Clinical trial results:
A phase III, open-label, multicentre study to evaluate the immunogenicity, safety and reactogenicity of a re-vaccination dose of the GlaxoSmithKline Biologicals' quadrivalent seasonal influenza candidate vaccine GSK2321138A, administered to children who previously participated in study 115345 (FLU D-QIV-004 PRI).

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	v3
This version publication date	19 March 2017
First version publication date	02 May 2015
Version creation reason	

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,
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, 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	0

months)	
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:

An additional pre-specified immunogenicity analysis was conducted on According-to-Protocol cohort for immunogenicity (ATP-I) excluding subjects who had an RT-PCR confirmed influenza infection in study 115345 and was dependent on the unblinding of the parent study, 115345. Micro-neutralising/Anti-neuraminidase analysis was done by age strata too.

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 withdrawal	-	1
Migrated/moved from study area	-	1
Lost to follow-up	3	6

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			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	33.2	32.5	
standard deviation	± 7.54	± 7.39	-
Gender categorical			
Gender categorical description			
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:	
Antibody titers were expressed as Geometric Mean Titers (GMTs). The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.	
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/Christchurch antibodies

Statistical analysis description:

The adjusted GMT of HI antibodies for A/Christchurch strain at post-vaccination dose 1, the GMT ratio of Fluarix Quadrivalent Primed Group/Fluarix Quadrivalent Unprimed Group and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination log-10 titer and age as regressors.

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[1]
Parameter estimate	Adjusted GMT Ratio
Point estimate	8.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.21
upper limit	12.96

Notes:

[1] - Criterion: The lower limit (LL) of the two-sided 95% Confidence Interval (CI) for the GMT ratio is above 1.
The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted GMT ratio with 95% confidence interval.

Statistical analysis title	Adjusted GMT ratio for A/Victoria antibodies

Statistical analysis description:

The adjusted GMT of HI antibodies for A/Victoria strain at post-vaccination dose 1, the GMT ratio of Fluarix Quadrivalent Primed Group/Fluarix Quadrivalent Unprimed Group and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination log-10 titer and age as regressors.

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[2]
Parameter estimate	Adjusted GMT Ratio
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.81
upper limit	4.02

Notes:

[2] - Criterion: The lower limit (LL) of the two-sided 95% Confidence Interval (CI) for the GMT ratio is above 1.
The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted

GMT ratio with 95% confidence interval.

Statistical analysis title	Adjusted GMT ratio for B/Brisbane antibodies

Statistical analysis description:

The adjusted GMT of HI antibodies for B/Brisbane strain at post-vaccination dose 1, the GMT ratio of Fluarix Quadrivalent Primed Group/Fluarix Quadrivalent Unprimed Group and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination log-10 titer and age as regressors.

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[3]
Parameter estimate	Adjusted GMT Ratio
Point estimate	3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.89
upper limit	5.37

Notes:

[3] - Criterion: The lower limit (LL) of the two-sided 95% Confidence Interval (CI) for the GMT ratio is above 1.
The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted GMT ratio with 95% confidence interval.

Statistical analysis title	Adjusted GMT ratio for B/Hub-Wuj antibodies

Statistical analysis description:

The adjusted GMT of HI antibodies for B/Hub-Wuj strain at post-vaccination dose 1, the GMT ratio of Fluarix Quadrivalent Primed Group/Fluarix Quadrivalent Unprimed Group and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination log-10 titer and age as regressors.

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[4]
Parameter estimate	Adjusted GMT Ratio
Point estimate	6.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.21
upper limit	8.63

Notes:

[4] - Criterion: The lower limit (LL) of the two-sided 95% Confidence Interval (CI) for the GMT ratio is above 1.
The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted GMT ratio with 95% confidence interval.

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[5]

End point description:

Seropositivity was defined as number of subjects with antibody titers greater than or equal to (≥) 1:10. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

End point type	Primary

End point timeframe:

At Day 0 and Day 7

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: 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 each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

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

End point description:

A seroconverted subject was defined as a subject who had either a pre-vaccination titer below 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

End point type	Primary

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	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/Christchurch antibodies

Statistical analysis description:

To assess the immune response in terms of SCR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.

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[6]
Parameter estimate	Difference in percentages
Point estimate	44.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.87
upper limit	52.84

Notes:

[6] - SCR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

Statistical analysis title	Difference in SCR for A/Victoria antibodies

Statistical analysis description:

To assess the immune response in terms of SCR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.

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[7]
Parameter estimate	Difference in percentages
Point estimate	45.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.58
upper limit	53.3

Notes:

[7] - SCR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

Statistical analysis title	Difference in SCR for B/Brisbane antibodies

Statistical analysis description:

To assess the immune response in terms of SCR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.

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[8]
Parameter estimate	Difference in percentages
Point estimate	37.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.83
upper limit	46.26

Notes:

[8] - SCR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

Statistical analysis title	Difference in SCR for B/Hu-Wuj antibodies

Statistical analysis description:

To assess the immune response in terms of SCR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.
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[9]
Parameter estimate	Difference in percentages
Point estimate	56
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.32
upper limit	63.04

Notes:

[9] - SCR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

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.[10]

End point description:

MGI was defined as the fold increase in serum HI GMT post-vaccination compared to Day 0. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

End point type	Primary

End point timeframe:

At Day 7 post dose 1

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: 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:

Seroprotection rate (SPR) was defined as the number of vaccinees with serum haemagglutination inhibition (HI) titer ≥ 1:40 that usually is accepted as indicating protection in adults. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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

Statistical analysis description:

To assess the immune response in terms of SPR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.

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[11]
Parameter estimate	Difference in SPR
Point estimate	62.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.27
upper limit	68.89

Notes:

[11] - SPR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

Statistical analysis title	Difference in SPR for A/Victoria antibodies

Statistical analysis description:

To assess the immune response in terms of SPR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.

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[12]
Parameter estimate	Difference in SPR
Point estimate	47.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.08
upper limit	55.06

Notes:

[12] - SPR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

Statistical analysis title	Difference in SPR for B/Brisbane antibodies

Statistical analysis description:

To assess the immune response in terms of SPR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.

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[13]
Parameter estimate	Difference in SPR
Point estimate	56.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.44
upper limit	63.43

Notes:

[13] - SPR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

Statistical analysis title	Difference in SPR for B/Hub-Wuj antibodies

Statistical analysis description:

To assess the immune response in terms of SCR difference at Day 7 after one dose of Fluarix Quadrivalent vaccine (2012-2013 formulation) in vaccine-primed and vaccine-unprimed subjects, for all the strains.
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[14]
Parameter estimate	Difference in SPR
Point estimate	56.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.41
upper limit	63.49

Notes:

[14] - SPR difference was calculated using standardized asymptotic 95% CI for the group difference in proportion.

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.[15]

End point description:

Antibody titers were expressed as Geometric Mean Titers (GMTs). The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

End point type	Primary

End point timeframe:

At Day 0 and Day 7

Notes:

[15] - 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	213	179		
Units: Titers				
geometric mean (confidence interval 95%)				
H1N1, Day 0 [N=210,173]	44 (34.2 to 56.7)	14.3 (11.2 to 18.3)		
H1N1, Day 7 [N=213,179]	442.3 (372 to 525.9)	42.7 (29 to 63)		
H3N2, Day 0 [N=210,173]	11 (9.8 to 12.5)	11.9 (9.6 to 14.7)		
H3N2, Day 7 [N=213,179]	125.9 (105.4 to 150.4)	28.7 (19.7 to 41.9)		
Victoria, Day 0 [N=210,173]	27.8 (23.2 to 33.2)	10.3 (8.5 to 12.5)		
Victoria, Day 7 [N=213,179]	193.3 (167.6 to 222.8)	46.1 (33.5 to 63.4)		
Yamagata, Day 0 [N=210,173]	11.9 (10.6 to 13.4)	6.5 (5.8 to 7.2)		
Yamagata, Day 7 [N=213,179]	184.1 (159.8 to 212.1)	25.2 (19.8 to 32)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects seropositive for HI antibody titers against each of the four vaccine strains after dose 1 of Fluarix Quadrivalent vaccine[16]

End point description:

Seropositivity was defined as number of subjects with antibody titers greater than or equal to (≥) 1:10. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

End point type	Primary

End point timeframe:

At Day 0 and Day 7

Notes:

[16] - 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	213	179		
Units: Subjects				
H1N1, Day 0 [N=210,173]	178	54		
H1N1, Day 7 [N=213,179]	209	113		
H3N2, Day 0 [N=210,173]	120	52		
H3N2, Day 7 [N=213,179]	207	72		
Victoria, Day 0[N=210,173]	177	50		
Victoria, Day 7[N=213,179]	213	145		
Yamagata, Day 0[N=210,173]	127	31		
Yamagata, Day 7 [N=213,179]	211	120		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects seroconverted for HI antibodies 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 each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.[17]

End point description:

A seroconverted subject was defined as a subject who had either a pre-vaccination titer <1:10 and a post-vaccination titer greater than or equal to 1:40 or a pre-vaccination titer greater than or equal to 1:10 and at least a four-fold increase in post-vaccination titer. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria)and B/Hubei-Wujiagang/158/2009 (Yamagata)antigens.

End point type	Primary

End point timeframe:

At Day 7 post dose 1

Notes:

[17] - 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	210	173		
Units: Subjects				
H1N1, Day 7 [N=210,173]	160	54		
H3N2, Day 7 [N=210,173]	173	49		
Victoria, Day 7 [N=210,173]	162	66		
Yamagata, Day 7 [N=210,173]	197	65		

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean geometric increase (MGI) for HI antibody titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.[18]

End point description:

Mean geometric increase was defined as the geometric mean of the within subject ratios of the post-vaccination reciprocal HI titer to the Day 0 reciprocal HI titer. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011(H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

End point type	Primary

End point timeframe:

At Day 7 post dose 1

Notes:

[18] - 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	210	173		
Units: Fold Increase				
geometric mean (confidence interval 95%)				
H1N1, Day 7 [N=210,173]	10 (8.1 to 12.2)	3.1 (2.5 to 3.9)		
H3N2, Day 7 [N=210,173]	11.2 (9.7 to 13.1)	2.4 (2 to 3)		
Victoria, Day 7 [N=210,173]	6.9 (6 to 7.8)	4.5 (3.7 to 5.4)		
Yamagata, Day 7 [N=210,173]	15.2 (13.3 to 17.4)	4 (3.2 to 4.9)		

Statistical analyses

No statistical analyses for this end point

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

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

	Quadrivalent vaccine.[19]

End point description:

Seroprotection rate was defined as the number of vaccinees with a serum HI titer greater than or equal to(≥) 1:40 that usually is accepted as indicating protection in adults. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011(H3N2), B/Brisbane/60/2008 (Victoria)and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

End point type	Primary

End point timeframe:

At Day 0 and Day 7

Notes:

[19] - 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	213	179		
Units: Subjects				
H1N1,Day 0 [N=210,173]	87	51		
H1N1, Day 7 [N=213,179]	206	59		
H3N2, Day 0 [N=210,173]	29	48		
H3N2, Day 7 [N=213,179]	182	54		
Victoria, Day 0 [N=210,173]	68	35		
Victoria, Day 7 [N=213,179]	206	70		
Yamagata, Day 0 [N=210,173]	27	10		
Yamagata, Day 7 [N=213,179]	205	70		

Statistical analyses

No statistical analyses for this end point

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:

The cut-off values assessed were less than (<) 1:10, 1:10 to < 1:40 and ≥ 1:40. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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:

Antibody titers were expressed as Geometric mean titers (GMTs). The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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:

Antibody titers were expressed as GMTs. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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:

VRR was defined as the number of vaccinees who had either a pre-vaccination titer <cut-off and a post-vaccination titer ≥ 4-fold of half of the cut-off or a pre-vaccination titer ≥cut-off and at least a 4-fold increase in post-vaccination titers. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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: MGI for neutralising antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	MGI for neutralising antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point description:

MGI was defined as the fold increase in serum HI GMT post-vaccination compared to Day 0. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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: 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: Vaccine response rate(VRR) for anti-neuraminidase antibody titers against each of the four vaccine strains.

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

End point description:

VRR was defined as the number of vaccinees who had either a pre-vaccination titer <cut-off and a post-vaccination titer ≥ 4-fold of half of the cut-off or a pre-vaccination titer ≥cut-off and at least a 4-fold increase in post-vaccination titers. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009

(Yamagata) antigens.

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 anti-neuraminidase antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	MGI for anti-neuraminidase antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point description:

MGI was defined as the fold increase in serum HI GMT post-vaccination compared to Day 0. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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 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:

The cut-off values assessed were less than (<) 1:10, 1:10 to < 1:40,≥ 1:40, ≥1:60 and ≥1:80 . The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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	213	179		
Units: Subjects				
H1N1, Day 0, <1:10 [N=210,173]	32	119		
H1N1, Day 7, <1:10 [N=213,179]	4	66		
H1N1, Day 0, 1:10 to <1:40 [N=210,173]	178	54		
H1N1, Day 7, 1:10 to <1:40 [N=213,179]	209	113		
H1N1, Day 0, ≥1:40 [N=210,173]	87	51		
H1N1, Day 7, ≥1:40 [N=213,179]	206	59		
H1N1, Day 0, ≥1:60 [N=210,173]	73	47		
H1N1, Day 7, ≥1:60 [N=213,179]	204	57		
H1N1, Day 0, ≥1:80 [N=210,173]	73	47		
H1N1, Day 7, ≥1:80 [N=213,179]	204	57		
H3N2, Day 0, <1:10 [N=210,173]	90	121		
H3N2, Day 7, <1:10 [N=213,179]	6	107		
H3N2, Day 0,1:10 to 1:40 [N=210,173]	120	52		
H3N2, Day 7,1:10 to 1:40 [N=213,179]	207	72		
H3N2, Day 0, ≥1:40 [N=210,173]	29	48		
H3N2, Day 7, ≥1:40 [N=213,179]	182	54		
H3N2, Day 0, ≥1:60 [N=210,173]	12	36		
H3N2, Day 7, ≥1:60 [N=213,179]	147	52		
H3N2, Day 0, ≥1:80 [N=210,173]	12	36		

H3N2, Day 7, ≥1:80 [N=213,179]	147	52		
Victoria, Day 0, <1:10 [N=210,173]	33	123		
Victoria, Day 7, <1:10 [N=213,179]	0	34		
Victoria, Day 0,1:10 to 1:40 [N=210,173]	177	50		
Victoria, Day 7,1:10 to 1:40 [N=213,179]	213	145		
Victoria, Day 0, ≥1:40 [N=210,173]	68	35		
Victoria, Day 7, ≥1:40 [N=213,179]	206	70		
Victoria, Day 0, ≥1:60 [N=210,173]	40	27		
Victoria, Day 7, ≥1:60 [N=213,179]	182	51		
Victoria, Day 0, ≥1:80 [N=210,173]	40	27		
Victoria, Day 7, ≥1:80 [N=213,179]	182	51		
Yamagata, Day 0, <1:10 [N=210,173]	83	142		
Yamagata, Day 7, <1:10 [N=213,179]	2	59		
Yamagata, Day 0,1:10 to 1:40 [N=210,173]	127	31		
Yamagata, Day 7,1:10 to 1:40 [N=213,179]	211	120		
Yamagata, Day 0, ≥1:40 [N=210,173]	27	10		
Yamagata, Day 7, ≥1:40 [N=213,179]	205	70		
Yamagata, Day 0, ≥1:60 [N=210,173]	7	4		
Yamagata, Day 7, ≥1:60 [N=213,179]	177	44		
Yamagata, Day 0, ≥1:80 [N=210,173]	7	4		
Yamagata, Day 7, ≥1:80 [N=213,179]	177	44		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum micro neutralizing(MN) antibody titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	Serum micro neutralizing(MN) antibody titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point description:

MN antibody titers were expressed as geometric mean titers(GMTs). The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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	100	89		
Units: Titer				
geometric mean (confidence interval 95%)				
H1N1,Day 0[N=90,72]	141.4 (97.6 to 205)	47.3 (32.1 to 69.6)		
H1N1,Day 7[N=100,76]	1461.3 (1132.8 to 1885.1)	138.4 (71.9 to 266.4)		
H3N2,Day 0[N=92,76]	60 (51.2 to 70.4)	59.6 (42.5 to 83.7)		
H3N2,Day 7[N=97,80]	374.6 (305.4 to 459.4)	177.7 (97.4 to 324.2)		
Victoria,Day 0[N=100,89]	37.1 (28.6 to 48.2)	23.5 (19.1 to 28.9)		
Victoria,Day 7[N=100,88]	189.9 (151.2 to 238.5)	52 (31.3 to 86.3)		
Yamagata,day 0[N=100,87]	37.1 (34.2 to 40.2)	30.9 (28.9 to 32.9)		
Yamagata, Day 7[N=100,88]	177.5 (154.2 to 204.5)	49.8 (40.5 to 61.1)		

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:

NI (Neuraminidase inhibitor) antibody titers were expressed as geometric mean titers(GMTs).The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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	100	89		
Units: Titer				
geometric mean (confidence interval 95%)				

H1N1, Day 0[N=99,86]	34.8 (25.1 to 48.1)	23.5 (17.8 to 31.1)		
H1N1, Day 7[N=99,89]	287.1 (239.8 to 343.6)	38.3 (25.7 to 57.1)		
H3N2, Day 0[N=100,86]	35 (31.3 to 39.1)	45.9 (36.7 to 57.4)		
H3N2, Day 7[N=100,89]	175.8 (143.9 to 214.7)	84.5 (60.7 to 117.6)		
Victoria, Day 0[N=99,86]	16.8 (13.7 to 20.7)	15 (12.7 to 17.6)		
Victoria, Day 7[N=99,89]	89.2 (72.5 to 109.7)	29.1 (19.6 to 43.2)		
Yamagata, Day 0[N=99,86]	25.1 (21.3 to 29.5)	15.4 (12.9 to 18.3)		
Yamagata, Day 7[N=100,89]	216.5 (180.5 to 259.6)	39.7 (27.9 to 56.6)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

VRR was defined as the number of vaccinees who had either a pre-vaccination titer <cut-off and a post-vaccination titer ≥ 4-fold of half of the cut-off or a pre-vaccination titer ≥cut-off and at least a 4-fold increase in post-vaccination titers. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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	100	88		
Units: Subjects				
H1N1, Day 7[N=90,71]	67	28		
H3N2, Day 7[N=90,74]	66	31		
Victoria, Day 7[N=100,88]	74	21		
Yamagata, Day 7[N=100,86]	42	11		

Statistical analyses

No statistical analyses for this end point

Secondary: MGI for neutralising antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point title	MGI for neutralising antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine.

End point description:

MGI was defined as the fold increase in GMTs post-vaccination compared to Day 0. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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	100	88		
Units: Fold Increase				
geometric mean (confidence interval 95%)				
H1N1, Day 7[N=90,71]	10 (7.7 to 13.1)	3.1 (2.2 to 4.3)		
H3N2, Day 7[N=90,74]	6.2 (5.2 to 7.5)	3.4 (2.4 to 4.9)		
Victoria, Day 7[N=100,88]	5.1 (4.4 to 5.9)	2.2 (1.6 to 3)		
Yamagata, Day 7[N=100,86]	4.8 (4.2 to 5.4)	1.6 (1.3 to 1.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine response rate(VRR) for anti-neuraminidase antibodies against each of the four vaccine strains.

End point title	Vaccine response rate(VRR) for anti-neuraminidase antibodies against each of the four vaccine strains.

End point description:

VRR was defined as the percentage of vaccinees who had either a pre-vaccination titer <cut-off and a post-vaccination titer ≥ 4-fold of half of the cut-off or a pre-vaccination titer ≥cut-off and at least a 4-fold increase in post-vaccination titers. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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	100	86		
Units: Subjects				
H1N1, Day 7[N=98,86]	70	23		
H3N2, Day 7[N=100,86]	70	22		
Victoria, Day 7[N=98,86]	74	20		
Yamagata, Day 7[N=99,86]	85	23		

Statistical analyses

No statistical analyses for this end point

Secondary: MGI for anti-neuraminidase antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point title	MGI for anti-neuraminidase antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine

End point description:

MGI was defined as the fold increase in GMTs post-vaccination compared to Day 0. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.

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	100	86		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1, Day 7[N=98,86]	8.1 (6.2 to 10.5)	1.7 (1.4 to 2.1)		
H3N2, Day 7[N=100,86]	5 (4.2 to 6)	1.8 (1.6 to 2.2)		
Victoria, Day 7[N=98,86]	5.2 (4.5 to 6.1)	1.9 (1.5 to 2.5)		
Yamagata, Day 7[N=99,86]	8.7 (7.4 to 10.2)	2.6 (2 to 3.5)		

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 by age strata.

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

End point description:

Antibody titers were expressed as geometric mean titers. The vaccine strains included A/Christchurch/16/2010 (H1N1),A/Victoria/361/2011 (H3N2), A/Victoria/361/2011 and B/Hubei-Wujiagang/158/2009)(Yamagata) antigens. The humoral response in terms of neutralising antibodies for all vaccine strains were calculated by age stratum which included 17-29 months and 30-48 months age groups for both the Fluarix primed and unprimed groups.

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	54	55		
Units: Titers				
geometric mean (confidence interval 95%)				
H1N1, Day 0,17-29M[N=47,44]	76.8 (48.8 to 120.9)	29 (18.7 to 44.9)		
H1N1, Day 7,17-29M [N=53,48]	1112 (746 to 1657.8)	53 (26.9 to 104.2)		
H1N1, Day 0,30-48M[N=50,46]	240 (146.2 to 394.1)	78.8 (46.6 to 133.1)		
H1N1, Day 7,30-48M[N=54,48]	2014.5 (1517.5 to 2674.4)	366.9 (155.6 to 865.4)		
H3N2,Day 0,17-29M[N=49,47]	58.1 (46.3 to 72.9)	74.5 (45.8 to 121.5)		
H3N2,Day 7,17-29M[N=51,50]	370.5 (272.7 to 503.2)	217.5 (97 to 488)		
H3N2,Day 0,30-48M[N=50,49]	76 (58.2 to 99.1)	91.5 (60.8 to 137.7)		
H3N2,Day 7,30-48M[N=53,50]	480.3 (356.7 to 646.8)	485.8 (226.2 to 1043.7)		
Victoria,Day 0,17-29M[N=53,54]	29.2 (21.7 to 39.2)	19.8 (15.9 to 24.8)		
Victoria,Day 7,17-29M[N=53,53]	156.3 (119.7 to 204.2)	35.5 (20 to 62.9)		
Victoria,Day 0,30-48M[N=54,55]	50.9 (33.1 to 78.2)	24.7 (18.8 to 32.6)		
Victoria,Day 7,30-48M[N=54,55]	239.1 (166.7 to 343)	61.8 (31.6 to 120.8)		
Yamagata, Day 0,17-29M[N=53,53]	35.6 (32.3 to 39.2)	29.6 (28 to 31.4)		
Yamagata, Day 7,17-29M[N=53,52]	156.9 (129.4 to 190.3)	45.6 (33.7 to 61.7)		
Yamagata, Day 0,30-48M[N=54,54]	38.3 (34 to 43.1)	32 (28.9 to 35.4)		

Yamagata, Day 7,30-48M[N=54,55]	212.2 (170.1 to 264.7)	58.3 (44.1 to 77)		

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 by age strata

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

End point description:

Antibody titers were expressed as geometric mean titers. The vaccine strains included A/Christchurch/16/2010(H1N1), A/Victoria/361/2011(H3N2),B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009(Yamagata) antigens. The humoral response in terms of anti-neuraminidase antibodies for all vaccine strains were calculated by age stratum which included 17-29 months and 30-48 months age groups for both the Fluarix primed and unprimed groups.

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	54	55		
Units: Titers				
geometric mean (confidence interval 95%)				
H1N1, Day 0,17-29M[N=53,52]	21.6 (15 to 31.3)	15.8 (11.9 to 21.1)		
H1N1, Day 7,17-29M[N=53,54]	246.3 (189.1 to 320.8)	22.9 (14.9 to 35.1)		
H1N1, Day 0,30-48M[N=53,54]	55.5 (34.2 to 89.9)	36.1 (24.2 to 53.9)		
H1N1, Day 7,30-48M[N=53,55]	350.7 (281.1 to 437.4)	73.7 (42.9 to 126.7)		
H3N2, Day 0,17-29M[N=53,52]	34.7 (29.2 to 41.2)	49.8 (35.9 to 69.3)		
H3N2, Day 7,17-29M[N=53,54]	158 (117.8 to 211.8)	85.3 (55.4 to 131.4)		
H3N2, Day 0,30-48M[N=54,54]	42.4 (34.9 to 51.6)	69 (51.1 to 93.2)		
H3N2, Day 7,30-48M[N=54,55]	226.4 (174.9 to 292.9)	152.2 (98.5 to 235.1)		
Victoria, Day 0,17-29M[N=53,52]	13.2 (11 to 16)	13.1 (10.9 to 15.7)		
Victoria, Day 7,17-29M[N=53,54]	68.8 (53.3 to 88.9)	21.1 (13.4 to 33.2)		

Victoria, Day 0,30-48M[N=53,54]	22.8 (16 to 32.4)	15.7 (12.6 to 19.4)		
Victoria, Day 7,30-48M[N=53,55]	119.2 (88.2 to 161.1)	35.9 (21 to 61.4)		
Yamagata, Day 0,17-29M[N=53,52]	20.5 (16.9 to 24.9)	13.2 (11.1 to 15.8)		
Yamagata, Day 7,17-29M[N=53,54]	181.4 (143.3 to 229.5)	29.3 (19.5 to 44)		
Yamagata, Day 0,30-48M[N=53,54]	31.1 (24.4 to 39.7)	17.9 (13.8 to 23.1)		
Yamagata, Day 7,30-48M[N=53,55]	271.8 (208.6 to 354.3)	55.8 (34.4 to 90.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine response rate(VRR) for serum neutralising antibody titers against each of the four vaccine strains by age strata

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

End point description:

VRR was defined as the percentage of vaccinees who had either a pre-vaccination titer <cut-off and a post-vaccination titer ≥ 4-fold of half of the cut-off or a pre-vaccination titer ≥cut-off and at least a 4-fold increase in post-vaccination titers. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011(H3N2), B/Brisbane/60/2008(Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens. The humoral response in terms of neutralising antibodies for all vaccine strains were calculated by age stratum which included 17-29 months and 30-48 months age groups for both the Fluarix primed and unprimed groups.

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	54	55		
Units: Subjects				
H1N1, Day 7, 17-29M[47,44]	39	12		
H1N1, Day 7, 30-48M[50,45]	35	24		
H3N2, Day 7,17-29M[N=48,46]	36	19		
H3N2, Day 7,30-48M[N=49,48]	36	29		
Victoria, Day 7,17-29M[N=53,53]	41	9		
Victoria, Day 7,30-48M[N=54,55]	37	15		
Yamagata, Day 7,17-29M[N=53,51]	17	6		
Yamagata, Day 7,30-48M[N=54,54]	28	9		

Statistical analyses

No statistical analyses for this end point

Secondary: MGI for neutralising antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine by age strata

End point title	MGI for neutralising antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine by age strata

End point description:

MGI was defined as the fold increase in GMTs post-vaccination compared to Day 0.The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens.The humoral response in terms of neutralising antibodies for all vaccine strains were calculated by age stratum which included 17-29 months and 30-48 months age groups for both the Fluarix primed and unprimed groups.

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	54	55		
Units: Fold Increase				
geometric mean (confidence interval 95%)				
H1N1, Day 7, 17-29M[N=47,44]	13.1 (9.2 to 18.8)	2 (1.4 to 3)		
H1N1, Day 7, 30-48M[N=50,45]	8.7 (6 to 12.5)	4.7 (3 to 7.3)		
H3N2, Day 7,17-29M[N=48,46]	6.1 (4.8 to 7.7)	3.4 (2.1 to 5.4)		
H3N2, Day 7,30-48M[N=49,48]	6.7 (5.1 to 8.8)	5.9 (3.8 to 9.2)		
Victoria, Day 7,17-29M[N=53,53]	5.4 (4.4 to 6.5)	1.8 (1.2 to 2.6)		
Victoria, Day 7,30-48M[N=54,55]	4.7 (3.8 to 5.8)	2.5 (1.6 to 3.8)		
Yamagata, Day 7,17-29M[N=53,51]	4.4 (3.8 to 5.2)	1.5 (1.2 to 2)		
Yamagata, Day 7,30-48M[N=54,54]	5.5 (4.5 to 6.9)	1.8 (1.4 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaccine response rate(VRR) for anti-neuraminidase antibody titers against each of the four vaccine strains by age strata.

End point title	Vaccine response rate(VRR) for anti-neuraminidase antibody titers against each of the four vaccine strains by age strata.

End point description:

VRR was defined as the percentage of vaccinees who had either a pre-vaccination titer <cut-off and a post-vaccination titer ≥ 4-fold of half of the cut-off or a pre-vaccination titer ≥cut-off and at least a 4-fold increase in post-vaccination titers. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria /361/2011(H3N2), B/Brisbane /60/2008(Victoria) and B/Hubei-Wujiagang/158/2009

(Yamagata) antigens. The humoral response in terms of anti-neuraminidase antibodies for all vaccine strains were calculated by age stratum which included 17-29 months and 30-48 months age groups for both the Fluarix primed and unprimed groups.

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	54	54		
Units: Subjects				
H1N1, Day 7,17-29M[N=53,52]	43	11		
H1N1, Day 7,30-48M[N=52,54]	32	20		
H3N2, Day 7,17-29M[N=53,52]	36	8		
H3N2, Day 7,30-48M[N=54,54]	39	23		
Victoria, Day 7,17-29M[N=53,52]	40	8		
Victoria, Day 7,30-48M[N=52,54]	39	16		
Yamagata, Day 7, 17-29M[N=53,52]	46	10		
Yamagata, Day 7, 30-48M[N=52,54]	44	19		

Statistical analyses

No statistical analyses for this end point

Secondary: MGI for anti-neuraminidase antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine by age strata.

End point title	MGI for anti-neuraminidase antibodies titers against each of the four vaccine strains after 1 dose of Fluarix Quadrivalent vaccine by age strata.

End point description:

MGI was defined as the fold increase in GMTs post-vaccination compared to Day 0. The vaccine strains included A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Brisbane/60/2008 (Victoria) and B/Hubei-Wujiagang/158/2009 (Yamagata) antigens. The humoral response in terms of anti-neuraminidase antibodies for all vaccine strains were calculated by age stratum which included 17-29 months and 30-48 months age groups for both the Fluarix primed and unprimed groups.

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	54	54		
Units: Fold Increase				
geometric mean (confidence interval 95%)				
H1N1, Day 7,17-29M[53,52]	11.4 (8.2 to 15.8)	1.5 (1.2 to 1.9)		
H1N1, Day 7,30-48M[N=52,54]	6 (4.1 to 8.8)	2.1 (1.7 to 2.7)		
H3N2, Day 7,17-29M[N=53,52]	4.6 (3.6 to 5.8)	1.7 (1.4 to 2)		
H3N2, Day 7,30-48M[N=54,54]	5.3 (4.2 to 6.8)	2.3 (1.9 to 2.8)		
Victoria, Day 7,17-29M[N=53,52]	5.2 (4.3 to 6.3)	1.5 (1.1 to 2.1)		
Victoria, Day 7,30-48M[N=52,54]	5.1 (4.1 to 6.5)	2.3 (1.6 to 3.4)		
Yamagata, Day 7, 17-29M[N=53,52]	8.8 (7.2 to 10.8)	2.2 (1.5 to 3.2)		
Yamagata, Day 7, 30-48M[N=52,54]	8.7 (6.9 to 11)	3.2 (2.3 to 4.5)		

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:

Solicited local AEs assessed were pain, redness and swelling. Any = any solicited local AE reported irrespective of intensity grade. Grade 3 pain = cried when limb was moved/spontaneously painful. Grade 3 redness and swelling was defined as redness/swelling above 50 millimeter (mm).

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 solicted symptoms

End point title	Duration of solicted symptoms

End point description:

Duration was defined as number of days with any grade of solicted local and/or general symptoms

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:

Solicited general symptoms assessed were drowsiness, Irritability/Fussiness, loss of appetite and Temperature. Any Temperature = axillary temperature ≥37.5 degrees Celsius (°C). Any = any solicited general symptom reported irrespective of intensity and relationship to vaccination. Related = symptoms considered by the investigator to have a causal relationship to vaccination. Grade 3 symptoms = symptoms that prevented normal activity. Grade 3 Irritability/Fussiness = Crying that could not be

comforted/prevented normal activity. Grade 3 loss of appetite = did not eat at all. Grade 3 temperature = axillary temperature > 39.0°C.

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:

MAVs were defined as an AEs with a medically-attended visits i.e. prompting emergency room (ER) visits, hospitalizations or physician visits and that were not routine visits for physical examination or vaccination. Any MAV was defined as at least one MAV experienced. Grade 3 was a MAV that prevented normal activities and related was defined as a MAV assessed by the investigator to be causally related to the study vaccination.

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:

pIMDs were defined as a subset of AEs that included autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have had an autoimmune aetiology. Any pIMDs= Any AEs that occured regardless of the relation with vaccination. Related pIMDs= Any pIMD assessed by the investigator as casually related to the study vaccination.

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		
Related 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:

Unsolicited AE covers any AE reported in addition to those solicited during the clinical study and any

solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as occurrence of any unsolicited symptom regardless of intensity grade or relation to vaccination. Grade 3 was an event that prevented normal activities and related was defined as an unsolicited AE assessed by the investigator to be causally related to the study vaccination.

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: Subjects				
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:

A serious adverse event was any untoward medical occurrence that: resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

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 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.

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

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

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

subjects affected / exposed	1 / 241 (0.41%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 Primed Group	Fluarix Quadrivalent Unprimed Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 241 (39.83%)	61 / 229 (26.64%)	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed[1]	96 / 239 (40.17%)	61 / 228 (26.75%)	
occurrences (all)	96	61	
Redness			
alternative assessment type: Systematic			
subjects affected / exposed[2]	82 / 239 (34.31%)	48 / 228 (21.05%)	
occurrences (all)	82	48	
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[3]	49 / 239 (20.50%)	25 / 228 (10.96%)	
occurrences (all)	49	25	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[4]	54 / 238 (22.69%)	44 / 224 (19.64%)	
occurrences (all)	54	44	
Irritability/Fussiness			
alternative assessment type: Systematic			
subjects affected / exposed[5]	77 / 238 (32.35%)	59 / 224 (26.34%)	
occurrences (all)	77	59	
Loss of Appetite			
alternative assessment type: Systematic			
subjects affected / exposed[6]	51 / 238 (21.43%)	46 / 224 (20.54%)	
occurrences (all)	51	46	

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

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