



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | VRV06 |
|-----------------------|-------|

##### Additional study identifiers

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

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

|                                                                      |     |
|----------------------------------------------------------------------|-----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No  |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 30 January 2017 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 14 April 2014   |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

- To demonstrate that Purified Vero Rabies Vaccine - Serum Free (VRVg) is non-inferior to Imovax Rabies in terms of proportion of subjects achieving a rabies virus neutralizing antibody (RVNA) titer  $\geq 0.5$  international units (IU)/mL at Day 42 (D42), i.e. 14 days after the last vaccination.
- To describe if at least 99% of subjects achieve an RVNA titer  $\geq 0.5$  IU/mL at D42 with a lower bound of the 95% confidence interval (CI) of at least 97%, in the VRVg group.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

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

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 03 September 2013 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Philippines: 342 |
| Worldwide total number of subjects   | 342              |
| EEA total number of subjects         | 0                |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |

|                           |     |
|---------------------------|-----|
| Children (2-11 years)     | 171 |
| Adolescents (12-17 years) | 171 |
| Adults (18-64 years)      | 0   |
| From 65 to 84 years       | 0   |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

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

### Arms

|                              |                                                  |
|------------------------------|--------------------------------------------------|
| Are arms mutually exclusive? | Yes                                              |
| <b>Arm title</b>             | Purified Vero Rabies Vaccine - Serum Free (VRVg) |

Arm description:

Subjects received a total of 3 VRVg vaccine injections.

|                                        |                                                 |
|----------------------------------------|-------------------------------------------------|
| Arm type                               | Experimental                                    |
| Investigational medicinal product name | VRVg                                            |
| Investigational medicinal product code |                                                 |
| Other name                             |                                                 |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection |
| Routes of administration               | Intramuscular use                               |

Dosage and administration details:

0.5 mL, intramuscular (alternating between the left and right deltoid for each injection, starting with the left deltoid for the first injection), 1 injection each on Day 0, 7, and 28 (for a total of 3 injections).

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Imovax Rabies |
|------------------|---------------|

Arm description:

Subjects received a total of 3 Imovax Rabies vaccine injections.

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

Dosage and administration details:

1 mL, intramuscular (alternating between the left and right deltoid for each injection, starting with the left deltoid for the first injection), 1 injection each on Day 0, 7, and 28 (for a total of 3 injections).

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

## Baseline characteristics

### Reporting groups

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

| Reporting group values                             | Purified Vero Rabies Vaccine - Serum Free (VRVg) | Imovax Rabies | Total |
|----------------------------------------------------|--------------------------------------------------|---------------|-------|
| Number of subjects                                 | 229                                              | 113           | 342   |
| Age categorical<br>Units: Subjects                 |                                                  |               |       |
| In utero                                           | 0                                                | 0             | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                                                | 0             | 0     |
| Newborns (0-27 days)                               | 0                                                | 0             | 0     |
| Infants and toddlers (28 days-23 months)           | 0                                                | 0             | 0     |
| Children (2-11 years)                              | 115                                              | 56            | 171   |
| Adolescents (12-17 years)                          | 114                                              | 57            | 171   |
| Adults (18-64 years)                               | 0                                                | 0             | 0     |
| From 65-84 years                                   | 0                                                | 0             | 0     |
| 85 years and over                                  | 0                                                | 0             | 0     |
| Age continuous<br>Units: years                     |                                                  |               |       |
| arithmetic mean                                    | 11.0                                             | 10.7          |       |
| standard deviation                                 | ± 4.3                                            | ± 4.5         | -     |
| Gender categorical<br>Units: Subjects              |                                                  |               |       |
| Female                                             | 110                                              | 63            | 173   |
| Male                                               | 119                                              | 50            | 169   |

## End points

### End points reporting groups

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

### Primary: Percentage of Subjects Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL at Day 42

|                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                     | Percentage of Subjects Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL at Day 42 |
| End point description:<br>Antibody titers to each vaccine were assessed using the rapid fluorescent focus inhibition test (RFFIT) method. Seroconversion was defined as rabies virus neutralizing antibody (RVNA) titers $\geq 0.5$ IU/mL. The analysis was performed using per-protocol analysis set (PPAS) which was a subset of full analysis set (FAS defined as: all randomized subjects who received at least one dose of the study vaccine). |                                                                                                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                      | Primary                                                                                                       |
| End point timeframe:<br>Day 42                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                               |

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

### Statistical analyses

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

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

Notes:

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

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

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Achieving Rabies Virus Neutralizing Antibodies (RVNA) Titer $\geq 0.5$ IU/mL at Days 0, 42 and Month 6 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

|                                             |           |
|---------------------------------------------|-----------|
| End point type                              | Secondary |
| End point timeframe:                        |           |
| Day 0 (pre-vaccination), Day 42 and Month 6 |           |

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                                           |           |
|-------------------------------------------|-----------|
| End point type                            | Secondary |
| End point timeframe:                      |           |
| Within 7 days after any vaccine injection |           |

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data were collected from Day 0 (pre-vaccination) up to 7 months

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |      |
|-----------------------|------|
| Reporting group title | VRVg |
|-----------------------|------|

Reporting group description:

Subjects received a total of 3 VRVg vaccine injections.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Imovax® Rabies |
|-----------------------|----------------|

Reporting group description:

Subjects received a total of 3 Imovax Rabies vaccine injections.

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported