Clinical trial results:
Safety and Immunogenicity of a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Child/Adolescent and Adult Subjects

Summary

EudraCT number	2011-005101-79
Trial protocol	Outside EU/EEA
Global end of trial date	24 May 2012

Results information

Result version number	v1
This version publication date	01 March 2016
First version publication date	27 March 2015

Trial information

Trial identification

Sponsor protocol code	GQM04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01481454
WHO universal trial number (UTN)	U1111-1122-2719

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon cedex 07, France, F-69367
Public contact	Director, Clinical Department, Sanofi Pasteur SA, 33 (0)437 37 58 50, stephanie.pepin@sanofipasteur.com
Scientific contact	Director, Clinical Department, Sanofi Pasteur SA, 33 (0)437 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	16 January 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 May 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To describe the safety profile of Quadrivalent Influenza Vaccine (QIV) compared to Trivalent Influenza Vaccine (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	19 March 2012
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	Australia: 700
Country: Number of subjects enrolled	Philippines: 1390
Worldwide total number of subjects	2090
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	154
Adolescents (12-17 years)	231

Adults (18-64 years)	1705
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 19 March 2012 to 28 April 2012 at 4 clinical centers in the Philippines and 6 clinical centers in Australia.

Pre-assignment

Screening details:

A total of 2090 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled and randomized, 2083 subjects were 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	Subject, Investigator

Blinding implementation details:

The study was conducted double-blind for QIV lots (i.e., neither the investigator nor the subject/subject's parent or legal representative, nor the study staff in charge of vaccination knew what lot of vaccine [QIV] was administered) for all subjects. The study was open for vaccine receipt (i.e. which vaccine [QIV or TIV] is administered).

Arms

Are arms mutually exclusive?	Yes
Arm title	QIV S4361

Arm description:

Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4361) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.

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

Dosage and administration details:

0.5 mL, intramuscular to be injected into the deltoid muscle or deep subcutaneous, administered on Day 0 and 21

Arm title	QIV S4362

Arm description:

Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4362) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.

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

Dosage and administration details:

0.5 mL, intramuscular to be injected into the deltoid muscle or deep subcutaneous, administered on Day 0 and 21

Arm title	QIV S4363

Arm description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4363) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Arm type	Experimental
Investigational medicinal product name	Quadrivalent influenza vaccine (split-virion, inactivated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use, Subcutaneous use
Dosage and administration details:	
0.5 mL, intramuscular to be injected into the deltoid muscle or deep subcutaneous, administered on Day 0 and 21	
Arm title	Trivalent Influenza Vaccine (TIV)
Arm description:	
Subjects who received Trivalent Influenza Vaccine (TIV) 2011-2012 Formulation administered on Day 0 and Day 21.	
Arm type	Active comparator
Investigational medicinal product name	Sanofi Pasteur 2011–2012 formulation TIV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use, Subcutaneous use
Dosage and administration details:	
0.5 mL, intramuscular to be injected into the deltoid muscle or deep subcutaneous, administered on Day 0 and 21	

Number of subjects in period 1[1]	QIV S4361	QIV S4362	QIV S4363
Started	654	664	655
Completed	653	662	653
Not completed	1	2	2
Consent withdrawn by subject	-	1	1
Lost to follow-up	1	1	-
Protocol deviation	-	-	1

Number of subjects in period 1[1]	Trivalent Influenza Vaccine (TIV)
Started	110
Completed	109
Not completed	1
Consent withdrawn by subject	-
Lost to follow-up	-
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported in the baseline period are the subjects who were enrolled and received the vaccination.

Baseline characteristics

Reporting groups	
Reporting group title	QIV S4361
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4361) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	QIV S4362
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4362) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	QIV S4363
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4363) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	Trivalent Influenza Vaccine (TIV)
Reporting group description:	
Subjects who received Trivalent Influenza Vaccine (TIV) 2011-2012 Formulation administered on Day 0 and Day 21.	

Reporting group values	QIV S4361	QIV S4362	QIV S4363
Number of subjects	654	664	655
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)	42	44	45
Adolescents (12-17 years)	67	67	63
Adults (18-64 years)	545	553	547
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.4	33.7	33.5
standard deviation	± 14.6	± 14.8	± 14.5
Gender categorical Units: Subjects			
Female	382	387	398
Male	272	277	257
Influenza vaccination 2011 Units: Subjects			
Yes	162	145	136
No	485	512	511
Unknown	7	7	8
Influenza vaccination 2010 Units: Subjects			
Yes	120	110	108

No	526	543	536
Unknown	8	11	11
Influenza vaccination 2009 Units: Subjects			
Yes	134	138	138
No	507	509	502
Unknown	13	17	15

Reporting group values	Trivalent Influenza Vaccine (TIV)	Total	
Number of subjects	110	2083	
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)	0	0	
Children (2-11 years)	21	152	
Adolescents (12-17 years)	33	230	
Adults (18-64 years)	56	1701	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	25.2		
standard deviation	± 14.5	-	
Gender categorical Units: Subjects			
Female	53	1220	
Male	57	863	
Influenza vaccination 2011 Units: Subjects			
Yes	26	469	
No	83	1591	
Unknown	1	23	
Influenza vaccination 2010 Units: Subjects			
Yes	22	360	
No	86	1691	
Unknown	2	32	
Influenza vaccination 2009 Units: Subjects			
Yes	18	428	
No	89	1607	
Unknown	3	48	

End points

End points reporting groups

Reporting group title	QIV S4361
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4361) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	QIV S4362
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4362) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	QIV S4363
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4363) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	Trivalent Influenza Vaccine (TIV)
Reporting group description:	
Subjects who received Trivalent Influenza Vaccine (TIV) 2011-2012 Formulation administered on Day 0 and Day 21.	

Primary: Geometric Mean Titers (GMTs) of influenza Antibodies Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 Years

End point title	Geometric Mean Titers (GMTs) of influenza Antibodies Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 Years[1]
End point description:	
Immunogenicity was assessed using the hemagglutination inhibition (HAI) assay.	
End point type	Primary
End point timeframe:	
Day 0 (pre-vaccination) and Day 21 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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	543	551	545	56
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/California/7/2009 (H1N1); Day 0	101 (87.5 to 117)	95.3 (82.1 to 111)	94.2 (81.3 to 109)	141 (91.9 to 215)
A/Victoria/210/2009 (H3N2); Day 0	115 (100 to 132)	103 (89.2 to 118)	102 (88.4 to 117)	115 (74.9 to 177)
B/Brisbane/60/2008; Day 0	113 (99.5 to 129)	103 (90.8 to 118)	97.3 (85.6 to 111)	91.1 (62.3 to 133)
B/Florida/04/2006; Day 0	320 (281 to 363)	302 (264 to 345)	309 (271 to 353)	400 (278 to 576)

A/California/7/2009 (H1N1); Day 21	878 (795 to 970)	834 (757 to 919)	967 (876 to 1068)	934 (670 to 1301)
A/Victoria/210/2009 (H3N2); Day 21	760 (690 to 838)	734 (666 to 809)	845 (763 to 937)	846 (602 to 1188)
B/Brisbane/60/2008; Day 21	1033 (945 to 1129)	1054 (963 to 1154)	1043 (950 to 1145)	851 (606 to 1195)
B/Florida/04/2006; Day 21	2537 (2336 to 2756)	2650 (2427 to 2894)	2609 (2401 to 2836)	1264 (854 to 1871)

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 in Subjects Aged 9 to 17 Years

End point title	Geometric Mean Titers (GMTs) of influenza Antibodies Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 9 to 17 Years[2]

End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HAI) assay.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

Notes:

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

End point values	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	111	108	54
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/California/7/2009 (H1N1); Day 0	154 (114 to 209)	127 (94.2 to 172)	124 (93.4 to 164)	312 (207 to 470)
A/Victoria/210/2009 (H3N2); Day 0	208 (156 to 277)	220 (164 to 295)	195 (145 to 263)	178 (108 to 294)
B/Brisbane/60/2008; Day 0	74.6 (55.4 to 100)	85.7 (64.1 to 115)	66 (49.6 to 87.9)	98.9 (66.4 to 147)
B/Florida/04/2006; Day 0	230 (162 to 327)	177 (125 to 250)	202 (144 to 284)	223 (132 to 378)
A/California/7/2009 (H1N1); Day 21	1554 (1262 to 1913)	1313 (1056 to 1632)	2045 (1687 to 2479)	2006 (1586 to 2538)
A/Victoria/210/2009 (H3N2); Day 21	1491 (1269 to 1752)	1668 (1407 to 1978)	1493 (1247 to 1788)	1720 (1262 to 2343)
B/Brisbane/60/2008; Day 21	1845 (1485 to 2293)	1738 (1438 to 2100)	1687 (1336 to 2130)	1644 (1147 to 2357)
B/Florida/04/2006; Day 21	3932 (3278 to 4717)	3466 (2833 to 4240)	4432 (3787 to 5185)	849 (557 to 1294)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 Years With Seroprotection Against Influenza Antigens Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 Years With Seroprotection Against Influenza Antigens Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[3]

End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HAI) assay. Seroprotection was defined as titers ≥ 40 (1/dil) on Day 21.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

Notes:

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

End point values	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	543	551	545	56
Units: Percentage of subjects				
number (not applicable)				
A/California/7/2009 (H1N1); Day 0	73.4	72.1	73.5	80.4
A/Victoria/210/2009 (H3N2); Day 0	77.7	74	73	75
B/Brisbane/60/2008; Day 0	77.4	75.3	72.1	69.6
B/Florida/04/2006; Day 0	92.3	92	90.8	96.4
A/California/7/2009 (H1N1); Day 21	99.3	99.3	99.3	100
A/Victoria/210/2009 (H3N2); Day 21	99.1	99.1	98.9	100
B/Brisbane/60/2008; Day 21	100	100	100	100
B/Florida/04/2006; Day 21	100	100	100	98.2

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 9 to 17 Years With Seroprotection Against Influenza Antigens Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 9 to 17 Years With Seroprotection Against Influenza Antigens Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[4]

End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HAI) assay. Seroprotection was defined as titers ≥ 40 (1/dil) on Day 21.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

Notes:

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

End point values	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	110	108	54
Units: Percentage of subjects				
number (not applicable)				
A/California/7/2009 (H1N1); Day 0	86.2	85.5	86.1	90.7
A/Victoria/210/2009 (H3N2); Day 0	89.9	88.2	85.2	81.5
B/Brisbane/60/2008; Day 0	67	72.7	64.8	81.5
B/Florida/04/2006; Day 0	82.6	82.9	84.3	79.6
A/California/7/2009 (H1N1); Day 21	98.2	98.2	100	100
A/Victoria/210/2009 (H3N2); Day 21	100	100	100	100
B/Brisbane/60/2008; Day 21	99.1	100	99.1	100
B/Florida/04/2006; Day 21	99.1	99.1	100	100

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 Years 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 Aged 18 to 60 Years Achieving Seroconversion or Significant increase Against Influenza Antigens after Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[5]

End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HAI) assay. Seroconversion for subjects with a pre-vaccination titer < 10 (1/dil): post-injection titer ≥ 40 (1/dil) on Day 21, or significant increase for subjects with a pre-vaccination titer ≥ 10 (1/dil): ≥ 4-fold increase from pre- to post-injection titer on Day 21.

End point type	Primary

End point timeframe:

Day 21 post-vaccination

Notes:

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

End point values	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	543	551	545	56
Units: Percentage of subjects				
number (not applicable)				
A/California/7/2009 (H1N1)	59.8	62.4	68.6	46.4
A/Victoria/210/2009 (H3N2)	56.5	58.1	63.2	58.9
B/Brisbane/60/2008	63.4	66.5	69.5	55.4
B/Florida/04/2006	64.6	65.6	67.3	44.6

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 9 to 17 Years 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 Aged 9 to 17 Years 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 assessed using the hemagglutination inhibition (HAI) assay. Seroconversion for subjects with a pre-vaccination titer < 10 (1/dil): post-injection titer ≥ 40 (1/dil) on Day 21, or significant increase for subjects with a pre-vaccination titer ≥ 10 (1/dil): ≥ 4-fold increase from pre- to post-injection titer on Day 21.

End point type	Primary

End point timeframe:

Day 21 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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	111	108	54
Units: Percentage of subjects				
number (not applicable)				
A/California/7/2009 (H1N1)	75.2	73.6	84.3	70.4
A/Victoria/210/2009 (H3N2)	56.9	61.8	66.7	63
B/Brisbane/60/2008	84.4	80.9	86.1	79.6
B/Florida/04/2006	81.7	83.8	88.9	50

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies after Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 Years

End point title	Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies after Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 Years[7]

End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HAI) assay. Geometric mean titer ratio is the geometric mean of the individual post-vaccination/pre-vaccination titer of influenza antibodies.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	543	551	545	56
Units: Titer Ratios				
geometric mean (confidence interval 95%)				
A/California/7/2009 (H1N1)	8.67 (7.48 to 10)	8.75 (7.56 to 10.1)	10.33 (8.86 to 11.9)	6.64 (4.05 to 10.9)
A/Victoria/210/2009 (H3N2)	6.62 (5.79 to 7.57)	7.16 (6.24 to 8.22)	8.3 (7.19 to 9.59)	7.34 (4.5 to 11.9)
B/Brisbane/60/2008	9.12 (7.93 to 10.5)	10.2 (8.87 to 11.7)	10.7 (9.33 to 12.3)	9.34 (5.63 to 15.5)
B/Florida/04/2006	7.94 (6.97 to 9.04)	8.77 (7.67 to 10)	8.43 (7.43 to 9.59)	3.16 (2.25 to 4.44)

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies after Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 9 to 17 Years

End point title	Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies after Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 9 to 17 Years[8]

End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HAI) assay. Geometric mean titer ratio is the geometric mean of the individual post-vaccination/pre-vaccination titer of influenza antibodies.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	111	108	54
Units: Titer Ratios				
geometric mean (confidence interval 95%)				
A/California/7/2009 (H1N1)	10.1 (7.67 to 13.3)	10.3 (7.81 to 13.6)	16.5 (12.6 to 21.6)	6.43 (4.35 to 9.5)
A/Victoria/210/2009 (H3N2)	7.16 (5.21 to 9.83)	7.58 (5.61 to 10.2)	7.65 (5.8 to 10.1)	9.64 (5.75 to 16.1)
B/Brisbane/60/2008	24.7 (18 to 34.1)	20.3 (15.1 to 27.2)	25.6 (19 to 34.4)	16.6 (10.7 to 25.8)
B/Florida/04/2006	17.1 (12.5 to 23.4)	19.6 (14.5 to 26.5)	21.9 (16.1 to 29.9)	3.8 (2.69 to 5.37)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 Years Reporting Solicited Injection-site or Systemic Reaction After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 Years Reporting Solicited Injection-site or Systemic Reaction After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[9]

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 (9-11 years): Pain – Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis - ≥50 mm. Grade 3 Solicited Injection site reactions (12-60 years): Pain – Significant, prevents daily activity; Erythema, Swelling, Induration, and Ecchymosis - >100 mm. Grade 3 Solicited systemic reactions (9-60 years): 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:

[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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	546	554	548	56
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	48.3	48.5	52	46.4
Grade 3 Injection site Pain	0	0.5	0.4	1.8
Injection site Erythema	5.7	7.2	5.1	5.4
Grade 3 Injection site Erythema	0	0.2	0	0
Injection site Swelling	5.9	6	6	1.8
Grade 3 Injection site Swelling	0	0	0	0
Injection site Induration	4.8	5.2	5.5	3.6
Grade 3 Injection site Induration	0	0	0	0
Injection site Ecchymosis	0.2	2	0.9	0
Grade 3 Injection site Ecchymosis	0	0.2	0	0
Fever	1.3	1.6	1.1	1.8
Grade 3 Fever	0	0	0	0
Headache	27	26.2	27.9	23.2
Grade 3 Headache	2.2	0.5	0.7	0
Malaise	21.8	20.8	17.9	12.5
Grade 3 Malaise	1.3	1.1	0.5	0
Myalgia	20.7	19.2	16.4	7.1
Grade 3 Myalgia	1.1	0.5	0.4	0
Shivering	5.3	2.7	3.1	1.8
Grade 3 Shivering	0.6	0.2	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 9 to 17 Years Reporting Solicited Injection-site or Systemic Reaction After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 9 to 17 Years Reporting Solicited Injection-site or Systemic Reaction After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[10]

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 (9-11 years): Pain – Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis - ≥50 mm. Grade 3 Solicited Injection site reactions (12-60 years): Pain – Significant, prevents daily activity; Erythema, Swelling, Induration, and Ecchymosis - >100 mm. Grade 3 Solicited systemic reactions (9-60 years): 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:

[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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	111	109	55
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	57.8	53.2	51.4	54.5
Grade 3 Injection site Pain	0	0	0	0
Injection site Erythema	10.1	12.6	10.1	5.5
Grade 3 Injection site Erythema	0.9	1.8	0	0
Injection site Swelling	15.6	9.9	12.8	7.3
Grade 3 Injection site Swelling	0.9	0	0	0
Injection site Induration	9.2	5.4	10.1	7.3
Grade 3 Injection site Induration	0.9	0.9	0	1.8
Injection site Ecchymosis	1.8	1.8	1.8	1.8
Grade 3 Injection site Ecchymosis	0	0	0	0
Fever	4.6	1.8	2.8	9.1
Grade 3 Fever	0	0	0.9	0
Headache	31.2	28.8	29.4	23.6
Grade 3 Headache	0.9	0	0	0
Malaise	25.7	18	22	16.4
Grade 3 Malaise	0.9	0	0.9	0
Myalgia	32.1	21.6	19.3	12.7
Grade 3 Myalgia	0.9	0	0	0
Shivering	2.8	5.4	3.7	0
Grade 3 Shivering	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 Years Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 Years Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[11]

End point description:

Solicited injection site reactions: Injection site Induration ≥5 cm for at least 4 consecutive days and Injection site Ecchymosis. Solicited systemic reactions: Pyrexia (recorded temperature > 38°C) for at least 1 day, Malaise, and Shivering.

End point type	Primary

End point timeframe:

Day 0 up to Day 3 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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	546	554	548	56
Units: Percentage of subjects				
number (not applicable)				
Reaction listed in the EMA recommendations	23.5	20.8	20.1	14.3
Injection site Induration ≥5 cm for 4 days	0	0	0	0
Injection site Ecchymosis	4.4	3.8	4.2	1.8
Pyrexia (temp. > 38°C) for at least 1 day	0.6	0.9	0.9	1.8
Malaise	19.8	18.1	15.7	10.7
Shivering	4.2	2.4	2.6	1.8

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 9 to 17 Years Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days after Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 9 to 17 Years Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days after Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route[12]

End point description:

Solicited injection site reactions: Injection site Induration ≥5 cm for at least 4 consecutive days and Injection site Ecchymosis. Solicited systemic reactions: Pyrexia (recorded temperature > 38°C) for at least 1 day, Malaise, and Shivering.

End point type	Primary

End point timeframe:

Day 0 up to Day 3 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	QIV S4361	QIV S4362	QIV S4363	Trivalent Influenza Vaccine (TIV)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	111	109	55
Units: Percentage of subjects				
number (not applicable)				
Reaction listed in the EMA recommendations	25.7	20.7	22.9	20
Injection site Induration ≥5 cm for 4 days	0.9	0	0	0
Injection site Ecchymosis	4.6	1.8	1.8	1.8
Pyrexia (temp. > 38°C) for at least 1 day	2.8	1.8	0.9	3.6
Malaise	21.1	17.1	20.2	14.5
Shivering	2.8	5.4	2.8	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 up to Day 21 after vaccination.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	QIV S4361
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4361) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	QIV S4362
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4362) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	QIV S4363
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine (Lot QIV S4363) 2011-2012 Formulation + B/Florida strain from the Yamagata lineage administered on Day 0 and Day 21.	
Reporting group title	Trivalent Influenza Vaccine (TIV)
Reporting group description:	
Subjects who received Trivalent Influenza Vaccine (TIV) 2011-2012 Formulation administered on Day 0 and Day 21.	

Serious adverse events	QIV S4361	QIV S4362	QIV S4363
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 655 (0.92%)	5 / 665 (0.75%)	2 / 657 (0.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Meniscus lesion			
subjects affected / exposed	1 / 655 (0.15%)	0 / 665 (0.00%)	0 / 657 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 655 (0.00%)	1 / 665 (0.15%)	0 / 657 (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

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 665 (0.15%)	0 / 657 (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
Respiratory, thoracic and mediastinal disorders			
Pleurisy			
subjects affected / exposed	0 / 655 (0.00%)	0 / 665 (0.00%)	1 / 657 (0.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 665 (0.00%)	0 / 657 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 655 (0.00%)	1 / 665 (0.15%)	0 / 657 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 665 (0.00%)	0 / 657 (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
Dengue fever			
subjects affected / exposed	1 / 655 (0.15%)	0 / 665 (0.00%)	0 / 657 (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 / 655 (0.15%)	0 / 665 (0.00%)	0 / 657 (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
Leptospirosis			

subjects affected / exposed	1 / 655 (0.15%)	0 / 665 (0.00%)	0 / 657 (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
Appendicitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 665 (0.15%)	0 / 657 (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
Arthritis bacterial			
subjects affected / exposed	0 / 655 (0.00%)	1 / 665 (0.15%)	0 / 657 (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
Viral infection			
subjects affected / exposed	0 / 655 (0.00%)	0 / 665 (0.00%)	1 / 657 (0.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Trivalent Influenza Vaccine (TIV)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 111 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Meniscus lesion			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleurisy			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leptospirosis			

subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	QIV S4361	QIV S4362	QIV S4363
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 655 (40.15%)	268 / 665 (40.30%)	285 / 657 (43.38%)
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	147 / 655 (22.44%)	145 / 665 (21.80%)	153 / 657 (23.29%)
occurrences (all)	147	145	153
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	263 / 655 (40.15%)	268 / 665 (40.30%)	285 / 657 (43.38%)
occurrences (all)	263	268	285
Injection site erythema			
alternative assessment type: Systematic			

subjects affected / exposed	31 / 655 (4.73%)	40 / 665 (6.02%)	28 / 657 (4.26%)
occurrences (all)	31	40	28
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	32 / 655 (4.89%)	33 / 665 (4.96%)	33 / 657 (5.02%)
occurrences (all)	32	33	33
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	119 / 655 (18.17%)	115 / 665 (17.29%)	98 / 657 (14.92%)
occurrences (all)	119	115	98
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	113 / 655 (17.25%)	106 / 665 (15.94%)	90 / 657 (13.70%)
occurrences (all)	113	106	90

Non-serious adverse events	Trivalent Influenza Vaccine (TIV)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 111 (27.03%)		
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 111 (11.71%)		
occurrences (all)	13		
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 111 (27.03%)		
occurrences (all)	30		
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Injection site swelling			
alternative assessment type: Systematic			

subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	4		
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 111 (8.11%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 111 (6.31%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2012	Included all child/adolescent subjects for the seroneutralization analysis and a subset of child/adolescent subjects for the anti-neuraminidase analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported