



## 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 |
|-----------------------|-------|

#### 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:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Philippines: 600 |
| Worldwide total number of subjects   | 600              |
| EEA total number of subjects         | 0                |

Notes:

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**Subjects enrolled per age group**

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|                                           |     |
|-------------------------------------------|-----|
| 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 |
|-------------------|---|

## 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     |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group 2 |
|------------------|---------|

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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group 3 |
|------------------|---------|

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.

| <b>Number of subjects in period 1</b> | 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:<br>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:<br>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:<br>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:<br>Seroconversion was defined as a rabies virus-neutralizing antibody titer $\geq 0.5$ 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 ( $\geq 0.2$ 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:<br>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 <sup>[1]</sup> |
| 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.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[2]</sup> |
| 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 $\geq 0.5$ 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) |
|-----------------|---------------------------------------------------------------------------------------------|

End point description:

Seroconversion was defined as rabies virus neutralizing antibody titers  $\geq 0.5$  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 |
|----------------|-----------|

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 |
|-----------------|----------------------------------------------------------------------|

End point description:

Seroconversion was defined as rabies virus neutralizing antibody titers  $\geq 0.5$  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 |
|----------------|-----------|

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:<br>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:<br>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) |
|-----------------|--------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|----------------------------------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|-------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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<br>(n=199,201,199)  | 0               | 2               | 5               |  |
| Immediate AE: Booster Phase<br>(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 |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

Solicited Injection (Inj.) site reactions were tenderness (for subjects aged  $\leq 23$  months), pain (for subjects aged  $\geq 2$  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 |
|----------------|-----------|

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 $\leq 23$ months and Fever (Temperature), Headache, Malaise, and Myalgia for subjects aged $\geq 2$ 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 |
|----------------|-----------|

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) |
|-----------------|-----------------------------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Group 1 |
|-----------------------|---------|

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 |
|-----------------------|---------|

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 |
|-----------------------|---------|

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 %

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