number of subjects in period 1</b>	VRVg	Verorab
Started	542	274
Completed	540	273
Not completed	2	1
Adverse event, non-fatal	1	1
Serious adverse event	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	VRVg
Reporting group description:	
Subjects received a total of 5 Purified Vero Rabies Vaccine - Serum Free (VRVg) vaccine injections.	
Reporting group title	Verorab
Reporting group description:	
Subjects received a total of 5 Purified Vero Rabies Vaccine (Verorab) vaccine injections.	

Reporting group values	VRVg	Verorab	Total
Number of subjects	542	274	816
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	117	59	176
Adolescents (12-17 years)	155	77	232
Adults (18-64 years)	270	138	408
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	28.1	28.4	
standard deviation	± 17.2	± 17.21	-
Gender categorical			
Units: Subjects			
Female	326	171	497
Male	216	103	319

## End points

### End points reporting groups

Reporting group title	VRVg
Reporting group description:	
Subjects received a total of 5 Purified Vero Rabies Vaccine - Serum Free (VRVg) vaccine injections.	
Reporting group title	Verorab
Reporting group description:	
Subjects received a total of 5 Purified Vero Rabies Vaccine (Verorab) vaccine injections.	

### Primary: Percentage of Healthy Subjects 10 to 17 Years Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL After Three Vaccinations with Either Purified Vero Rabies Vaccine – Serum Free or the Reference Purified Vero Rabies Vaccine

End point title	Percentage of Healthy Subjects 10 to 17 Years Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL After Three Vaccinations with Either Purified Vero Rabies Vaccine – Serum Free or the Reference Purified Vero Rabies Vaccine
End point description:	
Antibody titers to each vaccine were assessed using the rapid fluorescent focus inhibition test (RFFIT) method. Seroconversion was defined as rabies virus neutralizing antibody (RVNA) titers $\geq 0.5$ IU/mL.	
End point type	Primary
End point timeframe:	
Day 14 post-vaccination	

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	126		
Units: Percentage of subjects				
number (not applicable)				
Subjects with RVNA titers $\geq 0.5$ IU/mL	100	100		

### Statistical analyses

Statistical analysis title	Non-inferiority (VRVg-Verorab; Day 14)
Statistical analysis description:	
This was a non-inferiority analysis of the immunogenicity of VRVg vs Verorab, in terms of proportion of subjects with an RVNA titer $\geq 0.5$ IU/mL.	
Comparison groups	VRVg v Verorab

Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Parameter estimate	Difference in proportions (VRVg-Verorab)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	2.96

Notes:

[1] - Non-inferiority was demonstrated if the lower limit of the 95% confidence interval of the difference VRVg - Verorab for proportion of subjects with RVNA titer  $\geq 0.5$  IU/mL is  $> -5.0\%$ . VRG was non-inferior to Verorab.

**Primary: Percentage of Healthy Adult Subjects 18 Years and Older Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer  $\geq 0.5$  IU/mL After Three Vaccinations with Purified Vero Rabies Vaccine – Serum Free or Reference Purified Vero Rabies Vaccine**

End point title	Percentage of Healthy Adult Subjects 18 Years and Older Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL After Three Vaccinations with Purified Vero Rabies Vaccine – Serum Free or Reference Purified Vero Rabies Vaccine
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End point description:

Antibody titers to each vaccine were assessed using the rapid fluorescent focus inhibition test (RFFIT) method. Seroconversion was defined as rabies virus neutralizing antibody (RVNA) titers  $\geq 0.5$  IU/mL.

End point type	Primary
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End point timeframe:

Day 14 post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	125		
Units: Percentage of subjects				
number (not applicable)				
Subjects with RVNA titers $\geq 0.5$ IU/mL	99.6	99.2		

**Statistical analyses**

<b>Statistical analysis title</b>	Non-inferiority (VRVg-Verorab; Day 14)
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Statistical analysis description:

This was a non-inferiority analysis of the immunogenicity of VRVg vs Verorab, in terms of proportion of subjects with an RVNA titer  $\geq 0.5$  IU/mL.

Comparison groups	VRVg v Verorab
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Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
Parameter estimate	Difference in proportions (VRVg-Verorab)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	4.01

Notes:

[2] - Non-inferiority was demonstrated if the lower limit of the 95% confidence interval of the difference VRVg - Verorab for proportion of subjects with RVNA titer  $\geq 0.5$  IU/mL is  $> -5.0\%$ . VRG was non-inferior to Verorab.

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**Secondary: Percentage of Healthy Subjects 10 to 17 Years Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer  $\geq 0.5$  IU/mL Before and Following Primary Series Vaccinations with Purified Vero Rabies Vaccine – Serum Free or Reference Purified Vero Rabies Vaccine**

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End point title	Percentage of Healthy Subjects 10 to 17 Years Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL Before and Following Primary Series Vaccinations with Purified Vero Rabies Vaccine – Serum Free or Reference Purified Vero Rabies Vaccine
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End point description:

Antibody titers to each vaccine were assessed using the rapid fluorescent focus inhibition test (RFFIT) method. Seroconversion was defined as rabies virus neutralizing antibody (RVNA) titers  $\geq 0.5$  IU/mL.

End point type	Secondary
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End point timeframe:

Day 42 post-vaccination

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End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	136		
Units: Percentage of subjects				
number (not applicable)				
Subjects with RVNA titers $\geq 0.5$ IU/mL	100	100		

**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentage of Healthy Adult Subjects 18 Years and Older Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer  $\geq 0.5$  IU/mL After Primary Series Vaccinations with Purified Vero Rabies Vaccine – Serum Free or Purified Vero Rabies Vaccine**

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End point title	Percentage of Healthy Adult Subjects 18 Years and Older Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL After Primary Series Vaccinations with Purified Vero Rabies Vaccine – Serum Free or Purified Vero Rabies Vaccine
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End point description:

Antibody titers to each vaccine were assessed using the rapid fluorescent focus inhibition test (RFFIT) method. Seroconversion was defined as rabies virus neutralizing antibody (RVNA) titers  $\geq 0.5$  IU/mL.

End point type	Secondary
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End point timeframe:

Day 42 post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	136		
Units: Percentage of subjects				
number (not applicable)				
Subjects with RVNA titers $\geq 0.5$ IU/mL	100	100		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) Following Each Primary Series Vaccination with Purified Vero Rabies Vaccine – Serum Free or Purified Vero Rabies Vaccine in Pre-exposure Use in Healthy Subjects Aged 10 to 17 Years

End point title	Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) Following Each Primary Series Vaccination with Purified Vero Rabies Vaccine – Serum Free or Purified Vero Rabies Vaccine in Pre-exposure Use in Healthy Subjects Aged 10 to 17 Years
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End point description:

Antibody titers to each vaccine were assessed using the rapid fluorescent focus inhibition test (RFFIT) method.

End point type	Secondary
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End point timeframe:

Day 0 (pre-vaccination) and Day 14 and Day 42 post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	136		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Geometric mean; Day 0	0.072 (0.07 to 0.073)	0.073 (0.07 to 0.076)		
Geometric mean; Day 14	7.26 (6.5 to 8.11)	8.81 (7.6 to 10.2)		
Geometric mean; Day 42	9.61 (8.6 to 10.7)	11.8 (10.2 to 13.5)		

## Statistical analyses

No statistical analyses for this end point

### **Secondary: Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) After Each Primary Series Vaccination with Purified Vero Rabies Vaccine – Serum Free or Purified Vero Rabies Vaccine in Pre-exposure Use in Healthy Adult Subjects Aged 18 Years and Older**

End point title	Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) After Each Primary Series Vaccination with Purified Vero Rabies Vaccine – Serum Free or Purified Vero Rabies Vaccine in Pre-exposure Use in Healthy Adult Subjects Aged 18 Years and Older
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End point description:

Antibody titers to each vaccine were assessed using the rapid fluorescent focus inhibition test (RFFIT) method.

End point type	Secondary
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End point timeframe:

Day 0 (pre-vaccination) and Day 14 and Day 42 post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	136		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Geometric mean; Day 0	0.071 (0.07 to 0.072)	0.072 (0.07 to 0.075)		
Geometric mean; Day 14	2.75 (2.4 to 3.16)	3.76 (3.12 to 4.55)		
Geometric mean; Day 42	5.09 (4.52 to 5.74)	5.72 (4.86 to 6.73)		

## Statistical analyses

No statistical analyses for this end point

### **Secondary: Percentage of Healthy Subjects Reporting Solicited Injection-site or Systemic Reactions Following Any Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or The Reference Purified Vero Rabies Vaccine**

End point title	Percentage of Healthy Subjects Reporting Solicited Injection-site or Systemic Reactions Following Any Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or The Reference Purified Vero Rabies Vaccine
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End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, and Myalgia.

Grade 3 Solicited injection site reactions (10 to 11 years): Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, > 30 mm. Grade 3 Solicited injection site reactions (12 years and older): Pain, Significant, prevents daily activity; Erythema and Swelling, > 30 mm. Grade 3 Solicited systemic reactions: Fever,  $\geq 39.0^{\circ}\text{C}$ ; Headache, Malaise, and Myalgia, Significant, prevents daily activity.

End point type	Secondary
End point timeframe:	
Day 0 up to Day 7 post-vaccination	

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	274		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; All Subjects	10.2	12.4		
Grade 3 Injection site Pain; All Subjects	0	0.4		
Injection site Erythema; All Subjects	2.2	1.5		
Grade 3 Injection site Erythema; All Subjects	0	0.4		
Injection site Swelling; All Subjects	0.9	1.8		
Grade 3 Injection site Swelling; All Subjects	0	0.4		
Fever; All Subjects	6.9	6.8		
Grade 3 Fever; All Subjects	0	0.8		
Headache; All Subjects	6.3	6.9		
Grade 3 Headache; All Subjects	0.2	0.4		
Malaise; All Subjects	5.6	4		
Grade 3 Malaise; All Subjects	0.2	0		
Myalgia; All Subjects	5.4	4.4		
Grade 3 Myalgia; All Subjects	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Healthy Subjects Aged 10 to 17 Years Reporting Solicited Injection-site or Systemic Reactions Following Any Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or The Reference Purified Vero Rabies Vaccine

End point title	Percentage of Healthy Subjects Aged 10 to 17 Years Reporting Solicited Injection-site or Systemic Reactions Following Any Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or The Reference Purified Vero Rabies Vaccine
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End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, and Myalgia.

Grade 3 Solicited injection site reactions (10 to 11 years): Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, > 30 mm. Grade 3 Solicited injection site reactions (12 years and older): Pain, Significant, prevents daily activity; Erythema and Swelling, > 30 mm. Grade 3 Solicited systemic reactions: Fever,  $\geq 39.0^{\circ}\text{C}$ ; Headache, Malaise, and Myalgia, Significant, prevents daily activity.

End point type	Secondary
End point timeframe:	
Day 0 up to Day 7 post-vaccination	

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	136		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; 10 to 17 years	13.3	14		
Grade 3 Injection site Pain; 10 to 17 years	0	0.7		
Injection site Erythema; 10 to 17 years	3.3	2.2		
Grade 3 Injection site Erythema; 10 to 17 years	0	0		
Injection site Swelling; 10 to 17 years	1.9	2.9		
Grade 3 Injection site Swelling; 10 to 17 years	0	0		
Fever; 10 to 17 years	7.3	8.4		
Grade 3 Fever; 10 to 17 years	0	1.5		
Headache; 10 to 17 years	6.7	5.9		
Grade 3 Headache; 10 to 17 years	0.4	0		
Malaise; 10 to 17 years	5.9	5.1		
Grade 3 Malaise; 10 to 17 years	0.4	0		
Myalgia; 10 to 17 years	6.3	5.9		
Grade 3 Myalgia; 10 to 17 years	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Healthy Subjects Aged 18 Year and Older Reporting Solicited Injection-site or Systemic Reactions Following Any Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or The Reference Purified Vero Rabies Vaccine

End point title	Percentage of Healthy Subjects Aged 18 Year and Older Reporting Solicited Injection-site or Systemic Reactions Following Any Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or The Reference Purified Vero Rabies Vaccine
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End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, and Myalgia.

Grade 3 Solicited injection site reactions (10 to 11 years): Pain, Incapacitating, unable to perform usual

activities; Erythema and Swelling, > 30 mm. Grade 3 Solicited injection site reactions (12 years and older): Pain, Significant, prevents daily activity; Erythema and Swelling, > 30 mm. Grade 3 Solicited systemic reactions: Fever,  $\geq 39.0^{\circ}\text{C}$ ; Headache, Malaise, and Myalgia, Significant, prevents daily activity.

End point type	Secondary
End point timeframe:	
Day 0 up to Day 7 post-vaccination	

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	138		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; 18 Years and Over	7	10.9		
Grade 3 Injection site Pain; 18 Years and Over	0	0		
Injection site Erythema; 18 Years and Over	1.1	0.7		
Grade 3 Injection site Erythema; 18 Years and Over	0	0.7		
Injection site Swelling; 18 Years and Over	0	0.7		
Grade 3 Injection site Swelling; 18 Years and Over	0	0.7		
Fever; 18 Years and Over	6.4	5.3		
Grade 3 Fever; 18 Years and Over	0	0		
Headache; 18 Years and Over	5.9	8		
Grade 3 Headache; 18 Years and Over	0	0.7		
Malaise; 18 Years and Over	5.2	2.9		
Grade 3 Malaise; 18 Years and Over	0	0		
Myalgia; 18 Years and Over	4.4	2.9		
Grade 3 Myalgia; 18 Years and Over	0	0		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 up to Day 28 post-vaccination.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13
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### Reporting groups

Reporting group title	VRVg
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Reporting group description:

Subjects received a total of 5 Purified Vero Rabies Vaccine - Serum Free (VRVg) vaccine injections.

Reporting group title	Verorab
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Reporting group description:

Subjects received a total of 5 Purified Vero Rabies Vaccine (Verorab) vaccine injections.

Serious adverse events	VRVg	Verorab	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 542 (0.37%)	0 / 274 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 542 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VRVg	Verorab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 542 (10.15%)	34 / 274 (12.41%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	34 / 542 (6.27%)	19 / 274 (6.93%)	
occurrences (all)	34	19	

General disorders and administration site conditions			
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed	55 / 542 (10.15%)	34 / 274 (12.41%)	
occurrences (all)	55	34	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	36 / 542 (6.64%)	18 / 274 (6.57%)	
occurrences (all)	36	18	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 542 (5.54%)	11 / 274 (4.01%)	
occurrences (all)	30	11	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 542 (5.35%)	12 / 274 (4.38%)	
occurrences (all)	29	12	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2011	Exclusion criteria were modified and included clarification on non-inclusion of patients who self-reported seropositivity to hepatitis B, updated contraindications, and a more specific definition of bites by suspected rabid animals.
08 July 2011	The sample size was increased (due to an increase in the percentage of non-evaluable subjects) in order to appropriately assess the primary objective of the study.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24148575>