



Clinical trial results:

Efficacy and Immunogenicity Study of Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Healthy Children Aged 6 to 35 Months

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-001231-51 |
| Trial protocol | IT ES GR RO |
| Global end of trial date | 27 July 2016 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 15 October 2017 |
| First version publication date | 15 October 2017 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | GQM05 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | U1111-1127-7504 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Sanofi Pasteur SA |
| Sponsor organisation address | 2, avenue Pont Pasteur, Lyon, France, 69007 |
| Public contact | Director, Clinical Development, Sanofi Pasteur SA, 570 957-6185, sanjay.gurunathan@sanofi.com |
| Scientific contact | Director, Clinical Development, Sanofi Pasteur SA, 570 957-6185, sanjay.gurunathan@sanofi.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001254-PIP01-11 |
| 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 | 11 February 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical efficacy of 2 doses of QIV in previously unvaccinated subjects aged 6 to 35 months for the prevention of at least one of the following:

*Laboratory-confirmed influenza caused by any influenza A or B types

*Laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine

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 also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

| | |
|---|---------------|
| Actual start date of recruitment | 12 March 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Dominican Republic: 476 |
| Country: Number of subjects enrolled | Honduras: 614 |
| Country: Number of subjects enrolled | South Africa: 500 |
| Country: Number of subjects enrolled | Philippines: 2999 |
| Country: Number of subjects enrolled | Romania: 46 |
| Country: Number of subjects enrolled | Spain: 850 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Greece: 225 |
| Country: Number of subjects enrolled | Italy: 82 |
| Worldwide total number of subjects | 5805 |
| EEA total number of subjects | 1216 |

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) | 3741 |
| Children (2-11 years) | 2064 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 12 March 2014 to 4 December 2015 at a total of 43 clinical centers (19 clinical centers in Spain, 6 in the Philippines, 5 in Greece, 5 in Romania, 4 in Italy, 1 in South Africa, 1 in Honduras, 1 in Dominican Republic, and 1 in France).

Pre-assignment

Screening details:

A total of 5805 subjects who met all inclusion criteria and no exclusion criteria were randomized in the study; 1 subject was enrolled in the study and injected with placebo before having been randomized. This subject was withdrawn from the study due to non-compliance with protocol procedures; data are presented on 5805 subjects.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Year 1 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

This trial was observer-blinded, except for Trivalent Influenza Vaccine (TIV) groups which were open label. The person who administered the vaccine was different from the person assessing safety and identifying influenza-like illness (ILI) cases. Subjects' parents/representative also did not know which vaccine was administered.

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Quadrivalent Influenza Vaccine (QIV) - Year 1 |

Arm description:

Subjects in this group received 2 doses of Quadrivalent Influenza Vaccine (split-virion, inactivated; QIV) 28 days apart.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Quadrivalent influenza vaccine (split-virion, inactivated) |
| Investigational medicinal product code | 481 |
| Other name | QIV |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use, Subcutaneous use |

Dosage and administration details:

0.5 mL, intramuscular or deep subcutaneous to be injected into the deltoid or the thigh, 2 doses 28 days apart

| | |
|------------------|------------------|
| Arm title | Placebo - Year 1 |
|------------------|------------------|

Arm description:

Subjects in this group received 2 doses of placebo 28 days apart.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Normal saline (placebo) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Intramuscular use, Subcutaneous use |

Dosage and administration details:

0.5 mL, intramuscular or deep subcutaneous to be injected into the deltoid or the thigh, 2 doses 28 days apart.

| | |
|--|--|
| Arm title | Trivalent Influenza Vaccine (TIV1) - Year 1 |
| Arm description: Subjects received 2 doses of the Trivalent Influenza Vaccine (split-virion, inactivated; TIV1) 28 days apart. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Trivalent influenza vaccine (split-virion, inactivated) |
| Investigational medicinal product code | TIV1 |
| 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 or deep subcutaneous to be injected into the deltoid or the thigh, 2 doses 28 days apart | |
| Arm title | Trivalent Influenza Vaccine (TIV2) - Year 1 |
| Arm description: Subjects received 2 doses of Trivalent Influenza Vaccine (split-virion, inactivated; TIV2; Sanofi Pasteur licensed TIV for the NH 2014-2015 season) 28 days apart. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Trivalent influenza vaccine (split-virion, inactivated)(Sanofi Pasteur licensed TIV for the NH 2014-2015 season) |
| Investigational medicinal product code | TIV2 |
| 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 or deep subcutaneous to be injected into the deltoid or the thigh, 2 doses 28 days apart | |

| Number of subjects in period 1 | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Placebo - Year 1 | Trivalent Influenza Vaccine (TIV1) - Year 1 |
|---------------------------------------|---|------------------|---|
| Started | 2721 | 2715 | 183 |
| Vaccinated at D0 | 2717 | 2711 | 182 |
| Vaccinated at D28 | 2627 | 2623 | 174 |
| Completed | 2559 | 2570 | 173 |
| Not completed | 162 | 145 | 10 |
| Consent withdrawn by subject | 60 | 53 | 4 |
| Adverse event, non-fatal | 3 | - | - |
| Serious adverse event | 5 | 1 | - |
| Lost to follow-up | 32 | 28 | 1 |
| Protocol deviation | 62 | 63 | 5 |

| Number of subjects in period 1 | Trivalent Influenza Vaccine (TIV2) - Year 1 |
|---------------------------------------|---|
| Started | 186 |
| Vaccinated at D0 | 185 |
| Vaccinated at D28 | 180 |

| | |
|------------------------------|-----|
| Completed | 179 |
| Not completed | 7 |
| Consent withdrawn by subject | 5 |
| Adverse event, non-fatal | - |
| Serious adverse event | - |
| Lost to follow-up | - |
| Protocol deviation | 2 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Year 2 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

This trial was observer-blinded, except for Trivalent Influenza Vaccine (TIV) groups which were open label. The person who administered the vaccine was different from the person assessing safety and identifying influenza-like illness (ILI) cases. Subjects' parents/representative also did not know which vaccine was administered.

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Quadrivalent Influenza Vaccine (QIV) - Year 2 |

Arm description:

Subjects in this group were revaccinated with 2 doses of Quadrivalent Influenza Vaccine (split-virion, inactivated; QIV) 28 days apart.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Quadrivalent influenza vaccine (split-virion, inactivated) |
| Investigational medicinal product code | 481 |
| Other name | QIV |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use, Intramuscular use |

Dosage and administration details:

0.5 mL, intramuscular or deep subcutaneous to be injected into the deltoid or the thigh, 2 doses 28 days apart

| | |
|------------------|------------------|
| Arm title | Placebo - Year 2 |
|------------------|------------------|

Arm description:

Subjects in this group received 2 doses of QIV 28 days apart

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Normal saline (placebo) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Intramuscular use, Subcutaneous use |

Dosage and administration details:

0.5 mL, intramuscular or deep subcutaneous to be injected into the deltoid or the thigh, 2 doses 28 days apart.

| Number of subjects in period 2^[1] | Quadrivalent Influenza Vaccine (QIV) - Year 2 | Placebo - Year 2 |
|---|---|------------------|
| Started | 213 | 41 |
| Completed | 209 | 41 |
| Not completed | 4 | 0 |
| Consent withdrawn by subject | 2 | - |
| Protocol deviation | 2 | - |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects included in the Period Year 2 were a randomized subset of participants from Latin America and Europe who were asked to return the following year to receive QIV, 2 doses 28 days apart. Not all participants included in Period Year 1 were included in Period Year 2.

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Quadrivalent Influenza Vaccine (QIV) - Year 1 |
| Reporting group description: | |
| Subjects in this group received 2 doses of Quadrivalent Influenza Vaccine (split-virion, inactivated; QIV) 28 days apart. | |
| Reporting group title | Placebo - Year 1 |
| Reporting group description: | |
| Subjects in this group received 2 doses of placebo 28 days apart. | |
| Reporting group title | Trivalent Influenza Vaccine (TIV1) - Year 1 |
| Reporting group description: | |
| Subjects received 2 doses of the Trivalent Influenza Vaccine (split-virion, inactivated; TIV1) 28 days apart. | |
| Reporting group title | Trivalent Influenza Vaccine (TIV2) - Year 1 |
| Reporting group description: | |
| Subjects received 2 doses of Trivalent Influenza Vaccine (split-virion, inactivated; TIV2; Sanofi Pasteur licensed TIV for the NH 2014-2015 season) 28 days apart. | |

| Reporting group values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Placebo - Year 1 | Trivalent Influenza Vaccine (TIV1) - Year 1 |
|---|---|------------------|---|
| Number of subjects | 2721 | 2715 | 183 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 1756 | 1749 | 117 |
| Children (2-11 years) | 965 | 966 | 66 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 19.7 | 19.8 | 19.7 |
| standard deviation | ± 8.38 | ± 8.43 | ± 8.42 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1333 | 1290 | 89 |
| Male | 1388 | 1425 | 94 |
| Recruitment by cohort | | | |
| The trial spanned several influenza seasons in different regions and countries (Europe, Asia, Latin America, and Africa) and recruitment encompassed different independent cohorts defined according to the pursued objectives. The cohort 3 was not implemented in the study due to recruitment capacity issues. | | | |
| Units: Subjects | | | |
| Cohort 1 | 1250 | 1249 | 0 |
| Cohort 2 | 367 | 364 | 183 |

| | | | |
|----------|------|------|---|
| Cohort 4 | 1104 | 1102 | 0 |
|----------|------|------|---|

| Reporting group values | Trivalent Influenza Vaccine (TIV2) - Year 1 | Total | |
|---|---|-------|--|
| Number of subjects | 186 | 5805 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 119 | 3741 | |
| Children (2-11 years) | 67 | 2064 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 19.3 | | |
| standard deviation | ± 8.06 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 88 | 2800 | |
| Male | 98 | 3005 | |
| Recruitment by cohort | | | |
| The trial spanned several influenza seasons in different regions and countries (Europe, Asia, Latin America, and Africa) and recruitment encompassed different independent cohorts defined according to the pursued objectives. The cohort 3 was not implemented in the study due to recruitment capacity issues. | | | |
| Units: Subjects | | | |
| Cohort 1 | 0 | 2499 | |
| Cohort 2 | 186 | 1100 | |
| Cohort 4 | 0 | 2206 | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Quadrivalent Influenza Vaccine (QIV) - Year 1 |
| Reporting group description: Subjects in this group received 2 doses of Quadrivalent Influenza Vaccine (split-virion, inactivated; QIV) 28 days apart. | |
| Reporting group title | Placebo - Year 1 |
| Reporting group description: Subjects in this group received 2 doses of placebo 28 days apart. | |
| Reporting group title | Trivalent Influenza Vaccine (TIV1) - Year 1 |
| Reporting group description: Subjects received 2 doses of the Trivalent Influenza Vaccine (split-virion, inactivated; TIV1) 28 days apart. | |
| Reporting group title | Trivalent Influenza Vaccine (TIV2) - Year 1 |
| Reporting group description: Subjects received 2 doses of Trivalent Influenza Vaccine (split-virion, inactivated; TIV2; Sanofi Pasteur licensed TIV for the NH 2014-2015 season) 28 days apart. | |
| Reporting group title | Quadrivalent Influenza Vaccine (QIV) - Year 2 |
| Reporting group description: Subjects in this group were revaccinated with 2 doses of Quadrivalent Influenza Vaccine (split-virion, inactivated; QIV) 28 days apart. | |
| Reporting group title | Placebo - Year 2 |
| Reporting group description: Subjects in this group received 2 doses of QIV 28 days apart | |
| Subject analysis set title | TIV pooled |
| Subject analysis set type | Full analysis |
| Subject analysis set description: TIV1 arm and TIV2 arm pooled for immunogenicity and safety analysis | |

Primary: Number of Subjects With an Laboratory-confirmed Influenza-like Illness caused by any influenza A or B strains or vaccine similar strains

| | |
|--|---|
| End point title | Number of Subjects With an Laboratory-confirmed Influenza-like Illness caused by any influenza A or B strains or vaccine similar strains ^[1] |
| End point description: Influenza-like illness (ILI) was defined by the occurrence of fever $\geq 38^{\circ}\text{C}$ (that lasted at least 24 hours) concurrently with at least one of the following symptoms: cough, nasal congestion, rhinorrhea, pharyngitis, otitis, vomiting, or diarrhea. Laboratory-confirmed influenza was defined either by a positive influenza result on polymerase chain reaction (PCR) or viral culture of nasopharyngeal (NP) swab samples. | |
| End point type | Primary |
| End point timeframe: From 14 days post-last vaccination to the end of influenza season according to Global Influenza Surveillance and Response System according to the region | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Laboratory-confirmed ILI cases were reported in the QIV and Placebo groups for the assessment of vaccine efficacy

| | | | | |
|---|---|------------------|--|--|
| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Placebo - Year 1 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2489 | 2491 | | |
| Units: Number of subjects | | | | |
| number (not applicable) | | | | |
| Any influenza A or B type | 120 | 245 | | |
| Viral strains similar to those in vaccine | 24 | 76 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Vaccine efficacy; Any influenza A or B type |
|-----------------------------------|---|

Statistical analysis description:

This analysis assessed the clinical vaccine efficacy (VE) against laboratory-confirmed influenza illness caused by influenza A or B types.

| | |
|---|--|
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 50.98 |
| Confidence interval | |
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 37.36 |
| upper limit | 61.86 |

Notes:

[2] - The VE for one primary endpoint was considered demonstrated if the lower bound of the confidence interval (CI) for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

| | |
|-----------------------------------|--|
| Statistical analysis title | Vaccine efficacy; Viral strains similar to vaccine |
|-----------------------------------|--|

Statistical analysis description:

This analysis assessed the clinical vaccine efficacy (VE) against laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine.

| | |
|---|--|
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 68.4 |
| Confidence interval | |
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 47.07 |
| upper limit | 81.92 |

Notes:

[3] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

Secondary: Number of Subjects With an Influenza-like Illness (ILI) as confirmed by Laboratory, Culture, and PCR, as well as ILI Associated with Hospitalizations

| | |
|-----------------|--|
| End point title | Number of Subjects With an Influenza-like Illness (ILI) as confirmed by Laboratory, Culture, and PCR, as well as ILI Associated with Hospitalizations ^[4] |
|-----------------|--|

End point description:

ILI was defined by the occurrence of fever $\geq 38^{\circ}\text{C}$ (that lasted at least 24 hours) concurrently with at least one of the following symptoms: cough, nasal congestion, rhinorrhea, pharyngitis, otitis, vomiting, or diarrhea. Laboratory-confirmed ILI was defined either by a positive influenza result on PCR or viral culture of NP swab samples. Culture-confirmed ILI was defined by a positive influenza result on viral culture of NP swabs. A PCR-confirmed ILI was defined by a positive influenza result on PCR of NP swab samples. Laboratory-confirmed ILI associated with hospitalizations (referred to as 'Lab-ILI [hospitalization]' in the table) is also reported. VE was reported for each ILI category, except for laboratory-confirmed ILI associated with hospitalization caused by vaccine-similar strain.

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

End point timeframe:

From 14 days post-last vaccination to the end of influenza season according to Global Influenza Surveillance and Response System according to the region

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Laboratory-confirmed ILI cases were reported in the QIV and Placebo groups for the assessment of vaccine efficacy

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Placebo - Year 1 | | |
|---|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2489 | 2491 | | |
| Units: Number of subjects | | | | |
| number (not applicable) | | | | |
| Laboratory-confirmed ILI: Any influenza A or B type | 120 | 245 | | |
| Laboratory-confirmed ILI: Vaccine-similar strain | 24 | 76 | | |
| PCR-confirmed ILI: Any influenza A or B type | 118 | 243 | | |
| PCR-confirmed ILI: Vaccine-similar strain | 24 | 76 | | |
| Culture-confirmed ILI: Any influenza A or B type | 91 | 214 | | |
| Culture-confirmed ILI: Vaccine-similar strain | 22 | 74 | | |
| Lab-ILI (hospitalization): Any influenza A or B | 3 | 3 | | |
| Lab-ILI (hospitalization): Vaccine-similar strain | 0 | 0 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Vaccine efficacy; Laboratory; Any influenza A or B |
| Statistical analysis description: This analysis assessed the clinical VE against laboratory-confirmed influenza illness caused by influenza A or B types. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 50.98 |
| Confidence interval | |
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 38.77 |
| upper limit | 60.93 |

Notes:

[5] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

| | |
|--|--|
| Statistical analysis title | Vaccine efficacy;Laboratory;Vaccine-similar strain |
| Statistical analysis description: This analysis assessed the clinical VE against laboratory-confirmed influenza illness caused by vaccine-similar strain. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 68.4 |
| Confidence interval | |
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 49.42 |
| upper limit | 80.91 |

Notes:

[6] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

| | |
|---|--|
| Statistical analysis title | Vaccine efficacy; PCR; Any Influenza A or B type |
| Statistical analysis description: This analysis assessed the clinical VE against PCR-confirmed influenza illness caused by influenza A or B types. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 51.4 |

| | |
|---------------------|-------------|
| Confidence interval | |
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 39.2 |
| upper limit | 61.33 |

Notes:

[7] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

| | |
|-----------------------------------|---|
| Statistical analysis title | Vaccine efficacy; PCR; Vaccine-similar strain |
|-----------------------------------|---|

Statistical analysis description:

This analysis assessed the clinical VE against PCR-confirmed influenza illness caused by vaccine-similar strain.

| | |
|---|--|
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 68.4 |

Confidence interval

| | |
|-------------|-------------|
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 49.42 |
| upper limit | 80.91 |

Notes:

[8] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

| | |
|-----------------------------------|---|
| Statistical analysis title | Vaccine efficacy; Culture; Any Influenza A or B |
|-----------------------------------|---|

Statistical analysis description:

This analysis assessed the clinical VE against PCR-confirmed influenza illness caused by influenza A or B types.

| | |
|---|--|
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 57.44 |

Confidence interval

| | |
|-------------|-------------|
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 45.36 |
| upper limit | 67.07 |

Notes:

[9] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

| | |
|-----------------------------------|---|
| Statistical analysis title | Vaccine efficacy; Culture; Vaccine-similar strain |
|-----------------------------------|---|

Statistical analysis description:

This analysis assessed the clinical VE against culture-confirmed influenza illness caused by vaccine-similar strain.

| | |
|---|--|
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | 70.25 |
| Confidence interval | |
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | 51.56 |
| upper limit | 82.4 |

Notes:

[10] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

| | |
|-----------------------------------|--|
| Statistical analysis title | Vaccine efficacy;Lab/hospitalized;Influenza A or B |
|-----------------------------------|--|

Statistical analysis description:

This analysis assessed the clinical VE against laboratory-confirmed influenza illness associated with hospitalization caused by influenza A or B types.

| | |
|---|--|
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v Placebo - Year 1 |
| Number of subjects included in analysis | 4980 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| Parameter estimate | Vaccine efficacy (%) |
| Point estimate | -0.08 |
| Confidence interval | |
| level | Other: 97 % |
| sides | 2-sided |
| lower limit | -647.2 |
| upper limit | 86.6 |

Notes:

[11] - The VE for one primary endpoint was considered demonstrated if the lower bound of the CI for the corresponding VE was >20%. The primary objective of efficacy was considered demonstrated if efficacy was demonstrated for at least one of the two primary endpoints.

Secondary: Geometric Mean Titers (GMTs) of Influenza Antibodies In Cohort 2 (Non-inferiority Analysis -Per-protocol population)

| | |
|-----------------|--|
| End point title | Geometric Mean Titers (GMTs) of Influenza Antibodies In Cohort 2 (Non-inferiority Analysis -Per-protocol population) ^[12] |
|-----------------|--|

End point description:

GMTs were assessed using the hemagglutination inhibition (HAI) method. Depending on the assessed strain, data are provided in the pooled TIV group (A strains), TIV1 group (B/Victoria strain), or TIV2 group (B/Yamagata strain).

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

End point timeframe:

28 days post-second vaccination

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of non-inferiority of the antibody response was performed in the QIV group and TIV groups in Cohort 2.

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | TIV pooled | | |
|--|---|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 300 | 320 | | |
| Units: Titers (1/dil) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/California/7/2009 (H1N1) | 650 (549 to 769) | 629 (530 to 746) | | |
| A/Texas/50/2012 (H3N2) | 1075 (917 to 1261) | 989 (845 to 1158) | | |
| B/Brisbane/60/2008 (B/Victoria lineage) | 593 (519 to 678) | 806 (657 to 988) | | |
| B/Massachusetts/02/2012 (B/Yamagata lineage) | 997 (863 to 1153) | 983 (824 to 1172) | | |

Statistical analyses

| Statistical analysis title | Ratio of GMTs; H1N1 |
|--|--|
| Statistical analysis description: | |
| This non-inferiority analysis assessed the ratio of GMTs between groups (QIV/TIV) for the H1N1 strain. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v TIV pooled |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[13] |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.31 |

Notes:

[13] - Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups (QIV/TIV) is >0.667 for each strain.

| Statistical analysis title | Ratio of GMTs; H3N2 |
|---|--|
| Statistical analysis description: | |
| This non-inferiority analysis assessed the ratio of GMTs between groups (QIV/TIV) in the H3N2 strain. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v TIV pooled |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[14] |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.36 |

Notes:

[14] - Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups (QIV/TIV) is >0.667 for each strain.

| | |
|---|--|
| Statistical analysis title | Ratio of GMTs; B/Victoria lineage |
| Statistical analysis description: This non-inferiority analysis assessed the ratio of GMTs between groups (QIV/TIV) for the B/Victoria lineage strain. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v TIV pooled |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[15] |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.93 |

Notes:

[15] - Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups (QIV/TIV) is >0.667 for each strain.

| | |
|--|--|
| Statistical analysis title | Ratio of GMTs; B/Yamagata lineage |
| Statistical analysis description: This non-inferiority analysis assessed the ratio of GMTs between groups (QIV/TIV) in the B/Yamagata lineage strain. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v TIV pooled |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[16] |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.28 |

Notes:

[16] - Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups (QIV/TIV) is >0.667 for each strain.

Secondary: GMTs of Influenza Antibodies in Cohort 2 (Superiority Analysis - Full Analysis Set)

| | |
|---|---|
| End point title | GMTs of Influenza Antibodies in Cohort 2 (Superiority Analysis - Full Analysis Set) ^[17] |
| End point description: GMTs were assessed using the HAI method. Depending on the assessed strain, data are provided in TIV1 group (B/Yamagata strain) or TIV2 group (B/Victoria strain) for the superiority analysis | |
| End point type | Secondary |
| End point timeframe: 28 days post-second vaccination | |

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of superiority of the antibody response was performed in the QIV group and TIV groups in Cohort 2.

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | TIV pooled | | |
|--|---|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 341 | 351 ^[18] | | |
| Units: Titers (1/dil) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| B/Brisbane/60/2008 (B/Victoria lineage) | 623 (550 to 706) | 10 (8.26 to 12.1) | | |
| B/Massachusetts/02/2012 (B/Yamagata lineage) | 1010 (885 to 1153) | 39.9 (31.2 to 51) | | |

Notes:

[18] - 172 subjects in TIV1 group, 179 subjects in TIV2 group

Statistical analyses

| Statistical analysis title | Ratio of GMTs; B/Victoria lineage |
|--|--|
| Statistical analysis description: This superiority analysis assessed the ratio of GMTs between groups (QIV/TIV) in the B/Victoria lineage strain. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v TIV pooled |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 62.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 50.04 |
| upper limit | 77.64 |

Notes:

[19] - Superiority concluded if the lower limit of the 2-sided 95% CI of the ratio of the GMTs between groups (QIV/TIV) is >1 for each B strain.

| Statistical analysis title | Ratio of GMTs; B/Yamagata lineage |
|--|--|
| Statistical analysis description: This superiority analysis assessed the ratio of GMTs between groups (QIV/TIV) in the B/Yamagata lineage strain. | |
| Comparison groups | Quadrivalent Influenza Vaccine (QIV) - Year 1 v TIV pooled |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[20] |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 25.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.63 |
| upper limit | 32.62 |

Notes:

[20] - Superiority concluded if the lower limit of the 2-sided 95% CI of the ratio of the GMTs between groups (QIV/TIV) is >1 for each B strain.

Secondary: GMTs of Influenza Antibodies in Cohort 2

| | |
|--|--|
| End point title | GMTs of Influenza Antibodies in Cohort 2 ^[21] |
| End point description: | |
| GMTs were assessed using the HAI method. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 0 (pre-vaccination) and Day 56 post-second vaccination | |

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive results of the immune response are presented in Cohort 2

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Trivalent Influenza Vaccine (TIV1) - Year 1 | Trivalent Influenza Vaccine (TIV2) - Year 1 | |
|--|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 341 | 172 | 178 | |
| Units: Titers (1/dil) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1; Day 0 | 17.5 (13.9 to 22.1) | 18 (12.8 to 25.4) | 15.5 (11.3 to 21.3) | |
| A/H1N1; Day 56 | 641 (547 to 752) | 637 (500 to 812) | 628 (504 to 781) | |
| A/H3N2; Day 0 | 25.2 (19.5 to 32.5) | 23.2 (16.1 to 33.3) | 26.8 (18.5 to 38.7) | |
| A/H3N2; Day 56 | 1071 (925 to 1241) | 1021 (824 to 1266) | 994 (807 to 1224) | |
| B/Victoria lineage; Day 0 | 6.2 (5.61 to 6.85) | 7.32 (6.11 to 8.76) | 6.61 (5.61 to 7.78) | |
| B/Victoria lineage; Day 56 | 623 (550 to 706) | 835 (691 to 1008) | 10 (8.27 to 12.1) | |
| B/Yamagata lineage; Day 0 | 10.8 (9.17 to 12.6) | 9.2 (7.44 to 11.4) | 9.11 (7.47 to 11.1) | |
| B/Yamagata lineage; Day 56 | 1010 (885 to 1153) | 39.9 (31.2 to 51) | 1009 (850 to 1198) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies

| | |
|-----------------|--|
| End point title | Geometric Mean Titer Ratios (GMTRs) of Influenza |
|-----------------|--|

End point description:

GMTRs were assessed using the HAI method.

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

End point timeframe:

Day 0 (pre-vaccination) and Day 56 post-second vaccination

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive results of the immune response are presented in Cohort 2

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Trivalent Influenza Vaccine (TIV1) - Year 1 | Trivalent Influenza Vaccine (TIV2) - Year 1 | |
|--|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 341 | 172 | 178 | |
| Units: Titer ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1 | 36.6 (30.8 to 43.6) | 35.3 (27.4 to 45.5) | 40.6 (32.6 to 50.5) | |
| A/H3N2 | 42.6 (35.1 to 51.7) | 44.1 (33.1 to 58.7) | 37.1 (28.3 to 48.6) | |
| B/Victoria | 100 (88.9 to 114) | 114 (94.4 to 138) | 1.52 (1.4 to 1.64) | |
| B/Yamagata | 93.9 (79.5 to 111) | 4.34 (3.62 to 5.2) | 111 (91.3 to 135) | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMTs of Influenza Antibodies At Year 2

| | |
|-----------------|--|
| End point title | GMTs of Influenza Antibodies At Year 2 |
|-----------------|--|

End point description:

GMTs were assessed using the HAI method.

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

End point timeframe:

Day 365 and Day 393 post-vaccination (Year 2)

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 2 | Placebo - Year 2 | | |
|--|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 40 | | |
| Units: Titers (1/dil) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1; Day 365 | 65.7 (51.2 to 84.3) | 15.5 (7.9 to 30.2) | | |
| A/H1N1; Day 393 | 762 (643 to 904) | 150 (80 to 283) | | |
| A/H3N2; Day 365 | 41.5 (32.8 to 52.4) | 24.6 (14.1 to 43) | | |
| A/H3N2; Day 393 | 1484 (1210 to 1819) | 243 (91 to 646) | | |
| B/Victoria; Day 365 | 47.9 (40.6 to 56.5) | 6.77 (4.8 to 9.55) | | |
| B/Victoria; Day 393 | 708 (610 to 823) | 80.7 (48.4 to 135) | | |
| B/Yamagata; Day 365 | 55.9 (46.7 to 67) | 15.7 (9.03 to 27.3) | | |
| B/Yamagata; Day 393 | 867 (749 to 1003) | 204 (100 to 415) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMTRs of Influenza Antibodies At Year 2

| | |
|------------------------|---|
| End point title | GMTRs of Influenza Antibodies At Year 2 |
| End point description: | GMTRs were assessed using the HAI method. |
| End point type | Secondary |
| End point timeframe: | Day 365 and Day 393 post-vaccination (Year 2) |

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 2 | Placebo - Year 2 | | |
|--|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 40 | | |
| Units: Titer ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1 | 11.6 (9.71 to 13.9) | 9.73 (7.33 to 12.9) | | |
| A/H3N2 | 35.8 (30.4 to 42.1) | 9.85 (5.96 to 16.3) | | |

| | | | | |
|------------|---------------------|---------------------|--|--|
| B/Victoria | 14.8 (12.8 to 17.1) | 11.9 (8.63 to 16.5) | | |
| B/Yamagata | 15.5 (13.4 to 17.9) | 13 (9.37 to 18) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion or Significant Increase of Titers Against Influenza Antigens

| | |
|-----------------|---|
| End point title | Seroconversion or Significant Increase of Titers Against Influenza Antigens ^[23] |
|-----------------|---|

End point description:

Influenza antibodies were assessed using the HAI method. Seroconversion was defined as pre-vaccination titer < 10 (1/dil) to post-injection titer ≥ 40 (1/dil) on Day 56 and significant increase was defined as pre-vaccination titer ≥ 10 (1/dil) to ≥ 4-fold increase from pre- to post-injection titer on Day 56.

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

End point timeframe:

Day 56 post-second vaccination

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive results of the immune response are presented in Cohort 2

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Trivalent Influenza Vaccine (TIV1) - Year 1 | Trivalent Influenza Vaccine (TIV2) - Year 1 | |
|-------------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 341 | 172 | 178 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| A/H1N1 | 90.3 | 87.2 | 90.4 | |
| A/H3N2 | 90.3 | 88.4 | 87.6 | |
| B/Victoria | 98.8 | 99.4 | 2.2 | |
| B/Yamagata | 96.8 | 33.9 | 99.4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion or Significant Increase of Titers Against Influenza Antigens at Year 2

| | |
|-----------------|---|
| End point title | Seroconversion or Significant Increase of Titers Against Influenza Antigens at Year 2 |
|-----------------|---|

End point description:

Influenza antibodies were assessed using the HAI method. Seroconversion was defined as pre-vaccination titer < 10 (1/dil) to post-injection titer ≥ 40 (1/dil) and significant increase was defined as

pre-vaccination titer ≥ 10 (1/dil) to ≥ 4 -fold increase from pre- to post-injection titer.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 393 post-vaccination | |

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 2 | Placebo - Year 2 | | |
|-------------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 40 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| A/H1N1 | 78.8 | 69.2 | | |
| A/H3N2 | 96.7 | 55 | | |
| B/Victoria | 89.9 | 70 | | |
| B/Yamagata | 90 | 72.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Solicited Injection Site or Systemic Reactions After Injection 1

| | |
|-----------------|--|
| End point title | Solicited Injection Site or Systemic Reactions After Injection |
|-----------------|--|

End point description:

Solicited inj. site: Pain (≥ 24 months)/Tenderness (< 24 months), Erythema, Swelling, Induration, and Ecchymosis. Solicited systemic: Subjects < 24 months, Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability; Subjects ≥ 24 months, Fever, Headache, Malaise, Myalgia, and Shivering. Grade 3 injection-site: Pain, Incapacitating, unable to perform usual activities; Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema, Swelling, Induration, and Ecchymosis ≥ 50 mm. Grade 3 systemic: Fever (< 24 months), $> 39.5^{\circ}\text{C}$ and $\geq 39.0^{\circ}\text{C}$ (≥ 24 months); Vomiting, ≥ 6 episodes/24 hours or requiring parenteral hydration; Crying abnormal, > 3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥ 3 or most feeds/meals; Irritability, Inconsolable; Headache, Malaise, Myalgia, and Shivering, Significant; prevents daily activity. Both age groups for Pain/Tenderness and Fever are reported together.

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

End point timeframe:

Day 0 up to Day 7 post-injection 1

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Non-serious solicited reactions and unsolicited AEs were collected in Cohort 1 and Cohort 2.

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Placebo - Year 1 | TIV pooled | |
|--|---|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 1614 | 1612 | 367 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Any Inj. site Pain/Tenderness; Post-inj. 1 | 19.3 | 15.8 | 22.4 | |
| Grade 3 Inj. site Pain/Tenderness; Post-inj. 1 | 0.4 | 0.4 | 0.3 | |
| Any Inj. site Erythema; Post-inj. 1 | 10.6 | 9.4 | 7.2 | |
| Grade 3 Inj. site Erythema; Post-inj. 1 | 0.1 | 0 | 0.3 | |
| Any Inj. site Swelling; Post-inj. 1 | 4.6 | 3.4 | 2.8 | |
| Grade 3 Inj. site Swelling; Post-inj. 1 | 0 | 0 | 0 | |
| Any Inj. site Induration; Post-inj. 1 | 5.3 | 3.7 | 5 | |
| Grade 3 Inj. site Induration; Post-inj. 1 | 0.1 | 0 | 0 | |
| Any Inj. site Ecchymosis; Post-inj. 1 | 2.6 | 2.3 | 3.3 | |
| Grade 3 Inj. site Ecchymosis; Post-inj. 1 | 0 | 0 | 0 | |
| Any Fever; Post-inj. 1 | 12.9 | 11.6 | 10.3 | |
| Grade 3 Fever; Post-inj. 1 | 1 | 1.3 | 2.8 | |
| Any Headache; Post-inj. 1 | 8.8 | 8.4 | 10.6 | |
| Grade 3 Headache; Post-inj. 1 | 0.2 | 0.8 | 0.8 | |
| Any Malaise; Post-inj. 1 | 19 | 6 | 19.1 | |
| Grade 3 Malaise; Post-inj. 1 | 1 | 0.7 | 0.8 | |
| Any Shivering; Post-inj. 1 | 4.5 | 6 | 9.2 | |
| Grade 3 Shivering; Post-inj. 1 | 0.2 | 0.7 | 1.5 | |
| Any Vomiting; Post-inj. 1 | 10.4 | 12.4 | 11.4 | |
| Grade 3 Vomiting; Post-inj. 1 | 0.3 | 0.4 | 1.7 | |
| Any Crying abnormal; Post-inj. 1 | 21.1 | 21.1 | 21 | |
| Grade 3 Crying abnormal; Post-inj. 1 | 1.5 | 0.7 | 2.2 | |
| Any Drowsiness; Post-inj. 1 | 11.2 | 10.1 | 15.3 | |
| Grade 3 Drowsiness; Post-inj. 1 | 1.1 | 0.4 | 1.7 | |
| Any Appetite lost; Post-inj. 1 | 22.3 | 21 | 17.5 | |
| Grade 3 Appetite lost; Post-inj. 1 | 1.9 | 2 | 3.5 | |
| Any Irritability; Post-inj. 1 | 25.4 | 26.4 | 25.8 | |
| Grade 3 Irritability; Post-inj. 1 | 1.5 | 1.2 | 1.7 | |
| Any Myalgia; Post-inj. 1 | 7.8 | 8 | 6.2 | |
| Grade 3 Myalgia; Post-inj. 1 | 0 | 0.2 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Solicited Injection Site or Systemic Reactions After Injection 2

| | |
|-----------------|--|
| End point title | Solicited Injection Site or Systemic Reactions After Injection |
|-----------------|--|

End point description:

Solicited inj. site: Pain (≥ 24 months)/Tenderness (< 24 months), Erythema, Swelling, Induration, and Ecchymosis. Solicited systemic: Subjects < 24 months, Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability; Subjects ≥ 24 months, Fever, Headache, Malaise, Myalgia, and Shivering.

Grade 3 injection-site: Pain, Incapacitating, unable to perform usual activities; Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema, Swelling, Induration, and Ecchymosis ≥ 50 mm. Grade 3 systemic: Fever (< 24 months), $> 39.5^{\circ}\text{C}$ and $\geq 39.0^{\circ}\text{C}$ (≥ 24 months); Vomiting, ≥ 6 episodes/24 hours or requiring parenteral hydration; Crying abnormal, > 3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥ 3 or most feeds/meals; Irritability, Inconsolable; Headache, Malaise, Myalgia, and Shivering, Significant; prevents daily activity. Both age groups for Pain/Tenderness and Fever are reported together.

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

End point timeframe:

Day 0 up to Day 7 post-injection 2

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Non-serious solicited reactions and unsolicited AEs were collected in Cohort 1 and Cohort 2.

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Placebo - Year 1 | TIV pooled | |
|--|---|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 1566 | 1571 | 354 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Any Inj. site Pain/Tenderness; Post-inj. 2 | 17.9 | 11.6 | 17 | |
| Grade 3 Inj. site Pain/Tenderness; Post-inj. 2 | 0.5 | 0.1 | 0.3 | |
| Any Inj. site Erythema; Post-inj. 2 | 11.6 | 7.1 | 3.7 | |
| Grade 3 Inj. site Erythema; Post-inj. 2 | 0.1 | 0 | 0 | |
| Any Inj. site Swelling; Post-inj. 2 | 4.8 | 1.5 | 2 | |
| Grade 3 Inj. site Swelling; Post-inj. 2 | 0 | 0.5 | 0 | |
| Any Inj. site Induration; Post-inj. 2 | 6.1 | 1.8 | 3.1 | |
| Grade 3 Inj. site Induration; Post-inj. 2 | 0.1 | 0 | 0 | |
| Any Inj. site Ecchymosis; Post-inj. 2 | 2 | 1.1 | 1.4 | |
| Grade 3 Inj. site Ecchymosis; Post-inj. 2 | 0 | 0.1 | 0 | |
| Any Fever; Post-inj. 2 | 10.1 | 8.6 | 11.3 | |
| Grade 3 Fever; Post-inj. 2 | 0.8 | 0.5 | 1.5 | |
| Any Headache; Post-inj. 2 | 5.4 | 4.6 | 1.5 | |
| Grade 3 Headache; Post-inj. 2 | 0.2 | 0 | 0 | |
| Any Malaise; Post-inj. 2 | 14.3 | 10.6 | 9.2 | |
| Grade 3 Malaise; Post-inj. 2 | 0.7 | 0.3 | 0 | |
| Any Myalgia; Post-inj. 2 | 5.5 | 2.9 | 6.2 | |
| Grade 3 Myalgia; Post-inj. 2 | 0.5 | 0 | 0 | |
| Any Shivering; Post-inj. 2 | 2.3 | 1.5 | 1.5 | |
| Grade 3 Shivering; Post-inj. 2 | 0.2 | 0.2 | 0 | |
| Any Vomiting; Post-inj. 2 | 7.7 | 7.4 | 8.1 | |
| Grade 3 Vomiting; Post-inj. 2 | 0.4 | 0 | 0 | |
| Any Crying abnormal; Post-inj. 2 | 15 | 17 | 19.7 | |
| Grade 3 Crying abnormal; Post-inj. 2 | 0.5 | 0.7 | 1.3 | |
| Any Drowsiness; Post-inj. 2 | 6.8 | 7.5 | 8.5 | |
| Grade 3 Drowsiness; Post-inj. 2 | 0.3 | 0.1 | 0 | |
| Any Appetite lost; Post-inj. 2 | 15.6 | 15.3 | 16.1 | |
| Grade 3 Appetite lost; Post-inj. 2 | 1.5 | 1.1 | 0 | |
| Any Irritability; Post-inj. 2 | 17.5 | 17.2 | 20.2 | |

| | | | | |
|-----------------------------------|-----|-----|-----|--|
| Grade 3 Irritability; Post-inj. 2 | 0.7 | 0.7 | 1.3 | |
|-----------------------------------|-----|-----|-----|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Solicited Injection Site or Systemic Reactions After Any Injection

| | |
|-----------------|--|
| End point title | Solicited Injection Site or Systemic Reactions After Any Injection ^[26] |
|-----------------|--|

End point description:

Solicited inj. site: Pain (≥24 months)/Tenderness (<24 months), Erythema, Swelling, Induration, and Ecchymosis. Solicited systemic: Subjects <24 months, Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability; Subjects ≥24 months, Fever, Headache, Malaise, Myalgia, and Shivering. The TIV group represents pooled data (TIV1 and Licensed TIV) from patients in Europe and Latin America only. For this table, the pooled TIV data is reported in the TIV1 column. The QIV and placebo groups present data from patients in Asia, Africa, Europe, and Latin America. Both age groups for Pain/Tenderness and Fever are reported together.

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

End point timeframe:

Day 0 up to Day 7 post-any injection

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Non-serious solicited reactions and unsolicited AEs were collected in Cohort 1 and Cohort 2.

| End point values | Quadrivalent Influenza Vaccine (QIV) - Year 1 | Placebo - Year 1 | TIV pooled | |
|-------------------------------|---|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 1614 | 1612 | 367 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Inj. site Pain/Tenderness | 26.8 | 21.6 | 29.4 | |
| Inj. site Erythema | 17.2 | 12.9 | 8.9 | |
| Inj. site Swelling | 7.6 | 4.1 | 3.9 | |
| Inj. site Induration | 9.1 | 4.9 | 6.7 | |
| Inj. site Ecchymosis | 4.2 | 3.3 | 4.2 | |
| Fever | 20.4 | 18.2 | 20.2 | |
| Headache | 11.9 | 11.4 | 10.6 | |
| Malaise | 26.8 | 24.5 | 25.2 | |
| Myalgia | 11.6 | 9.3 | 14.5 | |
| Shivering | 5.6 | 7 | 9.9 | |
| Vomiting | 16.1 | 17.2 | 17 | |
| Crying abnormal | 27.1 | 29.7 | 31.9 | |
| Drowsiness | 13.9 | 14.2 | 19.2 | |
| Appetite lost | 28.9 | 28.4 | 27.9 | |
| Irritability | 32.3 | 33.3 | 34.9 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited reactions were collected up to Day 7 after each injection, non-serious unsolicited adverse events (AEs) were collected up to Day 28 after each injection, and serious AEs were collected throughout the study period.

Adverse event reporting additional description:

Non-serious solicited reactions and unsolicited AEs were reported in Cohort 1 and Cohort 2 in Year 1. Serious AEs were reported in all subjects throughout the study period.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

Reporting groups

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

Reporting group description: -

| | |
|-----------------------|------------|
| Reporting group title | Pooled TIV |
|-----------------------|------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Quadrivalent Influenza Vaccine (QIV) | Pooled TIV | Placebo |
|---|--------------------------------------|------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 124 / 2718 (4.56%) | 14 / 367 (3.81%) | 128 / 2711 (4.72%) |
| number of deaths (all causes) | 5 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Accidental Exposure | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 2 / 2711 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Animal Bite | | | |
| subjects affected / exposed | 8 / 2718 (0.29%) | 0 / 367 (0.00%) | 5 / 2711 (0.18%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Animal Scratch | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 2 / 2718 (0.07%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Burns Second Degree | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 1 / 367 (0.27%) | 4 / 2711 (0.15%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head Injury | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb Crushing Injury | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Poisoning | | | |
| subjects affected / exposed | 2 / 2718 (0.07%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Thermal Burn | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Phimosis | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 1 / 367 (0.27%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|--|-------------------|-----------------|-------------------|
| Kawasaki's Disease | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 2 / 2718 (0.07%) | 0 / 367 (0.00%) | 2 / 2711 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 2 / 2711 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile Convulsion | | | |
| subjects affected / exposed | 26 / 2718 (0.96%) | 1 / 367 (0.27%) | 28 / 2711 (1.03%) |
| occurrences causally related to treatment / all | 1 / 30 | 0 / 1 | 1 / 30 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viith Nerve Paralysis | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Lymphadenitis | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Sudden Death | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Immune system disorders | | | |
| Food Allergy | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 1 / 367 (0.27%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Food Poisoning | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 1 / 367 (0.27%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 2718 (0.07%) | 0 / 367 (0.00%) | 2 / 2711 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthmatic Crisis | | | |
| subjects affected / exposed | 3 / 2718 (0.11%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 2 / 367 (0.54%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|-----------------|------------------|
| Interstitial Lung Disease | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia Aspiration | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Status Asthmaticus | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillar Hypertrophy | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 2 / 2711 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess Limb | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amoebiasis | | | |
| subjects affected / exposed | 2 / 2718 (0.07%) | 0 / 367 (0.00%) | 3 / 2711 (0.11%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amoebic Dysentery | | | |
| subjects affected / exposed | 4 / 2718 (0.15%) | 0 / 367 (0.00%) | 3 / 2711 (0.11%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascariasis | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial Infection | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 1 / 367 (0.27%) | 4 / 2711 (0.15%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 3 / 2711 (0.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis Viral | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 6 / 2718 (0.22%) | 0 / 367 (0.00%) | 3 / 2711 (0.11%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carbuncle | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|---|-------------------|-----------------|-------------------|
| subjects affected / exposed | 3 / 2718 (0.11%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue Fever | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 1 / 367 (0.27%) | 2 / 2711 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysentery | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterovirus Infection | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 1 / 367 (0.27%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 10 / 2718 (0.37%) | 1 / 367 (0.27%) | 15 / 2711 (0.55%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 1 | 0 / 17 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastroenteritis Rotavirus | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpangina | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection Parasitic | | | |

| | | | |
|---|-------------------|-----------------|-------------------|
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lobar Pneumonia | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral Herpes | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngeal Abscess | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 18 / 2718 (0.66%) | 3 / 367 (0.82%) | 30 / 2711 (1.11%) |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 3 | 0 / 33 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia Measles | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Syncytial Virus Infection | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotavirus Infection | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic Shock | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 2 / 2718 (0.07%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 3 / 2718 (0.11%) | 1 / 367 (0.27%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection Bacterial | | | |
| subjects affected / exposed | 1 / 2718 (0.04%) | 0 / 367 (0.00%) | 0 / 2711 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicella | | | |
| subjects affected / exposed | 4 / 2718 (0.15%) | 0 / 367 (0.00%) | 3 / 2711 (0.11%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral Infection | | | |
| subjects affected / exposed | 2 / 2718 (0.07%) | 0 / 367 (0.00%) | 3 / 2711 (0.11%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 0 / 2718 (0.00%) | 0 / 367 (0.00%) | 1 / 2711 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Quadrivalent Influenza Vaccine (QIV) | Pooled TIV | Placebo |
|---|--------------------------------------|--------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1117 / 2718 (41.10%) | 264 / 367 (71.93%) | 1125 / 2711 (41.50%) |
| Nervous system disorders | | | |
| Crying | | | |
| subjects affected / exposed ^[1] | 267 / 1003 (26.62%) | 73 / 234 (31.20%) | 293 / 1004 (29.18%) |
| occurrences (all) | 267 | 73 | 293 |
| Somnolence | | | |
| subjects affected / exposed ^[2] | 137 / 1003 (13.66%) | 44 / 234 (18.80%) | 140 / 1004 (13.94%) |
| occurrences (all) | 137 | 44 | 140 |

| | | | |
|---|----------------------------|---------------------------|----------------------------|
| Headache subjects affected / exposed ^[3] occurrences (all) | 72 / 612 (11.76%) 72 | 14 / 135 (10.37%) 14 | 69 / 608 (11.35%) 69 |
| General disorders and administration site conditions | | | |
| Injection Site Erythema subjects affected / exposed ^[4] occurrences (all) | 274 / 1614 (16.98%) 274 | 32 / 367 (8.72%) 32 | 205 / 1612 (12.72%) 205 |
| Injection Site Pain subjects affected / exposed ^[5] occurrences (all) | 427 / 1614 (26.46%) 427 | 106 / 367 (28.88%) 106 | 343 / 1612 (21.28%) 343 |
| Irritability subjects affected / exposed ^[6] occurrences (all) | 318 / 1003 (31.70%) 318 | 80 / 234 (34.19%) 80 | 328 / 1004 (32.67%) 328 |
| Malaise subjects affected / exposed ^[7] occurrences (all) | 162 / 612 (26.47%) 162 | 33 / 135 (24.44%) 33 | 148 / 608 (24.34%) 148 |
| Shivering subjects affected / exposed ^[8] occurrences (all) | 34 / 612 (5.56%) 34 | 13 / 135 (9.63%) 13 | 42 / 608 (6.91%) 42 |
| Fever subjects affected / exposed ^[9] occurrences (all) | 324 / 1614 (20.07%) 324 | 73 / 367 (19.89%) 73 | 290 / 1612 (17.99%) 290 |
| Injection site swelling subjects affected / exposed ^[10] occurrences (all) | 121 / 1614 (7.50%) 121 | 14 / 367 (3.81%) 14 | 65 / 1612 (4.03%) 65 |
| Injection site induration subjects affected / exposed ^[11] occurrences (all) | 144 / 1614 (8.92%) 144 | 24 / 367 (6.54%) 24 | 78 / 1612 (4.84%) 78 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed ^[12] occurrences (all) | 65 / 1614 (4.03%) 73 | 41 / 367 (11.17%) 46 | 74 / 1612 (4.59%) 85 |
| Vomiting subjects affected / exposed ^[13] occurrences (all) | 159 / 1003 (15.85%) 159 | 39 / 234 (16.67%) 39 | 170 / 1004 (16.93%) 170 |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed ^[14] occurrences (all) | 164 / 1614 (10.16%) 188 | 31 / 367 (8.45%) 34 | 191 / 1612 (11.85%) 231 |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed ^[15] occurrences (all) | 70 / 612 (11.44%) 70 | 19 / 135 (14.07%) 19 | 56 / 608 (9.21%) 56 |
| Infections and infestations Bronchitis subjects affected / exposed ^[16] occurrences (all) Gastroenteritis subjects affected / exposed ^[17] occurrences (all) Nasopharyngitis subjects affected / exposed ^[18] occurrences (all) | 21 / 1614 (1.30%) 22 90 / 1614 (5.58%) 95 261 / 1614 (16.17%) 319 | 19 / 367 (5.18%) 20 21 / 367 (5.72%) 23 109 / 367 (29.70%) 132 | 21 / 1612 (1.30%) 22 74 / 1612 (4.59%) 81 262 / 1612 (16.25%) 316 |
| Upper Respiratory Tract Infection subjects affected / exposed ^[19] occurrences (all) | 287 / 1614 (17.78%) 328 | 31 / 367 (8.45%) 42 | 334 / 1612 (20.72%) 396 |
| Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed ^[20] occurrences (all) | 285 / 1003 (28.41%) 285 | 64 / 234 (27.35%) 64 | 280 / 1004 (27.89%) 280 |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious solicited reactions and unsolicited AEs were collected in Cohort 1 and Cohort 2.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious solicited reactions and unsolicited AEs were collected in Cohort 1 and Cohort 2.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious solicited reactions and unsolicited AEs were collected in Cohort 1 and Cohort 2.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious solicited reactions and unsolicited AEs were collected in Cohort 1 and Cohort 2.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 30 September 2013 | Latin American and European clinical sites were added to secure the sample size of children. |
| 27 January 2014 | The time window from 1st vaccination to 2nd second vaccination was extended from 25 to 38 days to ensure that there was no impact on the immune response. |
| 03 November 2014 | Addition of testing done on laboratory-confirmed influenza and Ferret antigenicity testing (culture-confirmed influenza) was added; and sequencing of virus strains to be used was defined as Sanger sequencing. |
| 18 March 2015 | A provision to the methodology protocol was added to allow for the update of alpha values according to actual number of cases reported in the trial; transient thrombocytopenia was moved from potential to expected rare adverse events; parents were notified of this change and provided a second informed consent form. |
| 14 September 2015 | Changed a secondary objective/endpoint (influenza cases caused by vaccine-similar strains) to a co-primary endpoint to accurately assess vaccine efficacy; further revised and clarified the criteria and terms of performing the interim analyses. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported