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)	EMEA-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 ≥38°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 ≥38°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°C and ≥39.0°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°C and ≥39.0°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]	72 / 612 (11.76%)	14 / 135 (10.37%)	69 / 608 (11.35%)
occurrences (all)	72	14	69
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed[4]	274 / 1614 (16.98%)	32 / 367 (8.72%)	205 / 1612 (12.72%)
occurrences (all)	274	32	205
Injection Site Pain			
subjects affected / exposed[5]	427 / 1614 (26.46%)	106 / 367 (28.88%)	343 / 1612 (21.28%)
occurrences (all)	427	106	343
Irritability			
subjects affected / exposed[6]	318 / 1003 (31.70%)	80 / 234 (34.19%)	328 / 1004 (32.67%)
occurrences (all)	318	80	328
Malaise			
subjects affected / exposed[7]	162 / 612 (26.47%)	33 / 135 (24.44%)	148 / 608 (24.34%)
occurrences (all)	162	33	148
Shivering			
subjects affected / exposed[8]	34 / 612 (5.56%)	13 / 135 (9.63%)	42 / 608 (6.91%)
occurrences (all)	34	13	42
Fever			
subjects affected / exposed[9]	324 / 1614 (20.07%)	73 / 367 (19.89%)	290 / 1612 (17.99%)
occurrences (all)	324	73	290
Injection site swelling			
subjects affected / exposed[10]	121 / 1614 (7.50%)	14 / 367 (3.81%)	65 / 1612 (4.03%)
occurrences (all)	121	14	65
Injection site induration			
subjects affected / exposed[11]	144 / 1614 (8.92%)	24 / 367 (6.54%)	78 / 1612 (4.84%)
occurrences (all)	144	24	78
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed[12]	65 / 1614 (4.03%)	41 / 367 (11.17%)	74 / 1612 (4.59%)
occurrences (all)	73	46	85
Vomiting			
subjects affected / exposed[13]	159 / 1003 (15.85%)	39 / 234 (16.67%)	170 / 1004 (16.93%)
occurrences (all)	159	39	170

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

[5] - 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.
[6] - 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.
[7] - 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.
[8] - 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.
[9] - 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.
[10] - 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.
[11] - 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.
[12] - 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.
[13] - 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.
[14] - 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.
[15] - 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.
[16] - 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.
[17] - 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.
[18] - 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.
[19] - 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.
[20] - 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 access 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