



## Clinical trial results: Immunogenicity and Safety of Quadrivalent Influenza Vaccine (VaxigripTetra™) in Pregnant Women

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-004763-40 |
| Trial protocol           | FI             |
| Global end of trial date | 14 June 2018   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 26 May 2019  |
| First version publication date | 26 May 2019  |

### Trial information

#### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | GQM14 |
|-----------------------|-------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | -               |
| WHO universal trial number (UTN)   | U1111-1183-5650 |

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? | No |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 23 November 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 14 June 2018     |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Immunogenicity:

To describe the immune response of VaxigripTetra and Vaxigrip, 21 days after vaccination in pregnant women.

Safety:

To describe the safety profile of one dose of VaxigripTetra or Vaxigrip, 21 days after vaccination in pregnant women.

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                          | 15 September 2017 |
| 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 | Finland: 346 |
| Worldwide total number of subjects   | 346          |
| EEA total number of subjects         | 346          |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |

|                      |     |
|----------------------|-----|
| Adults (18-64 years) | 346 |
| From 65 to 84 years  | 0   |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 10 centers in Finland from 15 September 2017 to 26 January 2018.

### Pre-assignment

Screening details:

A total of 346 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized in the 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, Assessor |

Blinding implementation details:

The study was conducted in a blind observer manner. Neither the Investigator responsible for safety assessment, nor the subject knew which vaccine was administered.

### Arms

|                              |                                                |
|------------------------------|------------------------------------------------|
| Are arms mutually exclusive? | Yes                                            |
| <b>Arm title</b>             | Quadrivalent Influenza Vaccine (VaxigripTetra) |

Arm description:

Pregnant women aged  $\geq 18$  years and who were in the late second/third trimester of pregnancy received a single dose of VaxigripTetra vaccine.

|                                        |                                                                                    |
|----------------------------------------|------------------------------------------------------------------------------------|
| Arm type                               | Experimental                                                                       |
| Investigational medicinal product name | Sanofi Pasteur licensed quadrivalent influenza vaccine (split-virion, inactivated) |
| Investigational medicinal product code |                                                                                    |
| Other name                             |                                                                                    |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe                                     |
| Routes of administration               | Intramuscular use, Subcutaneous use                                                |

Dosage and administration details:

0.5 mL, intramuscular (IM) or deep subcutaneous (SC) injection, single dose on Day 0.

|                  |                                        |
|------------------|----------------------------------------|
| <b>Arm title</b> | Trivalent Influenza Vaccine (Vaxigrip) |
|------------------|----------------------------------------|

Arm description:

Pregnant women aged  $\geq 18$  years and who were in the late second/third trimester of pregnancy received a single dose of Vaxigrip vaccine.

|                                        |                                                                                 |
|----------------------------------------|---------------------------------------------------------------------------------|
| Arm type                               | Active comparator                                                               |
| Investigational medicinal product name | Sanofi Pasteur licensed trivalent influenza vaccine (split-virion, inactivated) |
| Investigational medicinal product code |                                                                                 |
| Other name                             |                                                                                 |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe                                  |
| Routes of administration               | Intramuscular use, Subcutaneous use                                             |

Dosage and administration details:

0.5 mL, intramuscular (IM) or deep subcutaneous (SC) injection, single dose on Day 0.

| Number of subjects in period 1 | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |
|--------------------------------|------------------------------------------------|----------------------------------------|
|                                |                                                |                                        |
| Started                        | 230                                            | 116                                    |
| Completed                      | 228                                            | 115                                    |
| Not completed                  | 2                                              | 1                                      |
| Consent withdrawn by subject   | 1                                              | -                                      |
| Lost to follow-up              | -                                              | 1                                      |
| Protocol deviation             | 1                                              | -                                      |

## Baseline characteristics

### Reporting groups

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Quadrivalent Influenza Vaccine (VaxigripTetra) |
|-----------------------|------------------------------------------------|

Reporting group description:

Pregnant women aged  $\geq 18$  years and who were in the late second/third trimester of pregnancy received a single dose of VaxigripTetra vaccine.

|                       |                                        |
|-----------------------|----------------------------------------|
| Reporting group title | Trivalent Influenza Vaccine (Vaxigrip) |
|-----------------------|----------------------------------------|

Reporting group description:

Pregnant women aged  $\geq 18$  years and who were in the late second/third trimester of pregnancy received a single dose of Vaxigrip vaccine.

| Reporting group values                                                  | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) | Total |
|-------------------------------------------------------------------------|------------------------------------------------|----------------------------------------|-------|
| Number of subjects                                                      | 230                                            | 116                                    | 346   |
| Age categorical<br>Units: Subjects                                      |                                                |                                        |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 32.0<br>$\pm 4.39$                             | 31.4<br>$\pm 4.76$                     | -     |
| Gender categorical<br>Units: Subjects                                   |                                                |                                        |       |
| Female                                                                  | 230                                            | 116                                    | 346   |
| Male                                                                    | 0                                              | 0                                      | 0     |

## End points

### End points reporting groups

|                                                                                                                                                                                                    |                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Reporting group title                                                                                                                                                                              | Quadrivalent Influenza Vaccine (VaxigripTetra) |
| Reporting group description:<br>Pregnant women aged $\geq 18$ years and who were in the late second/third trimester of pregnancy received a single dose of VaxigripTetra vaccine.                  |                                                |
| Reporting group title                                                                                                                                                                              | Trivalent Influenza Vaccine (Vaxigrip)         |
| Reporting group description:<br>Pregnant women aged $\geq 18$ years and who were in the late second/third trimester of pregnancy received a single dose of Vaxigrip vaccine.                       |                                                |
| Subject analysis set title                                                                                                                                                                         | Quadrivalent Influenza Vaccine (VaxigripTetra) |
| Subject analysis set type                                                                                                                                                                          | Sub-group analysis                             |
| Subject analysis set description:<br>Babies born to pregnant women aged $\geq 18$ years, who were in the late second/third trimester of pregnancy received a single dose of VaxigripTetra vaccine. |                                                |
| Subject analysis set title                                                                                                                                                                         | Trivalent Influenza Vaccine (Vaxigrip)         |
| Subject analysis set type                                                                                                                                                                          | Sub-group analysis                             |
| Subject analysis set description:<br>Babies born to pregnant women aged $\geq 18$ years, who were in the late second/third trimester of pregnancy received a single dose of Vaxigrip vaccine.      |                                                |

### Primary: Hemagglutination Inhibition (HAI) Antibody Titers After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip)

|                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                      | Hemagglutination Inhibition (HAI) Antibody Titers After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip) <sup>[1]</sup> |
| End point description:<br>Serum antibody titers for the strains A/H1N1, A/H3N2, B1 and B2 were assessed by HAI assay. Antibody titers were expressed as geometric mean titers (GMTs). Analysis was performed on Per-Protocol Analysis set which included subjects who received one dose of any of the study vaccines and had no protocol deviations. |                                                                                                                                                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                       | Primary                                                                                                                                                                          |
| End point timeframe:<br>Day 0 (Pre-vaccination) and Day 21 (Post-vaccination)                                                                                                                                                                                                                                                                        |                                                                                                                                                                                  |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Only descriptive data was planned to be reported for this endpoint.                                                                                  |                                                                                                                                                                                  |

| End point values                         | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |  |
|------------------------------------------|------------------------------------------------|----------------------------------------|--|--|
| Subject group type                       | Reporting group                                | Reporting group                        |  |  |
| Number of subjects analysed              | 216                                            | 109                                    |  |  |
| Units: Titer (1/dilution)                |                                                |                                        |  |  |
| geometric mean (confidence interval 95%) |                                                |                                        |  |  |
| A/H1N1: Pre vaccination                  | 138 (114 to 166)                               | 121 (88.4 to 166)                      |  |  |
| A/H1N1: Post vaccination                 | 525 (466 to 592)                               | 638 (529 to 769)                       |  |  |
| A/H3N2: Pre vaccination                  | 39.6 (32.2 to 48.6)                            | 40.0 (29.4 to 54.5)                    |  |  |

|                          |                     |                     |  |  |
|--------------------------|---------------------|---------------------|--|--|
| A/H3N2: Post vaccination | 341 (286 to 407)    | 369 (283 to 483)    |  |  |
| B1: Pre vaccination      | 67.1 (55.2 to 81.4) | 72.5 (54.7 to 96.1) |  |  |
| B1: Post vaccination     | 568 (496 to 651)    | 697 (569 to 855)    |  |  |
| B2: Pre vaccination      | 159 (131 to 193)    | 155 (120 to 202)    |  |  |
| B2: Post vaccination     | 993 (870 to 1134)   | 529 (415 to 674)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Individual Antibody Titer Ratio After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip)

|                 |                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Individual Antibody Titer Ratio After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip) <sup>[2]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Individual antibody titer ratio for the strains A/H1N1, A/H3N2, B1 and B2 were assessed by HAI assay. Antibody titer ratio were expressed as Day 21/Day 0. Analysis was performed on Per-Protocol Analysis set.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (Pre-vaccination) and Day 21 (Post-vaccination)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values                         | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |  |
|------------------------------------------|------------------------------------------------|----------------------------------------|--|--|
| Subject group type                       | Reporting group                                | Reporting group                        |  |  |
| Number of subjects analysed              | 216                                            | 109                                    |  |  |
| Units: titer ratio                       |                                                |                                        |  |  |
| geometric mean (confidence interval 95%) |                                                |                                        |  |  |
| A/H1N1                                   | 3.81 (3.11 to 4.66)                            | 5.26 (3.66 to 7.55)                    |  |  |
| A/H3N2                                   | 8.63 (6.85 to 10.9)                            | 9.23 (6.56 to 13.0)                    |  |  |
| B1                                       | 8.48 (6.81 to 10.6)                            | 9.62 (6.89 to 13.4)                    |  |  |
| B2                                       | 6.26 (5.12 to 7.65)                            | 3.40 (2.68 to 4.32)                    |  |  |

## Statistical analyses

**Primary: Percentage of Subjects With Detectable Antibody Titer After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip)**

|                 |                                                                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Detectable Antibody Titer After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip) <sup>[3]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Detectable antibody titers for the strains A/H1N1, A/H3N2, B1 and B2 were assessed by HAI assay. Detectable antibody titer value was  $\geq 10$  (1/dilution [1/dil]). Analysis was performed on Per-Protocol Analysis set.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (Pre-vaccination) and Day 21 (Post-vaccination)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values              | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |  |
|-------------------------------|------------------------------------------------|----------------------------------------|--|--|
| Subject group type            | Reporting group                                | Reporting group                        |  |  |
| Number of subjects analysed   | 216                                            | 109                                    |  |  |
| Units: Percentage of Subjects |                                                |                                        |  |  |
| number (not applicable)       |                                                |                                        |  |  |
| A/H1N1: Pre vaccination       | 94.9                                           | 89.0                                   |  |  |
| A/H1N1: Post vaccination      | 100                                            | 100                                    |  |  |
| A/H3N2: Pre vaccination       | 77.8                                           | 75.2                                   |  |  |
| A/H3N2: Post vaccination      | 99.1                                           | 100                                    |  |  |
| B1: Pre vaccination           | 89.8                                           | 90.8                                   |  |  |
| B1: Post vaccination          | 100                                            | 100                                    |  |  |
| B2: Pre vaccination           | 94.9                                           | 99.1                                   |  |  |
| B2: Post vaccination          | 100                                            | 100                                    |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Percentage of Subjects With Antibody Titer  $\geq 40$  (1/Dilution) After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip)**

|                 |                                                                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Antibody Titer $\geq 40$ (1/Dilution) After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip) <sup>[4]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Antibody titer  $\geq 40$  (1/dilution) for the strains A/H1N1, A/H3N2, B1 and B2 were assessed by HAI assay. Analysis was performed on Per-Protocol Analysis set.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (Pre-vaccination) and Day 21 (Post-vaccination)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values              | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |  |
|-------------------------------|------------------------------------------------|----------------------------------------|--|--|
| Subject group type            | Reporting group                                | Reporting group                        |  |  |
| Number of subjects analysed   | 216                                            | 109                                    |  |  |
| Units: Percentage of Subjects |                                                |                                        |  |  |
| number (not applicable)       |                                                |                                        |  |  |
| A/H1N1: Pre vaccination       | 86.1                                           | 78.0                                   |  |  |
| A/H1N1: Post vaccination      | 99.5                                           | 100                                    |  |  |
| A/H3N2: Pre vaccination       | 55.1                                           | 53.2                                   |  |  |
| A/H3N2: Post vaccination      | 95.8                                           | 94.5                                   |  |  |
| B1: Pre vaccination           | 69.4                                           | 65.1                                   |  |  |
| B1: Post vaccination          | 100                                            | 99.1                                   |  |  |
| B2: Pre vaccination           | 85.2                                           | 83.5                                   |  |  |
| B2: Post vaccination          | 100                                            | 97.2                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Seroconversion or Significant Increase of Antibody Titers After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip)

|                 |                                                                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Seroconversion or Significant Increase of Antibody Titers After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip) <sup>[5]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Seroconversion was defined as the pre-vaccination titer < 10 (1/dil) on Day 0 and post-vaccination titer ≥ 40 (1/dil) on Day 21, or significant increase was defined as the pre vaccination titer ≥ 10 (1/dil) and ≥ 4-fold increase of post-injection titer on Day 21. Analysis was performed on Per-Protocol Analysis set.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (Pre-vaccination) and Day 21 (Post-vaccination)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values              | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |  |
|-------------------------------|------------------------------------------------|----------------------------------------|--|--|
| Subject group type            | Reporting group                                | Reporting group                        |  |  |
| Number of subjects analysed   | 216                                            | 109                                    |  |  |
| Units: percentage of subjects |                                                |                                        |  |  |
| number (not applicable)       |                                                |                                        |  |  |

|        |      |      |  |  |
|--------|------|------|--|--|
| A/H1N1 | 38.0 | 41.3 |  |  |
| A/H3N2 | 59.3 | 62.4 |  |  |
| B1     | 61.1 | 60.6 |  |  |
| B2     | 59.7 | 38.5 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects Reporting Solicited Injection Site or Systemic Reactions After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip)

|                 |                                                                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Solicited Injection Site or Systemic Reactions After Vaccination With Quadrivalent Influenza Vaccine (VaxigripTetra) or Trivalent Influenza Vaccine (Vaxigrip) <sup>[6]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Percentage of subjects experiencing at least 1 solicited injection site reaction (pain, erythema, swelling, induration and ecchymosis) and at least 1 systemic reaction (fever, headache, malaise, myalgia, and shivering) were reported. Analysis was performed on safety analysis set which included all subjects who had received at least 1 dose of the study or control vaccine; all subjects had their safety analyzed according to the vaccine actually received.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 to Day 7 (Post-vaccination)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values              | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |  |
|-------------------------------|------------------------------------------------|----------------------------------------|--|--|
| Subject group type            | Reporting group                                | Reporting group                        |  |  |
| Number of subjects analysed   | 230                                            | 115                                    |  |  |
| Units: Percentage of Subjects |                                                |                                        |  |  |
| number (not applicable)       |                                                |                                        |  |  |
| Injection site pain           | 88.7                                           | 76.5                                   |  |  |
| Injection site erythema       | 10.4                                           | 13.9                                   |  |  |
| Injection site swelling       | 5.7                                            | 5.2                                    |  |  |
| Injection site induration     | 3.5                                            | 4.3                                    |  |  |
| Injection site ecchymosis     | 0.9                                            | 1.7                                    |  |  |
| Fever                         | 0                                              | 1.7                                    |  |  |
| Headache                      | 41.7                                           | 47.8                                   |  |  |
| Malaise                       | 29.1                                           | 27.8                                   |  |  |
| Myalgia                       | 37.0                                           | 25.2                                   |  |  |
| Shivering                     | 26.5                                           | 26.1                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Ratio of the Hemagglutination-Inhibition Titers in Infants and Mothers at the Time of Delivery

|                 |                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Geometric Mean Ratio of the Hemagglutination-Inhibition Titers in Infants and Mothers at the Time of Delivery |
|-----------------|---------------------------------------------------------------------------------------------------------------|

End point description:

Geometric mean ratio of the Hemagglutination-Inhibition titers in infants and mothers for each strain at the time of delivery was reported. Analysis was performed on Other Immunogenicity Analysis Set which included subjects who received one dose of any of the study vaccines, delivered at least 2 weeks after injection and with available cord blood sample (BL) and mother BL at the time of delivery or at Visit 2 (Day 21) if delivery occurred during the time window of Visit 2 (Day 21).

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

End point timeframe:

At the time of Delivery (on average 103 day after vaccination)

| End point values                         | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |  |
|------------------------------------------|------------------------------------------------|----------------------------------------|--|--|
| Subject group type                       | Reporting group                                | Reporting group                        |  |  |
| Number of subjects analysed              | 178                                            | 89                                     |  |  |
| Units: geometric mean ratio              |                                                |                                        |  |  |
| geometric mean (confidence interval 95%) |                                                |                                        |  |  |
| A/H1N1                                   | 1.89 (1.72 to 2.08)                            | 1.83 (1.64 to 2.04)                    |  |  |
| A/H3N2                                   | 1.71 (1.56 to 1.87)                            | 1.75 (1.55 to 1.97)                    |  |  |
| B1                                       | 1.53 (1.37 to 1.71)                            | 1.64 (1.46 to 1.85)                    |  |  |
| B2                                       | 1.69 (1.54 to 1.85)                            | 1.47 (1.28 to 1.69)                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Birth Outcomes

|                 |                |
|-----------------|----------------|
| End point title | Birth Outcomes |
|-----------------|----------------|

End point description:

Number of babies with different birth outcomes assessed by methods used in routine at the hospital. Analysis was performed on the Babies other Safety analysis set which included babies of the subjects from the other Safety analysis set (defined as the subset of subjects who received one dose of the study or control vaccine and delivered at least 2 weeks after vaccination).

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

End point timeframe:

At the time of Delivery (on average 103 day after vaccination)

| <b>End point values</b>                        | Quadrivalent<br>Influenza<br>Vaccine<br>(VaxigripTetra) | Trivalent<br>Influenza<br>Vaccine<br>(Vaxigrip) |  |  |
|------------------------------------------------|---------------------------------------------------------|-------------------------------------------------|--|--|
| Subject group type                             | Subject analysis set                                    | Subject analysis set                            |  |  |
| Number of subjects analysed                    | 231                                                     | 119                                             |  |  |
| Units: babies                                  |                                                         |                                                 |  |  |
| Live Birth                                     | 231                                                     | 119                                             |  |  |
| Spontaneous Abortion (< 20 week gestation)     | 0                                                       | 0                                               |  |  |
| Early Fetal Death (20-27 weeks gestation)      | 0                                                       | 0                                               |  |  |
| Late Fetal Death (at least 28 weeks gestation) | 0                                                       | 0                                               |  |  |
| Elective Abortion                              | 0                                                       | 0                                               |  |  |
| Maternal Death Resulting in Fetal Death        | 0                                                       | 0                                               |  |  |
| Ectopic Pregnancy                              | 0                                                       | 0                                               |  |  |
| Congenital Abnormalities                       | 6                                                       | 5                                               |  |  |
| Death                                          | 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 collected from Day 0 (pre-vaccination) up to date of delivery (on an average 103 day after vaccination)

Adverse event reporting additional description:

Solicited adverse reaction (SAR): An AE, i.e. prelisted in electronic case report form (eCRF) and considered related to vaccination. SAR is an adverse drug reaction observed, reported under the conditions (nature and onset) prelisted (i.e. solicited) in eCRF. Unsolicited AE: an observed AE that does not fulfill conditions prelisted in eCRF. Safety set

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Quadrivalent Influenza Vaccine (VaxigripTetra) |
|-----------------------|------------------------------------------------|

Reporting group description:

Pregnant women aged  $\geq 18$  years and in late second/third trimester of pregnancy received a single dose of VaxigripTetra vaccine.

|                       |                                        |
|-----------------------|----------------------------------------|
| Reporting group title | Trivalent Influenza Vaccine (Vaxigrip) |
|-----------------------|----------------------------------------|

Reporting group description:

Pregnant women aged  $\geq 18$  years and in late second/third trimester of pregnancy received a single dose of Vaxigrip vaccine.

| Serious adverse events                            | Quadrivalent Influenza Vaccine (VaxigripTetra) | Trivalent Influenza Vaccine (Vaxigrip) |  |
|---------------------------------------------------|------------------------------------------------|----------------------------------------|--|
| Total subjects affected by serious adverse events |                                                |                                        |  |
| subjects affected / exposed                       | 26 / 230 (11.30%)                              | 18 / 116 (15.52%)                      |  |
| number of deaths (all causes)                     | 0                                              | 0                                      |  |
| number of deaths resulting from adverse events    | 0                                              | 0                                      |  |
| Injury, poisoning and procedural complications    |                                                |                                        |  |
| Perineal Injury                                   |                                                |                                        |  |
| subjects affected / exposed                       | 1 / 230 (0.43%)                                | 0 / 116 (0.00%)                        |  |
| occurrences causally related to treatment / all   | 0 / 1                                          | 0 / 0                                  |  |
| deaths causally related to treatment / all        | 0 / 0                                          | 0 / 0                                  |  |
| Uterine Rupture                                   |                                                |                                        |  |
| subjects affected / exposed                       | 0 / 230 (0.00%)                                | 1 / 116 (0.86%)                        |  |
| occurrences causally related to treatment / all   | 0 / 0                                          | 0 / 1                                  |  |
| deaths causally related to treatment / all        | 0 / 0                                          | 0 / 0                                  |  |
| Vascular disorders                                |                                                |                                        |  |
| Hypertension                                      |                                                |                                        |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 230 (0.87%)  | 0 / 116 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Nervous system disorders                        |                  |                   |  |
| Migraine                                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 230 (0.43%)  | 0 / 116 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pregnancy, puerperium and perinatal conditions  |                  |                   |  |
| Gestational Hypertension                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 230 (0.43%)  | 1 / 116 (0.86%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intrapartum Haemorrhage                         |                  |                   |  |
| subjects affected / exposed                     | 2 / 230 (0.87%)  | 0 / 116 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Obstructed Labour                               |                  |                   |  |
| subjects affected / exposed                     | 0 / 230 (0.00%)  | 1 / 116 (0.86%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Peripartum Haemorrhage                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 230 (0.00%)  | 1 / 116 (0.86%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Postpartum Haemorrhage                          |                  |                   |  |
| subjects affected / exposed                     | 16 / 230 (6.96%) | 13 / 116 (11.21%) |  |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pre-Eclampsia                                   |                  |                   |  |
| subjects affected / exposed                     | 2 / 230 (0.87%)  | 0 / 116 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Premature Labour                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 230 (0.43%) | 0 / 116 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Preterm Premature Rupture Of Membranes          |                 |                 |  |
| subjects affected / exposed                     | 1 / 230 (0.43%) | 0 / 116 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholestasis Of Pregnancy                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 230 (0.43%) | 0 / 116 (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                     |                 |                 |  |
| Amniotic Cavity Infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 230 (0.00%) | 1 / 116 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 230 (0.00%) | 1 / 116 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 230 (0.43%) | 0 / 116 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post Procedural Infection                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 230 (0.43%) | 0 / 116 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | <b>Quadrivalent Influenza Vaccine (VaxigripTetra)</b> | <b>Trivalent Influenza Vaccine (Vaxigrip)</b> |  |
|-------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                                       |                                               |  |
| subjects affected / exposed                           | 216 / 230 (93.91%)                                    | 107 / 116 (92.24%)                            |  |
| Nervous system disorders                              |                                                       |                                               |  |
| Headache                                              |                                                       |                                               |  |
| subjects affected / exposed                           | 102 / 230 (44.35%)                                    | 58 / 116 (50.00%)                             |  |
| occurrences (all)                                     | 112                                                   | 62                                            |  |
| General disorders and administration site conditions  |                                                       |                                               |  |
| Injection Site Erythema                               |                                                       |                                               |  |
| subjects affected / exposed                           | 24 / 230 (10.43%)                                     | 16 / 116 (13.79%)                             |  |
| occurrences (all)                                     | 24                                                    | 16                                            |  |
| Injection Site Pain                                   |                                                       |                                               |  |
| subjects affected / exposed                           | 204 / 230 (88.70%)                                    | 88 / 116 (75.86%)                             |  |
| occurrences (all)                                     | 204                                                   | 88                                            |  |
| Injection Site Swelling                               |                                                       |                                               |  |
| subjects affected / exposed                           | 13 / 230 (5.65%)                                      | 6 / 116 (5.17%)                               |  |
| occurrences (all)                                     | 13                                                    | 6                                             |  |
| Malaise                                               |                                                       |                                               |  |
| subjects affected / exposed                           | 67 / 230 (29.13%)                                     | 33 / 116 (28.45%)                             |  |
| occurrences (all)                                     | 67                                                    | 33                                            |  |
| Shivering                                             |                                                       |                                               |  |
| subjects affected / exposed                           | 61 / 230 (26.52%)                                     | 30 / 116 (25.86%)                             |  |
| occurrences (all)                                     | 61                                                    | 30                                            |  |
| Respiratory, thoracic and mediastinal disorders       |                                                       |                                               |  |
| Oropharyngeal Pain                                    |                                                       |                                               |  |
| subjects affected / exposed                           | 16 / 230 (6.96%)                                      | 4 / 116 (3.45%)                               |  |
| occurrences (all)                                     | 16                                                    | 4                                             |  |
| Musculoskeletal and connective tissue disorders       |                                                       |                                               |  |
| Back Pain                                             |                                                       |                                               |  |
| subjects affected / exposed                           | 8 / 230 (3.48%)                                       | 7 / 116 (6.03%)                               |  |
| occurrences (all)                                     | 9                                                     | 8                                             |  |
| Myalgia                                               |                                                       |                                               |  |
| subjects affected / exposed                           | 86 / 230 (37.39%)                                     | 29 / 116 (25.00%)                             |  |
| occurrences (all)                                     | 86                                                    | 29                                            |  |
| Infections and infestations                           |                                                       |                                               |  |

|                                   |                   |                   |  |
|-----------------------------------|-------------------|-------------------|--|
| Rhinitis                          |                   |                   |  |
| subjects affected / exposed       | 11 / 230 (4.78%)  | 6 / 116 (5.17%)   |  |
| occurrences (all)                 | 12                | 6                 |  |
| Upper Respiratory Tract Infection |                   |                   |  |
| subjects affected / exposed       | 26 / 230 (11.30%) | 14 / 116 (12.07%) |  |
| occurrences (all)                 | 28                | 14                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                    |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 February 2018 | Corrections made to the following sections of the protocol: the objectives, endpoints, statistical methods and sample size. Recently available information regarding vaccine development and strains content was also added to background of IP. One additional month was allotted to the enrollment period. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported