Clinical trial results:
Safety and Immunogenicity of the Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Children Aged 3 to 8 Years

Summary

EudraCT number	2011-005374-33
Trial protocol	FI
Global end of trial date	25 June 2014

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	17 July 2015

Trial information

Trial identification

Sponsor protocol code	GQM02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1127-7425

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, F-69367 Lyon Cedex 07, France,
Public contact	Director, Clinical Development, Sanofi Pasteur SA, +33 (4) 37 37 58 50, stephanie.pepin@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, +33 (4) 37 37 58 50, stephanie.pepin@sanofipasteur.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	02 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of antibody (Ab) responses induced by QIV compared with the TIV.

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 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 154
Country: Number of subjects enrolled	Poland: 288
Country: Number of subjects enrolled	Mexico: 600
Country: Number of subjects enrolled	Taiwan: 200
Worldwide total number of subjects	1242
EEA total number of subjects	442

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1242

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 September 2013 to 13 November 2013 in 11 clinical centers in Finland, 4 in Mexico, 4 in Poland, and 3 in Taiwan.

Pre-assignment

Screening details:

A total of 1242 subjects who met all the inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

Period 1

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

Blinding implementation details:

This study was blinded to the Investigator and subjects. The code could be broken by the Investigator in the event of a SAE and if identification of the vaccine received could influence SAE treatment (Responsible Medical Officer was to be notified first) by calling the IVRS/IWRS system and by the GPV department for reporting to Health authorities in the case of an SAE as described in International Conference on Harmonisation (only for the subject in question).

Arms

Are arms mutually exclusive?	Yes
Arm title	Quadrivalent influenza vaccine (QIV)

Arm description:

Children aged 3-8 years who received one dose of quadrivalent influenza vaccine (QIV) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

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

Dosage and administration details:

0.5 mL dose, intramuscular (IM) to be injected into the deltoid muscle or deep subcutaneous (SC), one dose on Day 0 and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Arm title	TIV1

Arm description:

Children aged 3-8 years who received one dose of trivalent influenza vaccine that contained the B strain from the Victoria lineage (TIV1) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Arm type	Active comparator
Investigational medicinal product name	TIV1 (split-virion, inactivated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular (IM) to be injected into the deltoid muscle or deep subcutaneous (SC), one dose on Day 0 and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Arm title	TIV2

Arm description:

Children aged 3-8 years who received one dose of trivalent influenza vaccine containing the B strain from the Yamagata lineage (TIV2) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Arm type	Active comparator
Investigational medicinal product name	TIV2 (split-virion, inactivated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, intramuscular (IM) to be injected into the deltoid muscle or deep subcutaneous (SC), one dose on Day 0 and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Number of subjects in period 1	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2
Started	887	181	174
Completed	864	175	169
Not completed	23	6	5
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	19	5	4
Lost to follow-up	1	1	1
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Quadrivalent influenza vaccine (QIV)
Reporting group description:	
Children aged 3-8 years who received one dose of quadrivalent influenza vaccine (QIV) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.	
Reporting group title	TIV1
Reporting group description:	
Children aged 3-8 years who received one dose of trivalent influenza vaccine that contained the B strain from the Victoria lineage (TIV1) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.	
Reporting group title	TIV2
Reporting group description:	
Children aged 3-8 years who received one dose of trivalent influenza vaccine containing the B strain from the Yamagata lineage (TIV2) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.	

Reporting group values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2
Number of subjects	887	181	174
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)	0	0	0
Children (2-11 years)	887	181	174
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: years			
arithmetic mean	5.11	5.24	5.18
standard deviation	± 1.67	± 1.68	± 1.66
Gender categorical Units: Subjects			
Female	447	66	92
Male	440	115	82
Primed/Unprimed status Units: Subjects			
Yes	390	82	79
No	497	99	95

Reporting group values	Total		
Number of subjects	1242		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	1242		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	605		
Male	637		
Primed/Unprimed status Units: Subjects			
Yes	551		
No	691		

End points

End points reporting groups

Reporting group title	Quadrivalent influenza vaccine (QIV)
Reporting group description:	
Children aged 3-8 years who received one dose of quadrivalent influenza vaccine (QIV) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.	
Reporting group title	TIV1
Reporting group description:	
Children aged 3-8 years who received one dose of trivalent influenza vaccine that contained the B strain from the Victoria lineage (TIV1) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.	
Reporting group title	TIV2
Reporting group description:	
Children aged 3-8 years who received one dose of trivalent influenza vaccine containing the B strain from the Yamagata lineage (TIV2) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.	

Primary: Geometric Mean Titers (GMTs) of Influenza Antibodies Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Geometric Mean Titers (GMTs) of Influenza Antibodies Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[1]
End point description:	
Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method.	
End point type	Primary
End point timeframe:	
Day 0 (pre-vaccination) and Day 28-Day 56 post-vaccination	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	819	168	159	
Units: Titer (1/dil)				
geometric mean (confidence interval 95%)				
A/California/07/2009 (H1N1); D0	144 (127 to 165)	165 (122 to 223)	127 (95.8 to 169)	
A/California/07/2009 (H1N1); D28-D56	979 (902 to 1064)	1262 (1049 to 1518)	1001 (831 to 1204)	
A/Texas/50/2012 (H3N2); D0	209 (181 to 240)	253 (187 to 343)	194 (140 to 270)	
A/Texas/50/2012 (H3N2); D28-D56	1559 (1440 to 1688)	1978 (1696 to 2308)	1475 (1220 to 1783)	
B/Brisbane/60/2008; D0	61.4 (53.9 to 69.9)	63.2 (47.6 to 84)	45.8 (34.2 to 61.3)	

B/Brisbane/60/2008; D28-D56	1044 (948 to 1151)	1140 (933 to 1394)	167 (122 to 230)	
B/Massachusetts/02/2012; D0	47.5 (41.8 to 54)	47.3 (35.3 to 63.5)	35.6 (26.9 to 47)	
B/Massachusetts/02/2012; D28-D56	1188 (1090 to 1295)	219 (171 to 280)	1150 (948 to 1396)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Seroprotection Against the Influenza Antigens Before or After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects with Seroprotection Against the Influenza Antigens Before or After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[2]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method. Seroprotection was defined as subjects with titers ≥ 40 (1/dil) on D0 and, on D28 or D56.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 28-Day 56 post-vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	819	168	159	
Units: Percentage of subjects				
number (not applicable)				
A/California/07/2009 (H1N1); D0	76.9	78	76.7	
A/California/07/2009 (H1N1); D28-D56	98.8	98.8	98.7	
A/Texas/50/2012 (H3N2); D0	78.3	81	76.1	
A/Texas/50/2012 (H3N2); D28-D56	99.8	100	100	
B/Brisbane/60/2008; D0	60.7	66.1	54.1	
B/Brisbane/60/2008; D28-D56	98.7	99.4	76.1	
B/Massachusetts/02/2012; D0	52.2	52.1	44.7	
B/Massachusetts/02/2012; D28-D56	99.4	83.3	98.7	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Achieving Seroconversion or Significant increase

Against Influenza Antigens After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Achieving Seroconversion or Significant increase Against Influenza Antigens After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[3]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method. Seroconversion was defined as subjects with pre-vaccination titer < 10 (1/dil) on D0, post-vaccination titer ≥40 (1/dil) or significant increase was for subjects with pre-vaccination titer ≥ 10 (1/dil), ≥ 4-fold increase of the titer after vaccination (post/pre).

End point type	Primary

End point timeframe:

Day 28-Day 56 post-vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	819	168	159	
Units: Percentage of subjects				
number (not applicable)				
A/California/07/2009 (H1N1)	65.6	64.3	67.9	
A/Texas/50/2012 (H3N2)	65	68.5	66.7	
B/Brisbane/60/2008	84.9	89.9	40.3	
B/Massachusetts/02/2012	88.4	45.5	90.6	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) of Influenza Antibodies In Primed Subjects Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Geometric Mean Titers (GMTs) of Influenza Antibodies In Primed Subjects Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[4]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 28-Day 56 post-vaccination

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	80	72	
Units: Titer (1/dil)				
geometric mean (confidence interval 95%)				
A/California/07/2009 (H1N1); D0	178 (151 to 210)	220 (154 to 316)	150 (103 to 220)	
A/California/07/2009 (H1N1); D28-D56	829 (732 to 940)	1067 (811 to 1404)	927 (707 to 1215)	
A/Texas/50/2012 (H3N2); D0	264 (219 to 318)	321 (217 to 476)	179 (111 to 287)	
A/Texas/50/2012 (H3N2); D28-D56	1313 (1160 to 1486)	1549 (1205 to 1990)	1119 (846 to 1479)	
B/Brisbane/60/2008; D0	84.3 (70.8 to 100)	96.4 (69.1 to 134)	53.1 (35.9 to 78.6)	
B/Brisbane/60/2008; D28-D56	927 (799 to 1075)	1022 (750 to 1392)	236 (152 to 368)	
B/Massachusetts/02/2012; D0	82.4 (68.8 to 98.8)	97.9 (65 to 147)	49.4 (34.4 to 71)	
B/Massachusetts/02/2012; D28-D56	1132 (984 to 1302)	392 (288 to 535)	1082 (785 to 1490)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Primed Subjects with Seroprotection Against the Influenza Antigens Before or After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Primed Subjects with Seroprotection Against the Influenza Antigens Before or After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[5]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method. Seroprotection was defined as subjects with titers ≥ 40 (1/dil) on D0 and, on D28 or D56.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 28-Day 56 post-vaccination

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	80	72	
Units: Percentage of subjects				
number (not applicable)				
A/California/07/2009 (H1N1); D0	83.7	85	81.9	

A/California/07/2009 (H1N1); D28-D56	97.9	98.8	97.2	
A/Texas/50/2012 (H3N2); D0	84.8	86.3	76.4	
A/Texas/50/2012 (H3N2); D28-D56	99.5	100	100	
B/Brisbane/60/2008; D0	68.5	78.8	59.7	
B/Brisbane/60/2008; D28-D56	97.6	98.8	86.1	
B/Massachusetts/02/2012; D0	63.9	67.1	52.8	
B/Massachusetts/02/2012; D28-D56	98.7	97.5	97.2	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Primed Subjects Achieving Seroconversion or Significant increase Against Influenza Antigens After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Primed Subjects Achieving Seroconversion or Significant increase Against Influenza Antigens After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[6]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method. Seroconversion was defined as subjects with pre-vaccination titer < 10 (1/dil) on D0, post-vaccination titer ≥40 (1/dil) or significant increase was for subjects with pre-vaccination titer ≥ 10 (1/dil), ≥ 4-fold increase of the titer after vaccination (post/pre).

End point type	Primary

End point timeframe:

Day 28-Day 56 post-vaccination

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	80	72	
Units: Percentage of subjects				
number (not applicable)				
A/California/07/2009 (H1N1)	55.9	51.3	61.1	
A/Texas/50/2012 (H3N2)	54.3	53.8	62.5	
B/Brisbane/60/2008	77.7	86.3	50	
B/Massachusetts/02/2012	82.4	48.1	90.3	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) of Influenza Antibodies in Unprimed

Subjects Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Geometric Mean Titers (GMTs) of Influenza Antibodies in Unprimed Subjects Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[7]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 28-Day 56 post-vaccination

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	438	88	87	
Units: Titer (1/dil)				
geometric mean (confidence interval 95%)				
A/California/07/2009 (H1N1); D0	120 (98.7 to 147)	127 (79.5 to 204)	111 (73.1 to 168)	
A/California/07/2009 (H1N1); D28-D56	1131 (1015 to 1261)	1469 (1144 to 1887)	1066 (823 to 1379)	
A/Texas/50/2012 (H3N2); D0	170 (138 to 209)	204 (130 to 322)	208 (131 to 330)	
A/Texas/50/2012 (H3N2); D28-D56	1810 (1637 to 2001)	2471 (2068 to 2952)	1854 (1438 to 2390)	
B/Brisbane/60/2008; D0	46.6 (38.7 to 56.2)	43.1 (27.7 to 67.1)	40.5 (26.3 to 62.2)	
B/Brisbane/60/2008; D28-D56	1159 (1020 to 1316)	1260 (968 to 1641)	125 (80 to 197)	
B/Massachusetts/02/2012; D0	29.5 (24.9 to 34.9)	24.6 (16.9 to 35.9)	27.1 (17.9 to 40.9)	
B/Massachusetts/02/2012; D28-D56	1239 (1114 to 1378)	129 (91 to 182)	1211 (952 to 1540)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Unprimed Subjects with Seroprotection Against the Influenza Antigens Before or After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Unprimed Subjects with Seroprotection Against the Influenza Antigens Before or After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[8]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method. Seroprotection was defined as subjects with titers ≥ 40 (1/dil) on D0 and, on D28 or D56.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 28-Day 56 post-vaccination

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	438	88	87	
Units: Percentage of subjects				
number (not applicable)				
A/California/07/2009 (H1N1); D0	71	71.6	72.4	
A/California/07/2009 (H1N1); D28-D56	99.5	98.9	100	
A/Texas/50/2012 (H3N2); D0	72.6	76.1	75.9	
A/Texas/50/2012 (H3N2); D28-D56	100	100	100	
B/Brisbane/60/2008; D0	53.9	54.5	49.4	
B/Brisbane/60/2008; D28-D56	99.5	100	67.8	
B/Massachusetts/02/2012; D0	42	38.6	37.9	
B/Massachusetts/02/2012; D28-D56	100	70.5	100	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Unprimed Subjects Achieving Seroconversion or Significant increase Against Influenza Antigens After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Unprimed Subjects Achieving Seroconversion or Significant increase Against Influenza Antigens After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[9]

End point description:

Immunogenicity was evaluated using the hemagglutination inhibition (HAI) method. Seroconversion was defined as subjects with pre-vaccination titer < 10 (1/dil) on D0, post-vaccination titer ≥40 (1/dil) or significant increase was for subjects with pre-vaccination titer ≥ 10 (1/dil), ≥ 4-fold increase of the titer after vaccination (post/pre).

End point type	Primary

End point timeframe:

Day 28-Day 56 post-vaccination

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	438	88	87	
Units: Percentage of subjects				
number (not applicable)				
A/California/07/2009 (H1N1)	74	76.1	73.6	
A/Texas/50/2012 (H3N2)	74.2	81.8	70.1	
B/Brisbane/60/2008	91.1	93.2	32.2	
B/Massachusetts/02/2012	93.6	43.2	90.8	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) of Influenza Antibodies Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Geometric Mean Titers (GMTs) of Influenza Antibodies Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[10]

End point description:

Immunogenicity was evaluated using the virus seroneutralization (SN) method.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 28-Day 56 post-vaccination

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	431	86	83	
Units: Titer (1/dil)				
geometric mean (confidence interval 95%)				
A/California/07/2009 (H1N1); D0	414 (335 to 512)	580 (357 to 945)	508 (314 to 820)	
A/California/07/2009 (H1N1); D28-D56	3499 (3138 to 3902)	4409 (3460 to 5617)	4517 (3581 to 5698)	
A/Texas/50/2012 (H3N2); D0	94.5 (81.8 to 109)	102 (75.4 to 137)	97.1 (70.5 to 134)	
A/Texas/50/2012 (H3N2); D28-D56	475 (430 to 525)	571 (466 to 699)	513 (411 to 641)	
B/Brisbane/60/2008; D0	66.7 (56 to 79.4)	62.8 (42.8 to 92.2)	57.9 (37.9 to 88.6)	
B/Brisbane/60/2008; D28-D56	905 (788 to 1039)	980 (722 to 1329)	203 (139 to 298)	
B/Massachusetts/02/2012; D0	38 (32.2 to 44.7)	33.7 (22.9 to 49.7)	37.8 (26 to 55)	

B/Massachusetts/02/2012; D28-D56	731 (638 to 838)	131 (94.4 to 181)	952 (709 to 1279)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After First Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After First Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[11]

End point description:

Solicited injection site: Pain, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering. Grade 3 Solicited Injection site reactions: Pain – Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis - ≥50 mm. Grade 3 Solicited systemic reactions: Fever - ≥39°C; Headache, Malaise, Myalgia, and Shivering – Significant, prevents daily activities.

End point type	Primary

End point timeframe:

Day 0 up to Day 7 post-vaccination

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	884	181	172	
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	46.7	51.1	43	
Grade 3 Injection site Pain	0.8	1.1	1.2	
Injection site Erythema	15.6	19.2	16.3	
Grade 3 Injection site Erythema	2.3	3.8	0.6	
Injection site Swelling	16.4	19.2	15.1	
Grade 3 Injection site Swelling	1.7	1.6	0	
Injection site Induration	13.3	13.7	11	
Grade 3 Injection site Induration	1	1.1	0.6	
Injection site Ecchymosis	4.8	5.5	2.9	
Grade 3 Injection site Ecchymosis	0.2	0	0	
Fever	6.2	5.6	2.9	
Grade 3 Fever	0.2	0.6	0	
Headache	20.5	16.5	15.1	
Grade 3 Headache	0.9	1.1	1.2	
Malaise	25.7	19.8	24.4	
Grade 3 Malaise	1.2	1.1	1.7	
Myalgia	22.9	21.4	24.4	

Grade 3 Myalgia	1	0	1.2	
Shivering	9.3	9.3	6.4	
Grade 3 Shivering	0.7	0.5	0.6	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Second Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Second Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[12]

End point description:

Solicited injection site: Pain, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering. Grade 3 Solicited Injection site reactions: Pain – Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis - ≥50 mm. Grade 3 Solicited systemic reactions: Fever - ≥39°C; Headache, Malaise, Myalgia, and Shivering – Significant, prevents daily activities.

End point type	Primary

End point timeframe:

Day 0 up to Day 7 post-vaccination

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	491	99	96	
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	45.9	46.3	43	
Grade 3 Injection site Pain	1.2	3.2	0	
Injection site Erythema	14.6	13.7	11.8	
Grade 3 Injection site Erythema	1.5	1.1	0	
Injection site Swelling	13.1	13.7	8.6	
Grade 3 Injection site Swelling	1.2	1.1	0	
Injection site Induration	11.4	9.5	7.5	
Grade 3 Injection site Induration	0.8	0	0	
Injection site Ecchymosis	3.5	2.1	6.5	
Grade 3 Injection site Ecchymosis	0.2	0	0	
Fever	5.5	4.2	4.3	
Grade 3 Fever	1.5	0	0	
Headache	17	16.8	11.8	
Grade 3 Headache	1.2	0	0	
Malaise	18.3	15.8	22.6	
Grade 3 Malaise	1.5	0	1.1	

Myalgia	20.4	16.8	15.1	
Grade 3 Myalgia	0.8	1.1	0	
Shivering	6	3.2	2.2	
Grade 3 Shivering	0.6	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post-vaccination) up to Day 28 post-vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Quadrivalent influenza vaccine (QIV)

Reporting group description:

Children aged 3-8 years who received one dose of quadrivalent influenza vaccine (QIV) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Reporting group title	TIV1

Reporting group description:

Children aged 3-8 years who received one dose of trivalent influenza vaccine that contained the B strain from the Victoria lineage (TIV1) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Reporting group title	TIV2

Reporting group description:

Children aged 3-8 years who received one dose of trivalent influenza vaccine containing the B strain from the Yamagata lineage (TIV2) and if previously unvaccinated, a second dose of vaccine was administered on Day 28.

Serious adverse events	Quadrivalent influenza vaccine (QIV)	TIV1	TIV2
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 884 (1.58%)	3 / 182 (1.65%)	1 / 172 (0.58%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Extradural haematoma			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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
Thrombocytopenia			

subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Strabismus			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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	1 / 884 (0.11%)	1 / 182 (0.55%)	0 / 172 (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
Bronchospasm			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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			
Adenoiditis			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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
Gastroenteritis			
subjects affected / exposed	1 / 884 (0.11%)	1 / 182 (0.55%)	0 / 172 (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
Herpangina			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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

Otitis media			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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
Parotitis			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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
Pneumococcal sepsis			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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 influenzal			
subjects affected / exposed	1 / 884 (0.11%)	0 / 182 (0.00%)	0 / 172 (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
Pyelonephritis			
subjects affected / exposed	0 / 884 (0.00%)	1 / 182 (0.55%)	0 / 172 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 884 (0.00%)	0 / 182 (0.00%)	1 / 172 (0.58%)
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)	TIV1	TIV2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	412 / 884 (46.61%)	93 / 182 (51.10%)	74 / 172 (43.02%)
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[1]	181 / 882 (20.52%)	16 / 95 (16.84%)	26 / 172 (15.12%)
occurrences (all)	181	16	26
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed[2]	412 / 882 (46.71%)	93 / 182 (51.10%)	74 / 172 (43.02%)
occurrences (all)	412	93	74
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed[3]	138 / 882 (15.65%)	35 / 182 (19.23%)	28 / 172 (16.28%)
occurrences (all)	138	35	28
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed[4]	145 / 882 (16.44%)	35 / 182 (19.23%)	26 / 172 (15.12%)
occurrences (all)	145	35	26
Injection site ecchymosis			
alternative assessment type: Systematic			
subjects affected / exposed[5]	42 / 882 (4.76%)	10 / 182 (5.49%)	6 / 93 (6.45%)
occurrences (all)	42	10	6
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[6]	54 / 877 (6.16%)	10 / 180 (5.56%)	4 / 93 (4.30%)
occurrences (all)	54	10	4
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed[7]	227 / 882 (25.74%)	36 / 182 (19.78%)	42 / 172 (24.42%)
occurrences (all)	227	36	42
Shivering			
alternative assessment type:			

Systematic			
subjects affected / exposed[8]	82 / 882 (9.30%)	17 / 182 (9.34%)	11 / 172 (6.40%)
occurrences (all)	82	17	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	65 / 884 (7.35%)	20 / 182 (10.99%)	11 / 172 (6.40%)
occurrences (all)	70	22	11
Skin and subcutaneous tissue disorders			
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed[9]	117 / 882 (13.27%)	25 / 182 (13.74%)	19 / 172 (11.05%)
occurrences (all)	117	25	19
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed[10]	202 / 882 (22.90%)	39 / 182 (21.43%)	42 / 172 (24.42%)
occurrences (all)	202	39	42
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	83 / 884 (9.39%)	13 / 182 (7.14%)	16 / 172 (9.30%)
occurrences (all)	96	14	18
Upper respiratory tract infection			
subjects affected / exposed	54 / 884 (6.11%)	12 / 182 (6.59%)	8 / 172 (4.65%)
occurrences (all)	58	15	10

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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data

were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[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: This was a solicited adverse event recorded in a diary card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2014	A first analysis on vaccination period data (D0-D56) was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported