



Clinical trial results:

Verorab® immunogenicity and safety after a one week, 4-site, intradermal (ID) post-exposure prophylaxis regimen (4-4-4-0-0) followed by a one visit, 4-site, ID booster at five years.

Summary

EudraCT number	2018-004707-40
Trial protocol	Outside EU/EEA
Global end of trial date	14 November 2018

Results information

Result version number	v1 (current)
This version publication date	24 July 2019
First version publication date	24 July 2019

Trial information

Trial identification

Sponsor protocol code	RAB40
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01622062
WHO universal trial number (UTN)	U1111-1117-7193

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 June 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that post-exposure prophylaxis (PEP) using the "one-week, 4-site" (4-4-4-0-0) intradermal (ID) vaccination regimen is non-inferior to PEP using the updated Thai Red Cross (TRC) (2-2-2-0-2) ID vaccination regimen in terms of seroconversion rate at Day 14 (Group 1 versus Group 3, and Group 2 versus Group 3).

Protection of trial subjects:

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2012
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: 600
Worldwide total number of subjects	600
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)	17
Children (2-11 years)	237
Adolescents (12-17 years)	65
Adults (18-64 years)	281
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Study was conducted at Philippines from 29 June 2012 to 14 November 2018.

Pre-assignment

Screening details:

A total of 600 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomised in the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Subjects with World Health Organization (WHO) Category II exposure received PEP with Purified Vero cell Rabies Vaccine (PVRV) using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.

Arm type	Experimental
Investigational medicinal product name	Purified Vero cell Rabies Vaccine
Investigational medicinal product code	
Other name	VERORAB®
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received 0.1 milliliter (mL) of vaccine administered intradermally in 4 site 'one week' (4-4-4-0-0) regimen at both deltoids and both anterior thighs.

Arm title	Group 2
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Arm description:

Subjects with WHO Category III exposure received PEP with PVRV using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7 and purified Equine Rabies Immunoglobulin (pERIG) Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.

Arm type	Experimental
Investigational medicinal product name	Purified Vero cell Rabies Vaccine
Investigational medicinal product code	
Other name	VERORAB®
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received 0.1 mL of vaccine administered intradermally in 4 site 'one week' (4-4-4-0-0) regimen at both deltoids and both anterior thighs.

Investigational medicinal product name	Purified Equine Rabies Immunoglobulin
Investigational medicinal product code	
Other name	FAVIRAB®
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

The dose was calculated according to the weight of the subject. The recommended dose was same for

children and adults: 40 international units per kilogram (IU/kg) of body weight.

Arm title	Group 3
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Arm description:

Subjects with WHO Category III exposure receive PEP with PVRV using the updated 2-site TRC (2-2-2-0-2) ID vaccination regimen on Day 0, Day 3, Day 7 and Day 28 and pERIG Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.

Arm type	Active comparator
Investigational medicinal product name	Purified Vero cell Rabies Vaccine
Investigational medicinal product code	
Other name	VERORAB®
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received 0.1 mL of vaccine administered intradermally in 2-site TRC (2-2-2-0-2) regimen at both deltoids.

Investigational medicinal product name	Purified Equine Rabies Immunoglobulin
Investigational medicinal product code	
Other name	FAVIRAB®
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

The dose was calculated according to the weight of the subject. The recommended dose was same for children and adults: 40 IU/kg of body weight.

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	200	201	199
Completed	133	139	134
Not completed	67	62	65
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	7	3	3
Lost to follow-up	7	6	9
Protocol deviation	53	51	53

Baseline characteristics

Reporting groups

Reporting group title	Group 1
Reporting group description:	
Subjects with World Health Organization (WHO) Category II exposure received PEP with Purified Vero cell Rabies Vaccine (PVRV) using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.	
Reporting group title	Group 2
Reporting group description:	
Subjects with WHO Category III exposure received PEP with PVRV using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7 and purified Equine Rabies Immunoglobulin (pERIG) Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.	
Reporting group title	Group 3
Reporting group description:	
Subjects with WHO Category III exposure receive PEP with PVRV using the updated 2-site TRC (2-2-2-0-2) ID vaccination regimen on Day 0, Day 3, Day 7 and Day 28 and pERIG Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	200	201	199
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	17.5	19.2	19.5
standard deviation	± 14.0	± 13.8	± 14.1
Gender categorical			
Units: Subjects			
Female	102	95	96
Male	98	106	103

Reporting group values	Total		
Number of subjects	600		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	293		
Male	307		

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description: Subjects with World Health Organization (WHO) Category II exposure received PEP with Purified Vero cell Rabies Vaccine (PVRV) using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.	
Reporting group title	Group 2
Reporting group description: Subjects with WHO Category III exposure received PEP with PVRV using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7 and purified Equine Rabies Immunoglobulin (pERIG) Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.	
Reporting group title	Group 3
Reporting group description: Subjects with WHO Category III exposure receive PEP with PVRV using the updated 2-site TRC (2-2-2-0-2) ID vaccination regimen on Day 0, Day 3, Day 7 and Day 28 and pERIG Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.	

Primary: Percentage of Subjects With Seroconversion on Day 14

End point title	Percentage of Subjects With Seroconversion on Day 14
End point description: Seroconversion was defined as a rabies virus-neutralizing antibody titer ≥ 0.5 IU/mL. Analysis was performed on Per Protocol Analysis Set (PPAS) which included all subjects who received at least one dose of the study vaccine during the Primary Vaccination Phase, and had a post-vaccination blood sample at Day 14 or Day 90. Subjects with following protocol deviations were excluded from PPAS: subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol specified exclusion criteria, subject did not complete the vaccination schedule at visits (V) 01, V02, and V03, subject received a vaccine other than the one that he / she was randomised to receive, subjects received a protocol-restricted therapy / medication / vaccine between V01 and V04, subjects with rabies virus-neutralizing antibodies (≥ 0.2 IU/mL or missing value) at baseline; sample collection not done at Day 14 or sample at V04 did not produced a valid test result.	
End point type	Primary
End point timeframe: Day 14 (post vaccination)	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	162	172	
Units: Percentage of subjects				
number (not applicable)	100.0	99.4	98.8	

Statistical analyses

Statistical analysis title	Group 1 versus (vs) Group 3
Comparison groups	Group 1 v Group 3

Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Percentage difference
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.145
upper limit	4.14

Notes:

[1] - Non-inferiority was concluded if the limit of the two-sided 95% Confidence Interval (CI) of the difference is above delta.

Statistical analysis title	Group 2 vs Group 3
Comparison groups	Group 2 v Group 3
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Percentage difference
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.375
upper limit	3.566

Notes:

[2] - Non-inferiority was concluded if the limit of the two-sided 95% CI of the difference is above delta.

Secondary: Percentage of Subjects With Seroconversion Before and After Primary Vaccination

End point title	Percentage of Subjects With Seroconversion Before and After Primary Vaccination
End point description:	
Seroconversion was defined as rabies virus neutralizing antibody titers ≥ 0.5 IU/mL. Analysis was performed on PPAS. Here, 'n' = subjects with available data for each specified category.	
End point type	Secondary
End point timeframe:	
Day 0, Day 14, Day 90	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	162	172	
Units: Percentage of subjects				
number (not applicable)				
Day 0 (n=175, 162, 172)	0.0	0.0	0.0	
Day 14 (n=175, 162, 172)	100.0	99.4	98.8	
Day 90 (n=166, 157, 165)	98.2	94.9	98.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroconversion After Primary Vaccination (Antibody Persistence)

End point title	Percentage of Subjects With Seroconversion After Primary Vaccination (Antibody Persistence)
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End point description:

Seroconversion was defined as rabies virus neutralizing antibody titers ≥ 0.5 IU/mL. Analysis was performed on Full analysis set which included all randomised subjects who received at least one dose of the study vaccine during the Primary Vaccination Phase, and had a post-vaccination blood sample at Day 14 or Day 90. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary
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End point timeframe:

Year 1 to Year 4

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	198	
Units: Percentage of subjects				
number (not applicable)				
Year 1 (n = 169, 182, 178)	97.6	89.0	79.8	
Year 2 (n= 150, 174, 153)	98.0	88.5	79.1	
Year 3 (n= 139, 151, 142)	95.7	89.4	71.8	
Year 4 (n= 130, 141, 130)	96.2	80.1	60.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroconversion After Booster Vaccination

End point title	Percentage of Subjects With Seroconversion After Booster Vaccination
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End point description:

Seroconversion was defined as rabies virus neutralizing antibody titers ≥ 0.5 IU/mL. Analysis was performed on booster full analysis set which included randomised subjects who received the booster vaccine at V13, and had a post-vaccination blood sample at Day 11 post-V13.

End point type	Secondary
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End point timeframe:

Year 5 and Year 5 + 11 days

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	136	130	
Units: Percentage of subjects				
number (not applicable)				
Year 5 (n=126, 132, 128)	97.6	84.8	64.1	
Year 5 + 11 days (n=124, 135, 130)	100.0	100.0	100.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) Ratio Against Rabies Virus Antibodies Before and After Primary Vaccination

End point title	Geometric Mean Titers (GMTs) Ratio Against Rabies Virus Antibodies Before and After Primary Vaccination
End point description: GMTs of rabies virus-neutralizing antibodies were assessed by the rapid fluorescent focus inhibition test. Analysis was performed on PPAS. Here, 'n' = subjects with available data for each specified category.	
End point type	Secondary
End point timeframe: Day 0, Day 14, Day 90	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	162	172	
Units: titer ratio				
geometric mean (confidence interval 95%)				
Day 14/Day 0 (n=175, 162, 172)	108 (95.0 to 123)	97.7 (83.1 to 115)	58.9 (50.8 to 68.4)	
Day 90/Day 0 (n=166, 157, 165)	31.5 (27.8 to 35.8)	17.6 (15.6 to 19.9)	25.3 (22.8 to 28.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: GMT Ratio Against Rabies Virus Antibodies After Primary Vaccination (Antibody Persistence)

End point title	GMT Ratio Against Rabies Virus Antibodies After Primary Vaccination (Antibody Persistence)
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End point description:

GMT ratio of rabies virus-neutralizing antibodies was assessed by the rapid fluorescent focus inhibition test. Analysis was performed on Full analysis set. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary
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End point timeframe:

Year 1, 2, 3, 4 and Day 90

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	198	
Units: titer ratio				
geometric mean (confidence interval 95%)				
Year 1/Day 90 (n=168, 180, 176)	0.894 (0.818 to 0.978)	0.750 (0.695 to 0.810)	0.362 (0.331 to 0.397)	
Year 2/Day 90 (n=148, 172, 152)	0.941 (0.859 to 1.03)	0.818 (0.738 to 0.905)	0.383 (0.342 to 0.429)	
Year 3/Day 90 (n=138, 149, 141)	0.773 (0.694 to 0.860)	0.733 (0.653 to 0.823)	0.336 (0.298 to 0.379)	
Year 4/Day 90 (n=129, 139, 129)	0.725 (0.647 to 0.812)	0.527 (0.466 to 0.596)	0.248 (0.213 to 0.289)	

Statistical analyses

No statistical analyses for this end point

Secondary: GMTs Against Rabies Virus Antibodies After Booster Vaccination

End point title	GMTs Against Rabies Virus Antibodies After Booster Vaccination
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End point description:

GMTs of rabies virus-neutralizing antibodies was assessed by the rapid fluorescent focus inhibition test. Analysis was performed on booster full analysis set.

End point type	Secondary
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End point timeframe:

Year 5, Year 5 + 11 days

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	136	130	
Units: titer (1/dilution)				
geometric mean (confidence interval 95%)				
Year 5 (n=126, 132, 128)	2.22 (1.90 to 2.60)	1.05 (0.918 to 1.21)	0.762 (0.649 to 0.896)	
Year 5 + 11 days (n=124, 135, 130)	193 (170 to 218)	137 (120 to 157)	138 (120 to 160)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Immediate Unsolicited Adverse Events Following Primary and Booster Vaccination

End point title	Number of Subjects Reporting Immediate Unsolicited Adverse Events Following Primary and Booster Vaccination
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End point description:

An unsolicited Adverse Event (AE) is an observed AE that does not fulfill the conditions prelisted in the case report form in terms of symptom and / or onset post-vaccination. Analysis was performed on safety analysis set which included subjects who received a dose of study or control vaccine. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary
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End point timeframe:

Within 30 minutes after vaccination

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	199	
Units: subjects				
number (not applicable)				
Immediate AE: Primary Phase (n=199,201,199)	0	2	5	
Immediate AE: Booster Phase (n=129,137, 130)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Injection Site Reactions Following Primary and Booster Vaccination

End point title	Number of Subjects Reporting Solicited Injection Site Reactions Following Primary and Booster Vaccination
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End point description:

Solicited Injection (Inj.) site reactions were tenderness (for subjects aged ≤ 23 months), pain (for subjects aged ≥ 2 years), erythema and swelling. Analysis was performed on safety analysis set. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary
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End point timeframe:

Within 7 days after vaccination

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	199	
Units: subjects				
number (not applicable)				
Inj. site tenderness/pain: Primary (n=199,201,199)	109	140	126	
Inj. site erythema: Primary (n=199,201,199)	85	78	56	
Inj. site swelling: Primary (n=199, 201,199)	33	37	33	
Inj. site tenderness/pain: Booster (n=129,137,130)	64	72	67	
Inj. site erythema: Booster (n=129, 137, 130)	53	62	53	
Inj. site swelling: Booster (n=129, 137, 130)	34	40	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Systemic Reactions Following Primary and Booster Vaccination

End point title	Number of Subjects Reporting Solicited Systemic Reactions Following Primary and Booster Vaccination
End point description:	
Solicited systemic reactions are Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability for subjects aged ≤ 23 months and Fever (Temperature), Headache, Malaise, and Myalgia for subjects aged ≥ 2 years. Analysis was performed on safety analysis set. Here, 'n' = subjects with available data for each specified category.	
End point type	Secondary
End point timeframe:	
From Day 0 up to 7 days after injection 1, 2 and 3, and 7 days after subsequent injections	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	199	
Units: subjects				
number (not applicable)				
Fever: Primary (n=199, 201, 199)	19	14	15	
Vomiting: Primary (n= 11, 3, 3)	2	0	0	
Crying Abnormal: Primary (n= 11, 3, 3)	3	0	1	
Drowsiness: Primary (n= 11, 3, 3)	2	0	1	
Appetite loss: Primary (n= 11, 3, 3)	5	0	0	

Irritability: Primary (n= 11, 3, 3)	5	0	1	
Headache: Primary (n= 188, 198, 196)	76	88	89	
Malaise: Primary (n=188,198,196)	78	83	103	
Myalgia: Primary (n=188, 198, 196)	66	83	92	
Fever: Booster (n= 129, 137, 130)	4	3	1	
Headache: Booster (n= 129,137, 130)	37	39	31	
Malaise: Booster (n=129, 137, 130)	32	34	30	
Myalgia: Booster (n=129, 137, 130)	28	29	32	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited Injection Site Reactions (Reac.)

End point title	Number of Subjects Reporting Unsolicited Injection Site Reactions (Reac.)
End point description:	
Analysis was performed on safety analysis set. Here, 'n' = subjects with available data for each specified category.	
End point type	Secondary
End point timeframe:	
Within 21 days after vaccination	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	199	
Units: subjects				
number (not applicable)				
Unsolicited inj. site reac.:Primary(n=199,201,199)	2	6	2	
Unsolicited inj. site reac.:Booster(n=129,137,130)	16	20	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited Systemic Adverse Events

End point title	Number of Subjects Reporting Unsolicited Systemic Adverse Events
End point description:	
Unsolicited systemic adverse events were defined as any unfavorable and unintended sign, symptom or disease not meeting the definition of solicited event and not occurring at the injection site of the investigational medicinal product, whether or not considered related to the investigational medicinal product. Analysis was performed on safety analysis set. Here, 'n' = subjects with available data for each	

specified category.

End point type	Secondary
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End point timeframe:

Between the first and the second vaccination, between the second and the third vaccination, between the third and the fourth vaccination (for Group 3), and up to 28 days after the remaining vaccination

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	199	
Units: subjects				
number (not applicable)				
Unsolicited systemic AE: Primary (n=199, 201,199)	102	89	110	
Unsolicited systemic AE: Booster (n=129, 137,130)	20	13	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Serious Adverse Events (SAE)

End point title	Number of Subjects Reporting Serious Adverse Events (SAE)
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End point description:

An SAE is any untoward medical occurrence that at any dose (including overdose): results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, is a congenital anomaly / birth defect, is an important medical event, whether or not considered related to the investigational medical product. Only related or fatal serious adverse events were reported during the period ranging from Day 28 post primary vaccination to the booster vaccination at Year 5. Analysis was performed on safety analysis set. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary
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End point timeframe:

Up to 28 days after primary vaccination and booster vaccination, during full study duration

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199	201	199	
Units: subjects				
number (not applicable)				
SAE: Primary (n=199, 201, 199)	5	3	9	
SAE: Booster (n= 129, 137, 130)	0	0	0	
SAE: Full study (n=199, 201, 199)	5	5	9	
Related SAE: Full study (n=199, 201, 199)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited reaction (SR) within 7 days after vaccination, unsolicited injection site reaction within 21 days after vaccination, unsolicited AEs between vaccinations up to fourth vaccination, then up to 28 days after remaining vaccinations, SAEs during study

Adverse event reporting additional description:

Safety Analysis Set. SR: AE prelisted (PL) in electronic case report form (eCRF), considered related to vaccination (adverse drug reaction). Unsolicited AE: observed AE not fulfilling conditions PL in eCRF in terms of symptom &/or onset post-vaccination. Only related/fatal SAEs reported from D28 post primary vaccination to booster vaccination at Year 5

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Group 1
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Reporting group description:

Subjects with WHO Category II exposure received PEP with PVRV using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.

Reporting group title	Group 3
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Reporting group description:

Subjects with WHO Category III exposure receive PEP with PVRV using the updated 2-site TRC (2-2-2-0-2) ID vaccination regimen on Day 0, Day 3, Day 7 and Day 28 and pERIG Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.

Reporting group title	Group 2
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Reporting group description:

Subjects with WHO Category III exposure received PEP with PVRV using "one-week, 4-site" (4-4-4-0-0) ID vaccination regimen on Day 0, Day 3 and Day 7 and pERIG Favirab® on Day 0, and a "single-visit, 4-site" booster vaccination with PVRV 5 years later.

Serious adverse events	Group 1	Group 3	Group 2
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 199 (2.51%)	9 / 199 (4.52%)	5 / 201 (2.49%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	0 / 199 (0.00%)	1 / 199 (0.50%)	0 / 201 (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
Nervous system disorders			
Cerebrovascular Accident			

subjects affected / exposed	0 / 199 (0.00%)	0 / 199 (0.00%)	1 / 201 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Syncope			
subjects affected / exposed	0 / 199 (0.00%)	1 / 199 (0.50%)	0 / 201 (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			
Electrocution			
subjects affected / exposed	0 / 199 (0.00%)	0 / 199 (0.00%)	1 / 201 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 199 (0.00%)	1 / 199 (0.50%)	0 / 201 (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
Type I Hypersensitivity			
subjects affected / exposed	0 / 199 (0.00%)	1 / 199 (0.50%)	1 / 201 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 199 (2.01%)	5 / 199 (2.51%)	2 / 201 (1.00%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	1 / 199 (0.50%)	0 / 199 (0.00%)	0 / 201 (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
Viral Rash			
subjects affected / exposed	0 / 199 (0.00%)	1 / 199 (0.50%)	0 / 201 (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

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

Non-serious adverse events	Group 1	Group 3	Group 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	183 / 199 (91.96%)	184 / 199 (92.46%)	188 / 201 (93.53%)
Nervous system disorders			
Headache			
subjects affected / exposed	95 / 199 (47.74%)	105 / 199 (52.76%)	103 / 201 (51.24%)
occurrences (all)	166	188	184
General disorders and administration site conditions			
Chills			
subjects affected / exposed	13 / 199 (6.53%)	15 / 199 (7.54%)	9 / 201 (4.48%)
occurrences (all)	14	16	9
Injection Site Erythema			
subjects affected / exposed	109 / 199 (54.77%)	87 / 199 (43.72%)	101 / 201 (50.25%)
occurrences (all)	705	386	668
Injection Site Pain			
subjects affected / exposed	134 / 199 (67.34%)	145 / 199 (72.86%)	161 / 201 (80.10%)
occurrences (all)	799	625	890
Injection Site Pruritus			
subjects affected / exposed	13 / 199 (6.53%)	11 / 199 (5.53%)	21 / 201 (10.45%)
occurrences (all)	28	22	45
Injection Site Swelling			
subjects affected / exposed	58 / 199 (29.15%)	63 / 199 (31.66%)	71 / 201 (35.32%)
occurrences (all)	213	192	264
Malaise			
subjects affected / exposed	97 / 199 (48.74%)	115 / 199 (57.79%)	101 / 201 (50.25%)
occurrences (all)	149	210	169
Pyrexia			
subjects affected / exposed	29 / 199 (14.57%)	27 / 199 (13.57%)	21 / 201 (10.45%)
occurrences (all)	32	29	26
Immune system disorders			

Hypersensitivity subjects affected / exposed occurrences (all)	3 / 199 (1.51%) 3	27 / 199 (13.57%) 29	20 / 201 (9.95%) 23
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	20 / 199 (10.05%) 21	15 / 199 (7.54%) 15	10 / 201 (4.98%) 10
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	75 / 199 (37.69%) 129	105 / 199 (52.76%) 191	103 / 201 (51.24%) 164
Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	36 / 199 (18.09%) 37	31 / 199 (15.58%) 34	26 / 201 (12.94%) 29

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2012	Following amendment changes were made: The wording in the primary objective, primary endpoint and secondary endpoints and other parts of the protocol was modified; mainly "seroprotection" was changed to "seroconversion"; women of childbearing potential and sexually active were required to use a medically acceptable and effective method of birth control during 1 month following booster vaccination. The wording was updated to reflect this; Favirab® was deleted from the primary study objective. Also it was clarified that Favirab® was a commercial product and not an investigational product; sentences were added to the primary objective to define the comparison between groups at Day 14.
01 July 2013	Following amendment changes were made: Originally, the countries planned to participate in the study were India, Pakistan and The Philippines. Due to organizational difficulties, India and Pakistan did not participate in the study. Therefore, all parts of the protocol related to the involvement of these 2 countries were deleted from the protocol; in order to avoid the drop out of the subjects in-between yearly visits, phone calls were given on a quarterly basis to the subjects to remind them to come back to the site for the next visits. The wording in the protocol was added to reflect this; clarification on the process to follow if re-exposure of subjects occurred during the study; clarification on collection of all SAEs during the study.
10 April 2014	Following amendment changes were made: Originally, two interim analyses (Day 90, Year 1) and corresponding interim reports were planned. The testing of the Day 90 blood samples at the laboratory was unexpectedly delayed and all Year 1 follow-up blood samples would be available before the Day 90 samples could be tested. Therefore it was decided by the Sponsor to test all Day 90 and Year 1 blood samples at the same time and delete the D90 interim analysis and interim report. The wording throughout the protocol was adapted accordingly; the timelines for different milestones of the study (eg, first visit of first patient) were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported