Clinical trial results:
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

Summary

EudraCT number	2009-009877-85
Trial protocol	FR
Global end of trial date	14 February 2011

Results information

Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	04 February 2015

Trial information

Trial identification

Sponsor protocol code	VRV01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00948272
WHO universal trial number (UTN)	U1111-1111-4382

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 5851, sylvie.pichon@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 4 37 37 5851, sylvie.pichon@sanofipasteur.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	20 April 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that VRVg (PR1) is at least as immunogenic as the reference vaccine, Verorab (PR2), in terms of seroconversion rate at Day 42, i.e. 14 days after the last vaccination of primary vaccination series.

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 kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Verorab, licensed since 1985 and also marketed as Vaccin Rabique Pasteur in France, was used as a reference vaccine.

Actual start date of recruitment	20 July 2009
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	France: 385
Worldwide total number of subjects	385
EEA total number of subjects	385

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)	385
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 20 July 2009 to 27 July 2009 in 6 clinical centers in France.

Pre-assignment

Screening details:

A total of 385 subjects who met all inclusion criteria and none of the exclusion criteria were randomized, 384 subjects were vaccinated.

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

Blinding implementation details:

Neither the Investigator, the subjects, nor the Sponsor knew the vaccine administered. The product preparation and administration, and the assessment of safety were performed by 2 different individuals in separate rooms. The Investigator or delegate included subjects and evaluated the immediate safety post- vaccination. The nurse/vaccinator prepared and administered the vaccine in a separate room and had sole access to the product accountability forms.

Arms

Are arms mutually exclusive?	Yes
Arm title	VRVg

Arm description:

Subjects aged 18 to 60 years who received three injections of Purified Vero Rabies Vaccine - Serum Free (VRVg) for primary series on Day 0, 7, and 28 and a VRVg booster 12 months after the first vaccine injection.

Arm type	Experimental
Investigational medicinal product name	Purified Vero Rabies Vaccine - Serum Free (VRVg)
Investigational medicinal product code	382
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular, 3 injections on Day 0, 7, and 28 (primary series) and a booster 12 months after the first vaccine injection.

Arm title	Verorab

Arm description:

Subjects aged 18 to 60 years who received three injections of Verorab for primary series on Day 0, 7, and 28 and randomized to receive either Verorab or VRVg booster 12 months after the first vaccine injection.

Arm type	Active comparator
Investigational medicinal product name	Verorab
Investigational medicinal product code	084
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular, 3 injections on Day 0, 7, and 28 (primary series) and a booster with either vaccine at 12 months after the first vaccine injection.

Investigational medicinal product name	Purified Vero Rabies Vaccine - Serum Free (VRVg)
Investigational medicinal product code	382
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular, 3 injections on Day 0, 7, and 28 (primary series) and a booster with either vaccine at 12 months after the first vaccine injection.

Number of subjects in period 1	VRVg	Verorab
Started	257	128
Completed	250	126
Not completed	7	2
Adverse event, serious fatal	-	1
Consent withdrawn by subject	3	1
Adverse event, non-fatal	2	-
Lost to follow-up	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	VRVg
Reporting group description:	
Subjects aged 18 to 60 years who received three injections of Purified Vero Rabies Vaccine - Serum Free (VRVg) for primary series on Day 0, 7, and 28 and a VRVg booster 12 months after the first vaccine injection.	
Reporting group title	Verorab
Reporting group description:	
Subjects aged 18 to 60 years who received three injections of Verorab for primary series on Day 0, 7, and 28 and randomized to receive either Verorab or VRVg booster 12 months after the first vaccine injection.	

Reporting group values	VRVg	Verorab	Total
Number of subjects	257	128	385
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	257	128	385
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	39	39	
standard deviation	± 13.3	± 13.1	-
Gender categorical Units: Subjects			
Female	156	74	230
Male	101	54	155

End points

End points reporting groups

Reporting group title	VRVg
Reporting group description:	
Subjects aged 18 to 60 years who received three injections of Purified Vero Rabies Vaccine - Serum Free (VRVg) for primary series on Day 0, 7, and 28 and a VRVg booster 12 months after the first vaccine injection.	
Reporting group title	Verorab
Reporting group description:	
Subjects aged 18 to 60 years who received three injections of Verorab for primary series on Day 0, 7, and 28 and randomized to receive either Verorab or VRVg booster 12 months after the first vaccine injection.	

Primary: Percentage of Healthy Adult Subjects Achieving Seroconversion After Primary Series Vaccination with Either Purified Vero Rabies Vaccine–Serum Free or Reference Purified Vero Rabies Vaccine in Pre-Exposure Use

End point title	Percentage of Healthy Adult Subjects Achieving Seroconversion After Primary Series Vaccination with Either Purified Vero Rabies Vaccine–Serum Free or Reference Purified Vero Rabies Vaccine in Pre-Exposure Use
End point description:	
Rabies virus neutralizing antibody titers were assessed using rapid fluorescent focus inhibition test (RFFIT). Seroconversion was defined as subject with a rabies virus neutralizing antibody (RVNA) titer ≥0.5 IU/mL on Day 42.	
End point type	Primary
End point timeframe:	
Day 42 post-vaccination	

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	118		
Units: Percentage of subjects				
number (not applicable)				
Subjects with RVNA titer ≥0.5 IU/mL	99.6	100		

Statistical analyses

Statistical analysis title	Non-inferiority of VRVg versus Verorab
Comparison groups	VRVg v Verorab

Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	2.7

Notes:

[1] - Non-inferiority concluded if the low limit of the two-sided 95% CI of the difference VRVg - Verorab for proportion of subjects with RVNA titer ≥0.5 IU/mL is > -5.0%.

Secondary: Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) Following Each Primary Series Vaccination with Either Purified Vero Rabies Vaccine – Serum Free or Reference Purified Vero Rabies Vaccine in Pre-exposure Use in Healthy Adult Subjects

End point title	Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) Following Each Primary Series Vaccination with Either Purified Vero Rabies Vaccine – Serum Free or Reference Purified Vero Rabies Vaccine in Pre-exposure Use in Healthy Adult Subjects

End point description:

Rabies virus neutralizing antibody titers were assessed using rapid fluorescent focus inhibition test (RFFIT).

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and Day 42, Month 6, and Month 12 post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	128		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Day 0	0.113 (0.104 to 0.122)	0.105 (0.099 to 0.111)		
Day 42	13.5 (12.1 to 15)	14.8 (13 to 16.9)		
Month 6	1.08 (0.954 to 1.23)	1.52 (1.28 to 1.8)		
Month 12	0.666 (0.58 to 0.765)	0.968 (0.797 to 1.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Seroconversion Before and After

Primary Series Vaccination with Either Purified Vero Rabies Vaccine–Serum Free or Reference Purified Vero Rabies Vaccine in Pre-exposure Use

End point title	Percentage of Subjects Achieving Seroconversion Before and After Primary Series Vaccination with Either Purified Vero Rabies Vaccine–Serum Free or Reference Purified Vero Rabies Vaccine in Pre-exposure Use

End point description:

Rabies virus neutralizing antibody titers were assessed using rapid fluorescent focus inhibition test (RFFIT). Seroconversion was defined as subject with a rabies virus neutralizing antibody (RVNA) titer ≥0.5 IU/mL.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and Day 42, Month 6, and Month 12 post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	128		
Units: Percentage of subjects				
number (not applicable)				
Day 0	2.7	1.6		
Day 42	99.6	100		
Month 6	89.1	93.5		
Month 12	77.5	80.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Seroconversion After Primary Series with Either Purified Vero Rabies Vaccine–Serum Free (VRVg) or Reference Purified Vero Rabies Vaccine and Booster with VRVg

End point title	Percentage of Subjects Achieving Seroconversion After Primary Series with Either Purified Vero Rabies Vaccine–Serum Free (VRVg) or Reference Purified Vero Rabies Vaccine and Booster with VRVg

End point description:

Rabies virus neutralizing antibody titers were assessed using rapid fluorescent focus inhibition test (RFFIT). Seroconversion was defined as subject with a rabies virus neutralizing antibody (RVNA) titer ≥0.5 IU/mL.

End point type	Secondary

End point timeframe:

Month 12 and Month 12 + 14 days post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	57		
Units: Percentage of subjects				
number (not applicable)				
Month 12	77.4	77.2		
Month 12 + 14 days	99.6	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Healthy Adult Subjects achieving Seroconversion Following Primary Series and Booster with Either Purified Vero Rabies Vaccine–Serum Free or Reference Purified Vero Rabies Vaccine

End point title	Percentage of Healthy Adult Subjects achieving Seroconversion Following Primary Series and Booster with Either Purified Vero Rabies Vaccine–Serum Free or Reference Purified Vero Rabies Vaccine

End point description:

Rabies virus neutralizing antibody titers were assessed using rapid fluorescent focus inhibition test (RFFIT). Seroconversion was defined as subject with a rabies virus neutralizing antibody (RVNA) titer ≥0.5 IU/mL.

End point type	Secondary

End point timeframe:

Month 12 and Month 12 + 14 days post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	60		
Units: Percentage of subjects				
number (not applicable)				
Month 12	77.4	83.3		
Month 12 + 14 days	99.6	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) After Primary Series with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or Reference Purified Vero Rabies Vaccine and Booster with VRVg in Healthy Adult Subjects

End point title	Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) After Primary Series with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or Reference Purified Vero Rabies

	Vaccine and Booster with VRVg in Healthy Adult Subjects

End point description:

Rabies virus neutralizing antibody titers were assessed using rapid fluorescent focus inhibition test (RFFIT).
The booster vaccine for this outcome is the Purified Vero Rabies Vaccine – Serum Free (VRVg)

End point type	Secondary

End point timeframe:

Month 12 and Month 12 + 14 days post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	57		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Month 12	0.667 (0.58 to 0.766)	0.912 (0.678 to 1.23)		
Month 12 + 14 days	27.1 (23.3 to 31.4)	28.4 (21.1 to 38.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) Following Primary Series Vaccination and Booster Vaccination with Either Purified Vero Rabies Vaccine – Serum Free or the Reference Purified Vero Rabies Vaccine

End point title	Geometric Mean Titers of Rabies Virus Neutralizing Antibodies (RVNA) Following Primary Series Vaccination and Booster Vaccination with Either Purified Vero Rabies Vaccine – Serum Free or the Reference Purified Vero Rabies Vaccine

End point description:

Rabies virus neutralizing antibody titers were assessed using rapid fluorescent focus inhibition test (RFFIT).
The booster vaccine was the same as same primary vaccine for this outcome.

End point type	Secondary

End point timeframe:

Month 12 and Month 12 + 14 days post-vaccination

End point values	VRVg	Verorab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	60		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Month 12	0.667 (0.58 to 0.766)	1.03 (0.792 to 1.34)		

Month 12 + 14 days	27.1 (23.3 to 31.4)	22.5 (17.9 to 28.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Healthy Adult Subjects Reporting Solicited Injection-site or Systemic Reactions Following Primary Series Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or the Reference Purified Vero Rabies Vaccine

End point title	Percentage of Healthy Adult Subjects Reporting Solicited Injection-site or Systemic Reactions Following Primary Series Vaccination with Either Purified Vero Rabies Vaccine – Serum Free (VRVg) or the Reference Purified Vero Rabies Vaccine

End point description:

Solicited injection site: Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, and Myalgia. Severe injection site: Pain – Significant; prevents daily activity; Erythema and Swelling – >10 cm. Severe systemic reactions: Fever – ≥39.0°C; Headache, Malaise, and Myalgia – Significant; prevents daily activities.

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	256	128		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain; Post-Any Injection	25	34.4		
Grade 3 Injection site Pain; Post-Any Injection	0	0		
Injection site Erythema; Post-Any Injection	0.8	3.9		
Grade 3 Injection site Erythema;Post-Any Injection	0	0		
Injection site Swelling; Post-Any Injection	1.2	4.7		
Grade 3 Injection site Swelling;Post-Any Injection	0	0		
Injection site Pain; Post-Injection 1	11.4	18.8		
Grade 3 Injection site Pain; Post-Injection 1	0	0		
Injection site Erythema; Post-Injection 1	0.4	1.6		
Grade 3 Injection site Erythema; Post-Injection 1	0	0		
Injection site Swelling; Post-Injection 1	1.2	1.6		
Grade 3 Injection site Swelling; Post-Injection 1	0	0		
Injection site Pain; Post-Injection 2	10.3	17.3		

Grade 3 Injection site Pain; Post-Injection 2	0	0		
Injection site Erythema; Post-Injection 2	0	1.6		
Grade 3 Injection site Erythema; Post-Injection 2	0	0		
Injection site Swelling; Post-Injection 2	0.4	0.8		
Grade 3 Injection site Swelling; Post-Injection 2	0	0		
Injection site Pain; Post-Injection 3	14.8	16.5		
Grade 3 Injection site Pain; Post-Injection 3	0	0		
Injection site Erythema; Post-Injection 3	0.8	2.4		
Grade 3 Injection site Erythema; Post-Injection 3	0	0		
Injection site Swelling; Post-Injection 3	0.8	2.4		
Grade 3 Injection site Swelling; Post-Injection 3	0	0		
Fever; Post-Any Injection	0.8	3.9		
Grade 3 Fever; Post-Any Injection	0	0.8		
Headache; Post-Any Injection	34.4	34.4		
Grade 3 Headache; Post-Any Injection	1.2	1.6		
Malaise; Post-Any Injection	9	16.4		
Grade 3 Malaise; Post-Any Injection	0.4	0.8		
Myalgia; Post-Any Injection	29.7	25		
Grade 3 Myalgia; Post-Any Injection	1.2	0.8		
Fever; Post-Injection 1	0.8	2.3		
Grade 3 Fever; Post-Injection 1	0	0.8		
Headache; Post-Injection 1	23.9	21.9		
Grade 3 Headache; Post-Injection 1	0	0.8		
Malaise; Post-Injection 1	6.7	12.5		
Grade 3 Malaise; Post-Injection 1	0.4	0		
Myalgia; Post-Injection 1	19.2	15.6		
Grade 3 Myalgia; Post-Injection 1	0.4	0		
Fever; Post-Injection 2	0	0.8		
Grade 3 Fever; Post-Injection 2	0	0		
Headache; Post-Injection 2	17	15.7		
Grade 3 Headache; Post-Injection 2	0.4	0.8		
Malaise; Post-Injection 2	2.4	3.9		
Grade 3 Malaise; Post-Injection 2	0	0.8		
Myalgia; Post-Injection 2	11.5	10.2		
Grade 3 Myalgia; Post-Injection 2	0.4	0.8		
Fever; Post-Injection 3	0	0.8		
Grade 3 Fever; Post-Injection 3	0	0		
Headache; Post-Injection 3	11.2	11.8		
Grade 3 Headache; Post-Injection 3	0.8	0		
Malaise; Post-Injection 3	0.8	2.4		
Grade 3 Malaise; Post-Injection 3	0	0		
Myalgia; Post-Injection 3	9.6	7.1		
Grade 3 Myalgia; Post-Injection 3	0.4	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 (post-vaccination) up to Day 28 post-vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	VRVg

Reporting group description:

Subjects aged 18 to 60 years who received three injections of Purified Vero Rabies Vaccine - Serum Free (VRVg) for primary series on Day 0, 7, and 28 and a VRVg booster 12 months after the first vaccine injection.

Reporting group title	Verorab

Reporting group description:

Subjects aged 18 to 60 years who received three injections of Verorab for primary series on Day 0, 7, and 28 and randomized to receive either Verorab or VRVg booster 12 months after the first vaccine injection.

Serious adverse events	VRVg	Verorab	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 256 (0.39%)	1 / 128 (0.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 256 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	88 / 256 (34.38%)	44 / 128 (34.38%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	88 / 256 (34.38%)	44 / 128 (34.38%)	
occurrences (all)	132	63	
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	64 / 256 (25.00%)	44 / 128 (34.38%)	
occurrences (all)	92	67	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 256 (8.98%)	21 / 128 (16.41%)	
occurrences (all)	25	24	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 256 (5.47%)	5 / 128 (3.91%)	
occurrences (all)	15	6	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	76 / 256 (29.69%)	32 / 128 (25.00%)	
occurrences (all)	102	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2009	Clarification on the volume of vaccine to be administered. The volume of the diluent was ≥0.5 mL; therefore, after reconstitution of the vaccine, the volume of the solution to be administered could vary from 0.49 to 0.57 mL.
15 April 2010	Updated information provided in the protocol and Informed Consent Form to ensure consistency across documents submitted to the Independent Ethics Committee and to French Health Authority.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported