Clinical trial results:
Immunogenicity and Safety of the Purified Vero Rabies Vaccine- Serum Free (VRVg) in Comparison with the Human Diploid Cell Vaccine, IMOVAX® Rabies in a Pre-exposure Prophylaxis Regimen in Healthy Children and Adolescents Aged 2 to 17 Years

Summary

EudraCT number	2015-003203-30
Trial protocol	Outside EU/EEA
Global end of trial date	14 April 2014

Results information

Result version number	v1
This version publication date	31 January 2018
First version publication date	31 January 2018

Trial information

Trial identification

Sponsor protocol code	VRV06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01930357
WHO universal trial number (UTN)	U1111-1127-7340
Other trial identifiers	The Philippine Health Research Registry: PHRR130822-000107

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
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 4 37 37 54 76, ada-maria.minutello@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 April 2014
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 (VRVg) is non-inferior to Imovax Rabies in terms of proportion of subjects achieving a rabies virus neutralizing antibody (RVNA) titer >=0.5 international units (IU)/mL at Day 42 (D42), i.e. 14 days after the last vaccination.

• To describe if at least 99% of subjects achieve an RVNA titer >=0.5 IU/mL at D42 with a lower bound of the 95% confidence interval (CI) of at least 97%, in the VRVg group.

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:

Human diploid cell vaccine (HDCV), licensed since 1975 and also marketed worldwide as Imovax® Rabies, was used as a reference vaccine.

Actual start date of recruitment	03 September 2013
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	Philippines: 342
Worldwide total number of subjects	342
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)	171
Adolescents (12-17 years)	171
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study subjects were enrolled in 2 main centers in the Philippines from 03 September 2013 to 16 October 2013.

Pre-assignment

Screening details:

A total of 342 subjects who met all of the inclusion and none of the exclusion criteria were randomized and vaccinated in this study.

Period 1

Period 1 title	Overall period (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
Arm title	Purified Vero Rabies Vaccine - Serum Free (VRVg)

Arm description:

Subjects received a total of 3 VRVg vaccine injections.

Arm type	Experimental
Investigational medicinal product name	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, 7, and 28 (for a total of 3 injections).

Arm title	Imovax Rabies

Arm description:

Subjects received a total of 3 Imovax Rabies vaccine injections.

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

Dosage and administration details:

1 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, 7, and 28 (for a total of 3 injections).

Number of subjects in period 1	Purified Vero Rabies Vaccine - Serum Free (VRVg)	Imovax Rabies
Started	229	113
Completed	224	110
Not completed	5	3
Adverse event, serious fatal	-	1
Consent withdrawn by subject	2	-
Adverse Event	1	-
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Purified Vero Rabies Vaccine - Serum Free (VRVg)
Reporting group description:	
Subjects received a total of 3 VRVg vaccine injections.	
Reporting group title	Imovax Rabies
Reporting group description:	
Subjects received a total of 3 Imovax Rabies vaccine injections.	

Reporting group values	Purified Vero Rabies Vaccine - Serum Free (VRVg)	Imovax Rabies	Total
Number of subjects	229	113	342
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)	115	56	171
Adolescents (12-17 years)	114	57	171
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	11.0	10.7	
standard deviation	± 4.3	± 4.5	-
Gender categorical Units: Subjects			
Female	110	63	173
Male	119	50	169

End points

End points reporting groups

Reporting group title	Purified Vero Rabies Vaccine - Serum Free (VRVg)
Reporting group description:	
Subjects received a total of 3 VRVg vaccine injections.	
Reporting group title	Imovax Rabies
Reporting group description:	
Subjects received a total of 3 Imovax Rabies vaccine injections.	

Primary: Percentage of Subjects Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer >=0.5 IU/mL at Day 42

End point title	Percentage of Subjects Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer >=0.5 IU/mL at Day 42
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 >=0.5 IU/mL. The analysis was performed using per-protocol analysis set (PPAS) which was a subset of full analysis set (FAS defined as: all randomized subjects who received at least one dose of the study vaccine).	
End point type	Primary
End point timeframe:	
Day 42	

End point values	Purified Vero Rabies Vaccine - Serum Free (VRVg)	Imovax Rabies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	112		
Units: Percentage of subjects				
number (not applicable)				
Subjects with RVNA titers >=0.5 IU/mL	100	100		

Statistical analyses

Statistical analysis title	Non-inferiority (VRVg-Imovax Rabies; Day 42)
Statistical analysis description:	
This was a non-inferiority analysis of the immunogenicity of VRVg vs Imovax Rabies, in terms of proportion of subjects with an RVNA titer >=0.5 IU/mL.	
Comparison groups	Purified Vero Rabies Vaccine - Serum Free (VRVg) v Imovax Rabies

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in proportions
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	3.32

Notes:

[1] - Non-inferiority was demonstrated if the lower limit of the 95% confidence interval of the difference VRVg - Imovax Rabies for proportion of subjects with RVNA titer >=0.5 IU/mL was >-5.0%.

Secondary: Percentage of Subjects Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer >=0.5 IU/mL at Days 0, 42 and Month 6

End point title	Percentage of Subjects Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer >=0.5 IU/mL at Days 0, 42 and Month 6

End point description:

Antibody titers to each vaccine were assessed using the RFFIT method. Seroconversion was defined as rabies virus neutralizing antibody (RVNA) titers >=0.5 IU/mL. Analysis was performed using FAS which included randomized subjects who received at least one dose of the study vaccine. Here 'n' signifies number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

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

End point values	Purified Vero Rabies Vaccine - Serum Free (VRVg)	Imovax Rabies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	113		
Units: Percentage of subjects				
number (not applicable)				
Day 0 (pre-vaccination) (n = 229, 113)	1.7	0.9		
Day 42 (n = 226, 113)	100	100		
Month 6 (n = 224, 110)	91.1	97.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Rabies Virus Neutralizing Antibodies (RVNA)

End point title	Geometric Mean Titers (GMTs) of Rabies Virus Neutralizing Antibodies (RVNA)

End point description:

Antibody titers to each vaccine were assessed using the RFFIT method. Analysis was performed using

FAS which included randomized subjects who received at least one dose of the study vaccine. Here 'n' signifies evaluable subjects in each specified categories.

End point type	Secondary

End point timeframe:

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

End point values	Purified Vero Rabies Vaccine - Serum Free (VRVg)	Imovax Rabies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	113		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Day 0 (pre-vaccination) (n = 229, 113)	0.105 (0.100 to 0.110)	0.102 (0.098 to 0.107)		
Day 42 (n = 226, 113)	14.3 (13.0 to 15.7)	17.2 (15.2 to 19.4)		
Month 6 (n = 224, 110)	1.22 (1.08 to 1.38)	1.54 (1.34 to 1.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, and Swelling) and Systemic Reactions (Fever, Headache, Malaise, Myalgia)

End point title	Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, and Swelling) and Systemic Reactions (Fever, Headache, Malaise, Myalgia)

End point description:

Solicited reaction: AE prelisted in eCRF and considered to be related to vaccination. A solicited reaction: an adverse drug reaction (ADR) observed and reported under conditions (nature and time to onset) prelisted (i.e., solicited) in the eCRF. Unsolicited AE: an observed AE not fulfill the conditions prelisted in eCRF in terms of symptom and/or time to onset post-vaccination. Solicited injection site reactions: Pain, Erythema, swelling. Solicited systemic reactions: Fever, Headache, Malaise, and Myalgia. Grade 3 Solicited injection site reactions: Pain, significant; prevents daily activity; Erythema and Swelling >100 mm. Grade 3 Solicited systemic reactions: Fever >=39.0°C; headache, malaise, and myalgia, significant: prevents daily activity. Number of subjects with any of Grade 1, 2 or 3 solicited injection-site, systemic reactions and Grade 3 solicited injection-site and systemic reactions were reported. Safety analysis set: subjects who had received the study or control vaccine.

End point type	Secondary

End point timeframe:

Within 7 days after any vaccine injection

End point values	Purified Vero Rabies Vaccine - Serum Free (VRVg)	Imovax Rabies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	113		
Units: Percentage of subjects				
number (not applicable)				
Any Injection site pain: After-Any Injection	27.9	39.8		
Grade 3 Injection site pain: After-Any Injection	0.4	0.0		
Any Injection site erythema: After-Any Injection	3.5	6.2		
Grade 3 Injection site erythema: After-Any Injecti	0.0	0.0		
Any Injection site swelling: After-Any Injection	3.5	5.3		
Grade 3 Injection site swelling: After-Any Injecti	0.0	0.0		
Any Fever: After-Any Injection	10.9	7.1		
Grade 3 Fever: After-Any Injection	1.7	0.0		
Any Headache: After-Any Injection	21.8	28.3		
Grade 3 Headache: After-Any Injection	0.0	0.0		
Any Malaise: After-Any Injection	15.7	20.4		
Grade 3 Malaise: After-Any Injection	0.0	0.0		
Any Myalgia: After-Any Injection	10.9	13.3		
Grade 3 Myalgia: After-Any Injection	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse event (AE) data were collected from Day 0 (pre-vaccination) up to 7 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	VRVg
Reporting group description:	
Subjects received a total of 3 VRVg vaccine injections.	
Reporting group title	Imovax® Rabies
Reporting group description:	
Subjects received a total of 3 Imovax Rabies vaccine injections.	

Serious adverse events	VRVg	Imovax® Rabies	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 229 (3.93%)	4 / 113 (3.54%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Animal Bite			
subjects affected / exposed	2 / 229 (0.87%)	2 / 113 (1.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal Scratch			
subjects affected / exposed	4 / 229 (1.75%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Complete			
subjects affected / exposed	1 / 229 (0.44%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion Incomplete			

subjects affected / exposed	1 / 229 (0.44%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 229 (0.44%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Meningitis Tuberculous			
subjects affected / exposed	0 / 229 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary Tract Infection			
subjects affected / exposed	0 / 229 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VRVg	Imovax® Rabies	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 229 (56.33%)	70 / 113 (61.95%)	
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 229 (21.83%)	33 / 113 (29.20%)	
occurrences (all)	71	41	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	8 / 229 (3.49%)	7 / 113 (6.19%)	
occurrences (all)	11	12	
Injection Site Pain			
subjects affected / exposed	64 / 229 (27.95%)	45 / 113 (39.82%)	
occurrences (all)	88	73	
Injection Site Swelling			

subjects affected / exposed	8 / 229 (3.49%)	6 / 113 (5.31%)	
occurrences (all)	10	10	
Malaise			
subjects affected / exposed	36 / 229 (15.72%)	23 / 113 (20.35%)	
occurrences (all)	41	31	
Pyrexia			
subjects affected / exposed	32 / 229 (13.97%)	10 / 113 (8.85%)	
occurrences (all)	33	11	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	25 / 229 (10.92%)	15 / 113 (13.27%)	
occurrences (all)	27	18	
Infections and infestations			
Rhinitis			
subjects affected / exposed	8 / 229 (3.49%)	11 / 113 (9.73%)	
occurrences (all)	8	13	
Upper Respiratory Tract Infection			
subjects affected / exposed	39 / 229 (17.03%)	15 / 113 (13.27%)	
occurrences (all)	42	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2013	Clarification on the post-exposure management of subjects in case of rabies exposure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported