Clinical trial results:
A phase III, open-label, multicentre study to evaluate the immunogenicity, safety and reactogenicity study of GSK Biologicals' quadrivalent seasonal influenza candidate vaccine GSK2321138A, administered to children who previously participated in study 115345

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2012-001230-34
Trial protocol	ES CZ GB PL
Global end of trial date	05 June 2013

Results information

Result version number	v2
This version publication date	28 May 2016
First version publication date	02 May 2015
Version creation reason	• Correction of full data set Data correction due to a system error in EudraCT – Results: Secondary endpoint -Serum neutralizing antibody titres against each of the vaccine strains after 1 dose of Fluarix Quadrivalent vaccine. In addition, some data (typos) were corrected in Adverse events section.

Trial information

Trial identification

Sponsor protocol code	116023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01702454
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000817-PIP02-11

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 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2013
Global end of trial reached?	Yes
Global end of trial date	05 June 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the immune response in terms of Haemagglutination Inhibition (HI) antibody titre at Day 7 after one dose of FLU D-QIV vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all strains included in the vaccine.

Protection of trial subjects:

All subjects were supervised closely for at least 30 minutes following vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up from the time the subject consents to participate in the study until she/he is discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 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	Poland: 103
Country: Number of subjects enrolled	Spain: 149
Country: Number of subjects enrolled	United Kingdom: 83
Country: Number of subjects enrolled	Czech Republic: 135
Worldwide total number of subjects	470
EEA total number of subjects	470

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)	470
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: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fluarix Quadrivalent Primed Group

Arm description:

Subjects in this group were previously primed with 2 doses of Fluarix Quadrivalent vaccine in the primary study 115345 (NCT01439360) and received 1 dose of Fluarix Quadrivalent vaccine at Day 0 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.

Arm type	Experimental
Investigational medicinal product name	Fluarix Quadrivalent
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine-primed subjects received a single 0.5 mL dose administered intramuscularly at Visit 1 (Day 0). Vaccines were administered in the deltoid region.

Arm title	Fluarix Quadrivalent Unprimed Group

Arm description:

Subjects in this group were unprimed in the primary study 115345 (NCT01439360) and received 2 doses of Fluarix Quadrivalent vaccine at Days 0 and 28 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.

Arm type	Experimental
Investigational medicinal product name	Fluarix Quadrivalent
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine-unprimed subjects received one 0.5 mL dose administered intramuscularly at Visit 1 (Day 0) and one 0.5 mL dose administered intramuscularly at Visit 3 (Day 28). Vaccines were administered in the deltoid region.

Number of subjects in period 1	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group
Started	241	229
Completed	238	221
Not completed	3	8
Consent withdrawn by subject	-	1
Lost to Follow-up	3	6
Migrated/moved from study area	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Fluarix Quadrivalent Primed Group
Reporting group description:	
Subjects in this group were previously primed with 2 doses of Fluarix Quadrivalent vaccine in the primary study 115345 (NCT01439360) and received 1 dose of Fluarix Quadrivalent vaccine at Day 0 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.	
Reporting group title	Fluarix Quadrivalent Unprimed Group
Reporting group description:	
Subjects in this group were unprimed in the primary study 115345 (NCT01439360) and received 2 doses of Fluarix Quadrivalent vaccine at Days 0 and 28 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.	

Reporting group values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group	Total
Number of subjects	241	229	470
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)			0
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	33.2	32.5	
standard deviation	± 7.54	± 7.39	-
Gender categorical Units: Subjects			
Female	114	96	210
Male	127	133	260

End points

End points reporting groups

Reporting group title	Fluarix Quadrivalent Primed Group
Reporting group description:	
Subjects in this group were previously primed with 2 doses of Fluarix Quadrivalent vaccine in the primary study 115345 (NCT01439360) and received 1 dose of Fluarix Quadrivalent vaccine at Day 0 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.	
Reporting group title	Fluarix Quadrivalent Unprimed Group
Reporting group description:	
Subjects in this group were unprimed in the primary study 115345 (NCT01439360) and received 2 doses of Fluarix Quadrivalent vaccine at Days 0 and 28 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.	

Primary: Serum Hemagglutination Inhibition (HI) antibody titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point title	Serum Hemagglutination Inhibition (HI) antibody titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine
End point description:	
End point type	Primary
End point timeframe:	
At Day 0 and Day 7	

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	209		
Units: Titer				
geometric mean (confidence interval 95%)				
H1N1, Day 0 [N=221,202]	43.1 (33.8 to 54.9)	14.5 (11.5 to 18.2)		
H1N1, Day 7 [N=224,209]	445.6 (376.9 to 526.7)	45.8 (32 to 65.5)		
H3N2, Day 0 [N=221,202]	12.3 (10.7 to 14.1)	16.4 (13.2 to 20.4)		
H3N2, Day 7 [N=224,209]	135.3 (113.6 to 161.2)	47.5 (32.6 to 69.3)		
Victoria, Day 0 [N=221,202]	28.5 (23.8 to 34.1)	10 (8.4 to 11.9)		
Victoria, Day 7 [N=224,209]	193.9 (168.7 to 222.8)	47.1 (35.2 to 63)		
Yamagata, Day 0 [N=221,202]	11.9 (10.6 to 13.3)	6.5 (5.9 to 7.2)		
Yamagata, Day 7 [N=224,209]	182.6 (159 to 209.6)	26.1 (20.9 to 32.7)		

Statistical analyses

Statistical analysis title	Adjusted GMT ratio for A/Christ antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMT ratio
Point estimate	8.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.21
upper limit	12.96

Statistical analysis title	Adjusted GMT ratio for A/Victoria antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMT ratio
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.81
upper limit	4.02

Statistical analysis title	Adjusted GMT ratio for B/Brisbane antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMT ratio
Point estimate	3.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.89
upper limit	5.37

Statistical analysis title	Adjusted GMT ratio for B/Hub-Wuj antibodies
Statistical analysis description:	
The B/Hub-Wuj = B/Hubei-Wujiagang/158/2009 (Yamagata) strain	
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMT ratio
Point estimate	6.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.21
upper limit	8.63

Primary: Number of seropositive subjects against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point title	Number of seropositive subjects against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine[1]
End point description:	
End point type	Primary
End point timeframe:	
At Day 0 and Day 7	

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	209		
Units: Subjects				
H1N1, Day 0 [N=221,202]	189	64		
H1N1, Day 7 [N=224,209]	220	137		
H3N2, Day 0 [N=221,202]	131	79		
H3N2, Day 7 [N=224,209]	218	99		
Victoria, Day 0 [N=221,202]	187	58		

Victoria, Day 7 [N=224,209]	224	174		
Yamagata, Day 0 [N=221,202]	134	36		
Yamagata, Day 7 [N=224,209]	222	144		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects seroconverted for HI antibodies against against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	Number of subjects seroconverted for HI antibodies against against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point description:

End point type	Primary

End point timeframe:

At Day 7

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	202		
Units: Subjects				
H1N1	170	65		
H3N2	180	73		
Victoria	169	78		
Yamagata	208	77		

Statistical analyses

Statistical analysis title	Difference in SCR for A/Christ antibodies

Statistical analysis description:

To assess the immune response in terms of haemagglutination inhibition (HI) antibody titre at Day 7 after one dose of FLU D-QIV vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all strains included in the vaccine.

Comparison groups	Fluarix Quadrivalent Unprimed Group v Fluarix Quadrivalent Primed Group

Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentages
Point estimate	44.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.87
upper limit	52.84

Statistical analysis title	Difference in SCR for A/Victoria antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentages
Point estimate	45.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.58
upper limit	53.3

Statistical analysis title	Difference in SCR for B/Brisbane antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentages
Point estimate	37.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.83
upper limit	46.26

Statistical analysis title	Difference in SCR for B/Hu-Wuj antibodies
Statistical analysis description:	
B/Hu-Wuj = B/Hubei-Wujiagang/158/2009 (Yamagata)	
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group

Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentages
Point estimate	56
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.32
upper limit	63.04

Primary: Mean geometric increase (MGI) for HI antibody titer against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	Mean geometric increase (MGI) for HI antibody titer against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.[2]

End point description:

End point type	Primary

End point timeframe:

At Day 7

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	202		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1	10.3 (8.5 to 12.4)	3.2 (2.6 to 3.9)		
H3N2	10.9 (9.4 to 12.6)	2.9 (2.4 to 3.6)		
Victoria	6.7 (5.9 to 7.6)	4.6 (3.8 to 5.5)		
Yamagata	15.2 (13.3 to 17.3)	4 (3.3 to 4.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects seroprotected for anti-HA antibodies against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	Number of subjects seroprotected for anti-HA antibodies against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point description:

End point type	Primary

End point timeframe:

At Day 0 and Day 7

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	209		
Units: Subjects				
H1N1, Day 0 [N=221,202]	89	61		
H1N1, Day 7 [N=224,209]	217	72		
H3N2, Day 0 [N=221,202]	37	74		
H3N2, Day 7 [N=224,209]	193	81		
Victoria, Day 0 [N=221,202]	72	39		
Victoria, Day 7 [N=224,209]	217	84		
Yamagata, Day 0 [N=221,202]	27	12		
Yamagata, Day 7 [N=224,209]	216	83		

Statistical analyses

Statistical analysis title	Difference in SPR for A/Christ antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in SPR
Point estimate	62.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.27
upper limit	68.89

Statistical analysis title	Difference in SPR for A/Victoria antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group

Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in SPR
Point estimate	47.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.08
upper limit	55.06

Statistical analysis title	Difference in SPR for B/Brisbane antibodies
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in SPR
Point estimate	56.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.44
upper limit	63.43

Statistical analysis title	Difference in SPR for B/Hub-Wuj antibodies
Statistical analysis description:	
The B/Hub-Wuj = B/Hubei-Wujiagang/158/2009 (Yamagata)	
Comparison groups	Fluarix Quadrivalent Primed Group v Fluarix Quadrivalent Unprimed Group
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in SPR
Point estimate	56.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.41
upper limit	63.49

Secondary: Number of subjects with HI antibody titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	Number of subjects with HI antibody titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent

	vaccine.

End point description:

End point type	Secondary

End point timeframe:

At Day 0 and Day 7

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	209		
Units: Subjects				
H1N1 (<1:10), Day 0 [N=221,202]	32	138		
H1N1 (<1:10), Day 7 [N=224,209]	4	72		
H3N2 (<1:10), Day 0 [N=221,202]	90	123		
H3N2 (<1:10), Day 7 [N=224,209]	6	110		
Victoria (<1:10), Day 0 [N=221,202]	34	144		
Victoria (<1:10), Day 7 [N=224,209]	0	35		
Yamagata (<1:10), Day 0 [N=221,202]	87	166		
Yamagata (<1:10), Day 7 [N=224,209]	2	65		
H1N1 (1:10 to <1:40), Day 0 [N=221,202]	100	3		
H1N1 (1:10 to <1:40), Day 7 [N=224,209]	3	65		
H3N2 (1:10 to <1:40), Day 0 [N=221,202]	94	5		
H3N2 (1:10 to <1:40), Day 7 [N=224,209]	25	18		
Victoria (1:10 to <1:40), Day 0 [N=221,202]	115	19		
Victoria (1:10 to <1:40), Day 7 [N=224,209]	7	90		
Yamagata (1:10 to <1:40), Day 0 [N=221,202]	107	24		
Yamagata (1:10 to <1:40), Day 7 [N=224,209]	6	61		
H1N1 (≥1: 40), Day 0 [N=221,202]	89	61		
H1N1 (≥1: 40), Day 7 [N=224,209]	217	72		
H3N2 (≥1: 40), Day 0 [N=221,202]	37	74		
H3N2 (≥1: 40), Day 7 [N=224,209]	193	81		
Victoria (≥1: 40), Day 0 [N=221,202]	72	39		
Victoria (≥1: 40), Day 7 [N=224,209]	217	84		
Yamagata (≥1: 40), Day 0 [N=221,202]	27	12		
Yamagata (≥1: 40), Day 7 [N=224,209]	216	83		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum neutralising antibody titers against each of the vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point title	Serum neutralising antibody titers against each of the vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point description:

End point type	Secondary

End point timeframe:

At Day 0 and Day 7

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	109		
Units: Titer				
geometric mean (confidence interval 95%)				
H1N1, Day 0 [N=97,90]	138.2 (97.4 to 196.2)	48.3 (33.9 to 68.7)		
H1N1, Day 7 [N=107, 96]	1500.9 (1172.7 to 1920.9)	139.4 (78.8 to 246.8)		
H3N2, Day 0 [N=99,96]	66.5 (55.9 to 79.2)	82.8 (60.6 to 113.1)		
H3N2, Day 7 [N=104,100]	422.9 (342.3 to 522.4)	325.1 (187.1 to 564.7)		
Victoria, Day 0 [N=107,109]	38.6 (29.7 to 50.3)	22.2 (18.6 to 26.5)		
Victoria, Day 7 [N=107, 108]	193.7 (154.7 to 242.6)	47 (30.3 to 72.9)		
Yamagata, Day 0 [N=107,107]	36.9 (34.2 to 39.8)	30.8 (29 to 32.6)		
Yamagata, Day 7 [N=107,107]	182.7 (157.7 to 211.8)	51.7 (42.2 to 63.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum anti-neuraminidase antibody titers against each of the vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point title	Serum anti-neuraminidase antibody titers against each of the vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point description:

End point type	Secondary

End point timeframe:

At Day 0 and Day 7

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	109		
Units: Titer				
geometric mean (confidence interval 95%)				
H1N1, Day 0 [N=106,106]	34.6 (25.3 to 47.3)	24.1 (18.6 to 31.1)		
H1N1, Day 7 [N=106, 109]	293.9 (247.2 to 349.3)	41.3 (28.9 to 59)		
H3N2, Day 0 [N=107,106]	38.4 (33.7 to 43.7)	58.8 (47.2 to 73.4)		
H3N2, Day 7 [N=107, 109]	189.4 (155.9 to 230.2)	114.2 (84.1 to 155.2)		
Victoria, Day 0 [N=106,106]	17.4 (14.2 to 21.3)	14.3 (12.4 to 16.5)		
Victoria, Day 7 [N=106,109]	90.6 (74.1 to 110.8)	27.6 (19.4 to 39.1)		
Yamagata, Day 0 [N=106, 106]	25.3 (21.6 to 29.6)	15.4 (13.2 to 18)		
Yamagata, Day 7 [N=106,109]	222 (185.7 to 265.4)	40.6 (29.5 to 55.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine response rate (VRR) for neutralising antibody titers against each of the four vaccine strains.

End point title	Vaccine response rate (VRR) for neutralising antibody titers against each of the four vaccine strains.

End point description:

End point type	Secondary

End point timeframe:

At Day 7 post dose 1

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	108		
Units: Subjects				
H1N1 [N=97,89]	74	36		
H3N2 [N=97,94]	72	48		
Victoria [N=107,108]	78	24		
Yamagata [N=107,105]	45	15		

Statistical analyses

No statistical analyses for this end point

Secondary: VRR for anti-neuraminidase antibody titers against each of the four vaccine strains.

End point title	VRR for anti-neuraminidase antibody titers against each of the four vaccine strains.

End point description:

End point type	Secondary

End point timeframe:

At Day 7 post dose 1

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	106		
Units: Subjects				
H1N1 [N=105,106]	75	31		
H3N2 [N=107,106]	75	31		
Victoria [N=105,106]	79	24		
Yamagata [N=105,106]	90	29		

Statistical analyses

No statistical analyses for this end point

Secondary: MGI for neutralising antibodies titres against each of the four vaccine strains.

End point title	MGI for neutralising antibodies titres against each of the four vaccine strains.

End point description:

End point type	Secondary

End point timeframe:

At Day 7

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	108		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1 [N=97, 89]	10.6 (8.2 to 13.7)	3.1 (2.3 to 4.2)		
H3N2 [N=97, 94]	6.4 (5.4 to 7.6)	4.5 (3.2 to 6.2)		
Victoria [N=107,108]	5 (4.3 to 5.8)	2.1 (1.6 to 2.8)		
Yamagata [N=107,105]	5 (4.3 to 5.7)	1.7 (1.4 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: MGI for anti-neuraminidase antibodies titers against each of the four vaccine strains.

End point title	MGI for anti-neuraminidase antibodies titers against each of the four vaccine strains.

End point description:

End point type	Secondary

End point timeframe:

At Day 7 post dose 1

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	106		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1 [N=105,106]	8.3 (6.5 to 10.7)	1.8 (1.5 to 2.1)		
H3N2 [N=105,106]	5.2 (4.4 to 6)	1.9 (1.5 to 2.4)		

Victoria [N=105,106]	8.8 (7.5 to 10.2)	2.7 (2.1 to 3.4)		
Yamagata [N=107,106]	4.9 (4.2 to 5.8)	2 (1.7 to 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and grade 3 solicited local adverse events (AEs)

End point title	Number of subjects reporting any and grade 3 solicited local adverse events (AEs)

End point description:

End point type	Secondary

End point timeframe:

During a 7-day (Day 0 to 6) follow-up period after first vaccination

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	228		
Units: Subjects				
Any Pain	96	61		
Grade 3 Pain	2	1		
Any Redness	82	48		
Grade 3 Redness	2	0		
Any Swelling	49	25		
Grade 3 Swelling	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of solicited symptoms

End point title	Duration of solicited symptoms

End point description:

End point type	Secondary

End point timeframe:

During the 7-day (Days 0-6) post-vaccination Dose 1 period

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	61		
Units: Days				
median (full range (min-max))				
Drowsiness	1 (1 to 7)	1 (1 to 4)		
Irritability/fussiness	2 (1 to 7)	2 (1 to 7)		
Loss of appetite	2 (1 to 7)	2 (1 to 5)		
Pain	1 (1 to 5)	1 (1 to 5)		
Redness	2 (1 to 7)	2 (1 to 6)		
Swelling	2 (1 to 5)	1 (1 to 5)		
Temperature	1 (1 to 5)	2 (1 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related solicited general symptoms.

End point title	Number of subjects reporting any, grade 3 and related solicited general symptoms.

End point description:

End point type	Secondary

End point timeframe:

During the 7 days (Days 0 – 6) post dose 1 vaccination

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	224		
Units: Subjects				
Any Drowsiness	54	44		
Grade 3 Drowsiness	5	1		
Related Drowsiness	36	28		
Any Irritability/Fussiness	77	59		
Grade 3 Irritability/Fussiness	5	5		
Related Irritability/Fussiness	51	43		
Any Loss of appetite	51	46		
Grade 3 Loss of appetite	8	5		

Related Loss of appetite	31	31		
Any Temperature	13	26		
Grade 3 Temperature	2	1		
Related Temperature	6	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting AEs with Medically Attended Visits (MAV)

End point title	Number of subjects reporting AEs with Medically Attended Visits (MAV)

End point description:

End point type	Secondary

End point timeframe:

During the entire study period (Day 0 – Day 179)

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	229		
Units: Subjects				
Any MAV	149	130		
Grade 3 MAV	5	8		
Related MAV	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Potential Immune-Mediated Diseases (pIMDs)

End point title	Number of subjects reporting Potential Immune-Mediated Diseases (pIMDs)

End point description:

End point type	Secondary

End point timeframe:

During the entire study period (Days 0 - 179)

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	229		
Units: Subjects				
Any pIMD	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related unsolicited AEs.

End point title	Number of subjects reporting any, grade 3 and related unsolicited AEs.

End point description:

End point type	Secondary

End point timeframe:

Within 28 days (Days 0-27) after first vaccination

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	229		
Units: Subject				
Any Unsolicted AEs	66	66		
Grade 3 Unsolicted AEs	6	7		
Related Unsolicted AEs	5	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and related serious adverse events (SAEs)

End point title	Number of subjects reporting any and related serious adverse events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

During the entire study period (Day 0 – Day 179)

End point values	Fluarix Quadrivalent Primed Group	Fluarix Quadrivalent Unprimed Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	229		
Units: Subjects				
Any SAE(s)	7	8		
Related SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events: From Day 0 to Day 179; Solicited local and general symptoms: During the 7-day (Days 0-6) post-vaccination period; Unsolicited symptoms: During the 28-day (Day 0-27) post-vaccination period.

Adverse event reporting additional description:

For the frequent adverse events, the number of participants at risk included those from Total Vaccinated cohort who had the symptom sheet completed.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Fluarix Quadrivalent Unprimed Group

Reporting group description:

Subjects in this group were unprimed in the primary study 115345 (NCT01439360) and received 2 doses of Fluarix Quadrivalent vaccine at Days 0 and 28 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.

Reporting group title	Fluarix Quadrivalent Primed Group

Reporting group description:

Subjects in this group were previously primed with 2 doses of Fluarix Quadrivalent vaccine in the primary study 115345 (NCT01439360) and received 1 dose of Fluarix Quadrivalent vaccine at Day 0 in the current study. The vaccine was administered intramuscularly in the deltoid region of arm.

Serious adverse events	Fluarix Quadrivalent Unprimed Group	Fluarix Quadrivalent Primed Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 229 (3.49%)	7 / 241 (2.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Adenoidal hypertrophy			
subjects affected / exposed	1 / 229 (0.44%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 229 (0.87%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis bacterial			
subjects affected / exposed	1 / 229 (0.44%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 229 (0.44%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	0 / 229 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fluarix Quadrivalent Unprimed Group	Fluarix Quadrivalent Primed Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 229 (26.64%)	96 / 241 (39.83%)	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed[1]	61 / 228 (26.75%)	96 / 239 (40.17%)	
occurrences (all)	61	96	
Redness			
alternative assessment type: Systematic			
subjects affected / exposed[2]	48 / 228 (21.05%)	82 / 239 (34.31%)	
occurrences (all)	48	82	
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[3]	25 / 228 (10.96%)	49 / 239 (20.50%)	
occurrences (all)	25	49	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[4]	44 / 224 (19.64%)	54 / 238 (22.69%)	
occurrences (all)	44	54	
Irritability/Fussines			
alternative assessment type: Systematic			
subjects affected / exposed[5]	59 / 224 (26.34%)	77 / 238 (32.35%)	
occurrences (all)	59	77	
Loss of Appetite			
subjects affected / exposed[6]	46 / 224 (20.54%)	51 / 238 (21.43%)	
occurrences (all)	46	51	
Temperature			

alternative assessment type: Systematic			
subjects affected / exposed[7]	26 / 224 (11.61%)	13 / 238 (5.46%)	
occurrences (all)	26	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 229 (5.68%)	9 / 241 (3.73%)	
occurrences (all)	13	9	

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: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed.

[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: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed.

[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: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed.

[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: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed.

[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: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed.

[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: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed.

[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: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported