



Clinical trial results:

A Phase 3, observer blind, randomized, non-influenza vaccine comparator-controlled, multi-country and multi-centre study of the efficacy of GSK Biologicals' quadrivalent, inactivated, split virion, seasonal influenza vaccine candidate, GSK2282512A (FLU Q-QIV), administered intramuscularly in healthy children 3 to 8 years of age

Summary

EudraCT number	2015-001514-97
Trial protocol	Outside EU/EEA
Global end of trial date	09 January 2012

Results information

Result version number	v1
This version publication date	04 May 2016
First version publication date	09 July 2015

Trial information

Trial identification

Sponsor protocol code	114541
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01218308
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, 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)	No
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	31 May 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2012
Global end of trial reached?	Yes
Global end of trial date	09 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To evaluate the efficacy of Q-QIV in the prevention of reverse transcriptase polymerase chain reaction (RT-PCR) confirmed influenza A and or B disease presenting as influenza like illness (ILI), compared to a non-influenza vaccine comparator (Havrix) in children 3 to 8 years of age.

Influenza-like illness (ILI) was defined as the presence of an oral or axillary temperature $\geq 37.8^{\circ}\text{C}$ in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion

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 were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up for one month (minimum 30 days) following administration of the last dose of study vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2010
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	Bangladesh: 1000
Country: Number of subjects enrolled	Lebanon: 150
Country: Number of subjects enrolled	Turkey: 153
Country: Number of subjects enrolled	Dominican Republic: 1204
Country: Number of subjects enrolled	Honduras: 400
Country: Number of subjects enrolled	Panama: 204
Country: Number of subjects enrolled	Thailand: 1009
Country: Number of subjects enrolled	Philippines: 1100
Worldwide total number of subjects	5220
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	5220
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:

A total of 5168 subjects have been enrolled in this study. Primed subjects had received at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine and had received 2 doses of seasonal influenza vaccine. Unprimed subjects had not received any influenza A (H1N1) 2009 monovalent vaccine or seasonal influenza vaccine.

Pre-assignment

Screening details:

The duration of the study was approximately 4-8 weeks to complete enrolment, with at least six months extended safety follow-up (ESFU) after first vaccination, and lasted until the end of the influenza like illness (ILI) surveillance period.

Period 1

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

Blinding implementation details:

Data was collected in an observer-blinded manner. Observer-blinded indicates that during the course of the study, the subjects (and their parents/LARs), the investigator, and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity, and immunogenicity) and review/analysis of study data were all unaware of the treatment assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	FluLaval® Quadrivalent Group

Arm description:

Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of FluLaval® Quadrivalent vaccine at Day 0 and, if unprimed, 2 doses of FluLaval® Quadrivalent vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.

Arm type	Experimental
Investigational medicinal product name	FluLaval® Quadrivalent
Investigational medicinal product code	GSK2282512A
Other name	Quadrivalent seasonal influenza vaccine GSK2282512A (FLU Q-QIV)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One intramuscular dose for primed subjects. Two intramuscular doses for unprimed subjects.

Arm title	Havrix Group
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Arm description:

Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of Havrix™ vaccine at Day 0 and, if unprimed, 2 doses of Havrix™ vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.

Arm type	Active comparator
Investigational medicinal product name	Havrix™
Investigational medicinal product code	HAV Antigen
Other name	Havrix 720 Junior
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Two intramuscular doses (booster dose included) for primed subjects. Three intramuscular doses (booster dose included) for unprimed subjects. The booster dose was administered after the study was completed.

Number of subjects in period 1^[1]	FluLaval® Quadrivalent Group	Havrix Group
Started	2584	2584
Completed	2481	2464
Not completed	103	120
Adverse event, serious fatal	1	1
Consent withdrawn by subject	61	64
Adverse event, non-fatal	-	1
Unspecified	14	21
Protocol Violation	-	2
Lost to follow-up	27	31

Notes:

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

Justification: 45 subjects from 1 center were excluded from the study due to GCP-related irregularities and the data (invalidated) from this center was not included in the subsequent data analysis of this study.

Of the remaining 5175 subjects, 7 subjects enrolled in the study were allocated subject numbers but the study vaccine dose was not administered.

Baseline characteristics

Reporting groups

Reporting group title	FluLaval® Quadrivalent Group
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Reporting group description:

Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of FluLaval® Quadrivalent vaccine at Day 0 and, if unprimed, 2 doses of FluLaval® Quadrivalent vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.

Reporting group title	Havrix Group
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Reporting group description:

Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of Havrix™ vaccine at Day 0 and, if unprimed, 2 doses of Havrix™ vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.

Reporting group values	FluLaval® Quadrivalent Group	Havrix Group	Total
Number of subjects	2584	2584	5168
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	5.4	5.4	
standard deviation	± 1.66	± 1.65	-
Gender categorical Units: Subjects			
Female	1251	1245	2496
Male	1333	1339	2672

End points

End points reporting groups

Reporting group title	FluLaval® Quadrivalent Group
Reporting group description: Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of FluLaval® Quadrivalent vaccine at Day 0 and, if unprimed, 2 doses of FluLaval® Quadrivalent vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.	
Reporting group title	Havrix Group
Reporting group description: Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of Havrix™ vaccine at Day 0 and, if unprimed, 2 doses of Havrix™ vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.	

Primary: Number of subjects reporting at least one confirmed occurrence of influenza A or B.

End point title	Number of subjects reporting at least one confirmed occurrence of influenza A or B. ^[1]
End point description: To confirm influenza A and/or B disease, a positive reverse transcriptase polymerase chain reaction (RT-PCR) result for influenza A or B virus from a nose and throat swab obtained concurrently with an influenza like illness (ILI) was required. ILI was defined as the presence of an oral or axillary temperature ≥ 37.8 degrees Celsius (°C) in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion.	
End point type	Primary
End point timeframe: From Day 14 to Day 180	
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	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2379	2398		
Units: Subjects	58	128		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting at least one moderate to severe occurrence of influenza A or B.

End point title	Number of subjects reporting at least one moderate to severe occurrence of influenza A or B.
End point description: To confirm influenza A and/or B disease moderate to severe cases, a positive RT-PCR result for influenza	

A or B virus from a nose and throat swab obtained concurrently with an ILI was required. Moderate to severe influenza was defined as RT-PCR-confirmed ILI with: - Fever >39°C, and/or at least one of the following manifestations, - Physician-verified shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup, or acute otitis media, and/or one of the following, - Physician-diagnosed serious extra-pulmonary complication of influenza, including myositis, encephalitis, seizure, or myocarditis

End point type	Secondary
End point timeframe:	
From Day 14 to Day 180	

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2379	2398		
Units: Subjects	14	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting at least one Culture Confirmed occurrence of influenza A or B due to antigenically matched strain.

End point title	Number of subjects reporting at least one Culture Confirmed occurrence of influenza A or B due to antigenically matched strain.
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End point description:

To confirm influenza A and/or B disease due to antigenically matched strain, a positive reverse transcriptase polymerase chain reaction (RT-PCR) result for influenza A or B virus from a nose and throat swab obtained concurrently with an influenza like illness (ILI) was required. ILI was defined as the presence of an oral or axillary temperature ≥ 37.8 degrees Celsius (°C) in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion.

End point type	Secondary
End point timeframe:	
From Day 14 to Day 180	

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2379	2398		
Units: Subjects	31	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting at least one Culture Confirmed occurrence of influenza A or B due to any strain.

End point title	Number of subjects reporting at least one Culture Confirmed occurrence of influenza A or B due to any strain.
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End point description:

To confirm influenza A and/or B disease due to any strain, a positive reverse transcriptase polymerase chain reaction (RT-PCR) result for influenza A or B virus from a nose and throat swab obtained concurrently with an influenza like illness (ILI) was required. ILI was defined as the presence of an oral or axillary temperature ≥ 37.8 degrees Celsius ($^{\circ}\text{C}$) in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion.

End point type	Secondary
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End point timeframe:

From Day 14 to Day 180

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2379	2398		
Units: Subjects	50	112		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers for serum Hemagglutination Inhibition (HI) antibodies against 4 strains of influenza disease.

End point title	Titers for serum Hemagglutination Inhibition (HI) antibodies against 4 strains of influenza disease.
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End point description:

Titers are presented as geometric mean titers (GMTs). The reference cut-off value was the seropositivity cut-off of 1:10. The 4 influenza strains assessed were the Flu A/California/7/09 (H1N1), Flu A/Victoria/210/09 (H3N2), FluB/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06 (Yamagata).

End point type	Secondary
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End point timeframe:

At Day 0 [PRE] and 28 days post vaccination (Day 28 for primed subjects and day 56 for unprimed subjects) [POST]

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	122		
Units: Titers				
geometric mean (confidence interval)				

95%)				
H1N1, PRE [N=457;117]	15.3 (13.6 to 17.3)	16.1 (12.6 to 20.5)		
H1N1, POST [N=457;121]	318.8 (291 to 349.2)	16.1 (12.8 to 20.2)		
H3N2, PRE [N=457;117]	24.3 (21.9 to 27)	28.6 (23.5 to 34.8)		
H3N2, POST [N=457;122]	264.7 (244.3 to 286.8)	30.3 (24.8 to 36.9)		
Victoria, PRE [N=457;117]	13.7 (12.2 to 15.4)	15.6 (12.2 to 20.1)		
Victoria, POST [N=457;120]	239.9 (214.6 to 268.2)	17.8 (13.7 to 23.1)		
Yamagata, PRE [N=457;117]	16.2 (14.3 to 18.4)	18.8 (14.4 to 24.5)		
Yamagata, POST [N=457;117]	361.5 (330.7 to 395.3)	19.2 (14.9 to 24.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects against 4 strains of influenza disease.

End point title	Number of seroconverted subjects against 4 strains of influenza disease.
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End point description:

A seroconverted subject was defined as a vaccinated subject who had either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a four-fold increase in post-vaccination titer. The 4 influenza strains assessed were the Flu A/California/7/09 (H1N1), Flu A/Victoria/210/09 (H3N2), FluB/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06

End point type	Secondary
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End point timeframe:

At 28 days post vaccination (Day 28 for primed subjects and day 56 for unprimed subjects) [POST]

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	117		
Units: Subjects				
H1N1, POST	438	1		
H3N2, POST	385	2		
Victoria, POST	425	3		
Yamagata, POST	435	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects against 4 strains of influenza disease.

End point title	Number of seroprotected subjects against 4 strains of influenza disease.
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End point description:

A seroprotected subject was defined as a vaccinated subject who had a serum HI titer $\geq 1:40$. The 4 influenza strains assessed were the Flu A/California/7/09 (H1N1), Flu A/Victoria/210/09 (H3N2), FluB/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06 (Yamagata).

End point type	Secondary
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End point timeframe:

At Day 0 [PRE] and 28 days post vaccination (Day 28 for primed subjects and day 56 for unprimed subjects) [POST]

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	122		
Units: Subjects				
H1N1, PRE [N=457;117]	151	37		
H1N1, POST [N=457;121]	451	39		
H3N2, PRE [N=457;117]	205	63		
H3N2, POST [N=457;122]	445	63		
Victoria, PRE [N=457;117]	127	35		
Victoria, POST [N=457;120]	443	38		
Yamagata, PRE [N=457;117]	159	45		
Yamagata, POST [N=457;117]	452	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion factor for Hemagglutination Inhibition (HI) antibodies against 4 strains of influenza disease.

End point title	Seroconversion factor for Hemagglutination Inhibition (HI) antibodies against 4 strains of influenza disease.
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End point description:

The seroconversion factor (SCF) was defined as the fold increase in serum Hemagglutination Inhibition (HI) geometric mean titers (GMTs) post vaccination compared to Day 0. The 4 influenza strains assessed were the Flu A/California/7/09 (H1N1), Flu A/Victoria/210/09 (H3N2), FluB/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06 (Yamagata).

End point type	Secondary
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End point timeframe:

At 28 days post vaccination (Day 28 for primed subjects and day 56 for unprimed subjects) [POST]

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	117		
Units: fold increase				
geometric mean (confidence interval 95%)				
H1N1, POST	20.8 (19 to 22.8)	1 (0.9 to 1.1)		
H3N2, POST	10.9 (9.8 to 12.1)	1 (0.9 to 1.2)		
Victoria, POST	17.5 (16 to 19.1)	1.1 (1 to 1.3)		
Yamagata, POST	22.3 (20.1 to 24.8)	1 (1 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Haemagglutination Inhibition (HI) antibody titers against each of the 4 vaccine strains

End point title	Haemagglutination Inhibition (HI) antibody titers against each of the 4 vaccine strains
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End point description:

HI antibody titers were expressed as Geometric mean titers (GMTs). The vaccine strains assessed were Flu A/California/7/2009 (H1N1), Flu A/Victoria/210/09 (H3N2), Flu B/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06 (Yamagata).

End point type	Secondary
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End point timeframe:

On Day 0 and at least 6 months after first vaccination (Month 6)

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	112		
Units: Titer				
geometric mean (confidence interval 95%)				
H1N1, PRE [N=444;112]	15.5 (13.8 to 17.6)	16.5 (12.9 to 21.2)		
H1N1, POST [N=444;112]	138.6 (122.6 to 156.6)	23.2 (17.9 to 30.1)		
H3N2, PRE [N=444;112]	24.6 (22.1 to 27.4)	29.1 (23.8 to 35.5)		
H3N2, POST [N=443;112]	136.5 (124.3 to 149.9)	43.6 (34.9 to 54.5)		
Victoria, PRE [N=444;112]	13.7 (12.2 to 15.4)	15.1 (11.8 to 19.5)		
Victoria, POST [N=443;112]	110.2 (97.1 to 125)	19.7 (15 to 25.8)		

Yamagata, PRE [N=444;112]	16.1 (14.2 to 18.4)	18.7 (14.3 to 24.6)		
Yamagata, POST [N=444;112]	157 (143.1 to 172.3)	21.8 (16.5 to 28.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for HI antibody titers against each of the 4 vaccine influenza strains.

End point title	Number of seroconverted subjects for HI antibody titers against each of the 4 vaccine influenza strains.
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End point description:

A seroconverted subject was defined as a vaccinated subject with either a pre-vaccination titer less than ($<$) 1:10 and a post-vaccination titer greater than or equal to (\geq) 1:40, or a pre-vaccination titer \geq 1:10 and at least a 4-fold increase in post-vaccination titer. The vaccine strains assessed were Flu A/California/7/09 (H1N1), Flu A/Victoria/210/09 (H3N2), FluB/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06 (Yamagata).

End point type	Secondary
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End point timeframe:

At least 6 months after first vaccination (Month 6)

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	112		
Units: Subjects				
H1N1, POST [N=444;112]	349	9		
H3N2, POST [N=443;112]	290	10		
Victoria, POST [N=443;112]	323	12		
Yamagata, POST [N=444;112]	354	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects for HI antibody titers against each of the 4 vaccine influenza strains.

End point title	Number of seroprotected subjects for HI antibody titers against each of the 4 vaccine influenza strains.
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End point description:

A seroprotected subject was defined as a vaccinated subject with a serum HI titer greater than or equal to (\geq) 1:40 that usually is accepted as indicating protection in adults. The vaccine strains assessed were Flu A/California/7/09 (H1N1), Flu A/Victoria/210/09 (H3N2), FluB/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06 (Yamagata).

End point type	Secondary
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End point timeframe:

At Day 0 and at least 6 months after first vaccination (Month 6)

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	112		
Units: Subjects				
H1N1, PRE [N=444;112]	148	36		
H1N1, POST [N=444;112]	383	49		
H3N2, PRE [N=444;112]	204	60		
H3N2, POST [N=443;112]	412	71		
Victoria, PRE [N=444;112]	123	32		
Victoria, POST [N=443;112]	374	39		
Yamagata, PRE [N=444;112]	153	43		
Yamagata, POST [N=444;112]	427	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion factors for HI antibodies against 4 strains of influenza disease.

End point title	Seroconversion factors for HI antibodies against 4 strains of influenza disease.
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End point description:

Seroconversion factors were defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0. The 4 influenza strains assessed were the Flu A/California/7/09 (H1N1), Flu A/Victoria/210/09 (H3N2), FluB/Brisbane/60/08 (Victoria) and Flu B/Florida/4/06 (Yamagata).

End point type	Secondary
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End point timeframe:

At least 6 months after first vaccination (Month 6)

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	112		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1, POST [N=444;112]	8.9 (8.1 to 9.8)	1.4 (1.2 to 1.6)		
H3N2, POST [N=443;112]	5.5 (5 to 6.1)	1.5 (1.2 to 1.8)		
Victoria, POST [N=443;112]	8 (7.3 to 8.9)	1.3 (1.1 to 1.6)		

Yamagata, POST [N=444;112]	9.7 (8.7 to 10.8)	1.2 (1 to 1.4)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related solicited local symptoms.

End point title	Number of subjects with any, grade 3 and related solicited local symptoms.
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End point description:

Assessed solicited local symptoms were pain, redness and swelling at the injection site. Any = Incidence of a particular symptom regardless of intensity grade. Grade 3 pain = Cried when limb was moved/spontaneously painful for subjects < 5 years of age or significant pain at rest that prevented normal, everyday activities for subjects ≥ 5 years of age. Grade 3 redness/swelling = Redness/swelling above 100 millimeters (mm) of the injection site. All solicited local symptoms were considered related to vaccination.

End point type	Secondary
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End point timeframe:

During the 7-day (Days 0-6) follow-up period after any vaccination

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2546	2551		
Units: Subjects				
Any Pain	1251	888		
Grade 3 Pain	36	20		
Any Redness	17	5		
Grade 3 Redness	0	0		
Any Swelling	46	10		
Grade 3 Swelling	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related solicited general symptoms in subjects below 5 years of age.

End point title	Number of subjects with any, grade 3 and related solicited general symptoms in subjects below 5 years of age.
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End point description:

Assessed solicited general symptoms were drowsiness, irritability, loss of appetite and temperature. Any = Occurrence of any solicited general symptom regardless of intensity grade and relation to vaccination.

Any temperature = Axillary temperature $\geq 38.0^{\circ}\text{C}$. Grade 3 Drowsiness = Drowsiness that prevented normal activity. Grade 3 Irritability = Crying that could not be comforted/prevented normal activity. Grade 3 Loss of appetite = not eating at all. Related = General symptom assessed by the investigator as causally related to the study vaccination. Grade 3 temperature = Axillary temperature $\geq 39.0^{\circ}\text{C}$.

End point type	Secondary
End point timeframe:	
During the 7-day (Days 0-6) follow-up period after any vaccination	

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	899	896		
Units: Subjects				
Any Drowsiness	100	93		
Grade 3 Drowsiness	5	4		
Related Drowsiness	57	61		
Any Irritability	102	91		
Grade 3 Irritability	5	4		
Related Irritability	60	59		
Any Loss of appetite	119	120		
Grade 3 Loss of appetite	6	7		
Related Loss of appetite	55	61		
Any Temperature	74	74		
Grade 3 Temperature	21	18		
Related Temperature	35	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related solicited general symptoms in subjects of 5 years of age and above.

End point title	Number of subjects with any, grade 3 and related solicited general symptoms in subjects of 5 years of age and above.
End point description:	
Assessed solicited general symptoms were fatigue, gastrointestinal symptoms (Gastro.), headache, joint pain at other location (Joint pain), muscle aches, shivering and temperature. Any = Occurrence of any solicited general symptom regardless of intensity grade or relation to vaccination. Any temperature = Axillary temperature $\geq 38.0^{\circ}\text{C}$. Grade 3 symptom = Symptom that prevented normal activity. Related = Symptom assessed by the investigator as causally related to the vaccination. Grade 3 temperature = Axillary temperature $\geq 39.0^{\circ}\text{C}$.	
End point type	Secondary
End point timeframe:	
During the 7-day (Days 0-6) follow-up period after any vaccination	

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1648	1654		
Units: Subjects				
Any Fatigue	188	145		
Grade 3 Fatigue	1	6		
Related Fatigue	101	78		
Any Gastro.	133	146		
Grade 3 Gastro.	9	9		
Related Gastro.	68	54		
Any Headache	243	217		
Grade 3 Headache	9	14		
Related Headache	154	125		
Any Joint pain	143	93		
Grade 3 Joint pain	3	2		
Related Joint pain	98	54		
Any Muscle aches	257	194		
Grade 3 Muscle aches	3	5		
Related Muscle aches	162	109		
Any Shivering	63	59		
Grade 3 Shivering	2	2		
Related Shivering	32	26		
Any Temperature	72	82		
Grade 3 Temperature	21	17		
Related Temperature	46	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related unsolicited adverse events (AEs).

End point title	Number of subjects with any, grade 3 and related unsolicited adverse events (AEs).
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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 = Any unsolicited AE regardless of intensity or relationship to vaccination. Grade 3 = Unsolicited AE that prevented normal activity. Related = Unsolicited AE assessed by the investigator as causally related to the vaccination.

End point type	Secondary
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End point timeframe:

During the 28-day (Days 0-27) follow-up period after vaccination

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2584	2584		
Units: Subjects				
Any unsolicited AE(s)	843	855		
Grade 3 unsolicited AE(s)	25	20		
Related unsolicited AE(s)	30	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and related medically attended adverse events (MAEs).

End point title	Number of subjects with any and related medically attended adverse events (MAEs).
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End point description:

MAEs were defined as AEs that resulted in medical attention (defined as hospitalization, an emergency room visit or a visit to or from medical personnel for any reason). Any = Any MAE regardless of intensity or relationship to vaccination. Related = MAE assessed by the investigator as causally related to the vaccination.

End point type	Secondary
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End point timeframe:

During the entire study period (Day 0 - Day 180)

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2584	2584		
Units: Subjects				
Any MAE(s)	792	749		
Related MAE(s)	6	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and related potential immune-mediated diseases (pIMDs).

End point title	Number of subjects with any and related potential immune-mediated diseases (pIMDs).
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End point description:

pIMDs were defined as a subset of AEs that included both clearly autoimmune diseases (AID) and also other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology.

Any = Any pIMD(s) regardless of intensity or relationship to vaccination. Related = pIMDs assessed by the investigator as causally related to the vaccination.

End point type	Secondary
End point timeframe:	
During the entire study period (Day 0 - Day 180)	

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2584	2584		
Units: Subjects				
Any pIMD(s)	0	1		
Related pIMD(s)	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with any and related serious adverse events (SAEs).
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End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity. Any = Any SAE(s) regardless of intensity or relationship to vaccination. Related = SAEs assessed by the investigator as causally related to the vaccination.

End point type	Secondary
End point timeframe:	
During the entire study period (Day 0 - Day 180)	

End point values	FluLaval® Quadrivalent Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2584	2584		
Units: Subjects				
Any SAE(s)	36	24		
Related SAE(s)	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: during the entire study period (Day 0-Day 180); Unsolicited AEs: during the 28-day (Day 0-Day 27) follow-up period after vaccination; Solicited local/general symptoms: during the 7-day (Day 0-Day 6) follow-up period after any vaccination.

Adverse event reporting additional description:

For the systematically assessed other non-serious AEs, the number of participants at risk included those from Total Vaccinated cohort whose symptom sheet had been completed.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	FluLaval® Quadrivalent Group
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Reporting group description:

Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of FluLaval® Quadrivalent vaccine at Day 0 and, if unprimed, 2 doses of FluLaval® Quadrivalent vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.

Reporting group title	Havrix Group
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Reporting group description:

Subjects between 3 and 8 years of age at the time of first vaccination received, if primed, 1 dose of Havrix™ vaccine at Day 0 and, if unprimed, 2 doses of Havrix™ vaccine at Days 0 and 28. The vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm.

Serious adverse events	FluLaval® Quadrivalent Group	Havrix Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 2584 (1.39%)	24 / 2584 (0.93%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Optic nerve glioma			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	3 / 2584 (0.12%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Animal scratch			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 2584 (0.04%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drowning			
subjects affected / exposed	1 / 2584 (0.04%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Influenza like illness			
subjects affected / exposed	1 / 2584 (0.04%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			

subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (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			
Asthma			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (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 occurrences causally related to treatment / all deaths causally related to treatment / all	6 / 2584 (0.23%) 0 / 6 0 / 0	3 / 2584 (0.12%) 0 / 3 0 / 0	
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 2584 (0.15%) 0 / 4 0 / 0	3 / 2584 (0.12%) 0 / 3 0 / 0	
Dengue fever subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2584 (0.04%) 0 / 1 0 / 0	3 / 2584 (0.12%) 0 / 3 0 / 0	
Bronchopneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2584 (0.08%) 0 / 2 0 / 0	1 / 2584 (0.04%) 0 / 1 0 / 0	
Upper respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2584 (0.04%) 0 / 1 0 / 0	2 / 2584 (0.08%) 0 / 2 0 / 0	
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 2584 (0.12%) 0 / 3 0 / 0	0 / 2584 (0.00%) 0 / 0 0 / 0	
Amoebiasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 2584 (0.04%) 0 / 1 0 / 0	1 / 2584 (0.04%) 0 / 1 0 / 0	
Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2584 (0.08%) 1 / 2 0 / 0	0 / 2584 (0.00%) 0 / 0 0 / 0	
Acute tonsillitis			

subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpangina			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 2584 (0.04%)	0 / 2584 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visceral leishmaniasis			
subjects affected / exposed	0 / 2584 (0.00%)	1 / 2584 (0.04%)	
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	FluLaval® Quadrivalent Group	Havrix Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1251 / 2584 (48.41%)	888 / 2584 (34.37%)	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed ^[1]	1215 / 2546 (47.72%)	888 / 2551 (34.81%)	
occurrences (all)	1215	888	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed ^[2]	100 / 899 (11.12%)	93 / 896 (10.38%)	
occurrences (all)	100	93	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed ^[3]	102 / 899 (11.35%)	91 / 896 (10.16%)	
occurrences (all)	102	91	
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed ^[4]	119 / 899 (13.24%)	120 / 896 (13.39%)	
occurrences (all)	119	120	
Temperature			
alternative assessment type: Systematic			
subjects affected / exposed ^[5]	74 / 899 (8.23%)	74 / 896 (8.26%)	
occurrences (all)	74	74	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed ^[6]	188 / 1648 (11.41%)	145 / 1654 (8.77%)	
occurrences (all)	188	145	
Gastro.			
alternative assessment type: Systematic			
subjects affected / exposed ^[7]	133 / 1648 (8.07%)	146 / 1654 (8.83%)	
occurrences (all)	133	146	
Headache			
alternative assessment type: Systematic			

subjects affected / exposed ^[8]	243 / 1648 (14.75%)	217 / 1654 (13.12%)	
occurrences (all)	243	217	
Joint pain			
alternative assessment type: Systematic			
subjects affected / exposed ^[9]	143 / 1648 (8.68%)	93 / 1654 (5.62%)	
occurrences (all)	143	93	
Muscle aches			
alternative assessment type: Systematic			
subjects affected / exposed ^[10]	257 / 1648 (15.59%)	194 / 1654 (11.73%)	
occurrences (all)	257	194	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	145 / 2584 (5.61%)	137 / 2584 (5.30%)	
occurrences (all)	145	137	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	213 / 2584 (8.24%)	231 / 2584 (8.94%)	
occurrences (all)	213	231	

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 only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[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 only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[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 only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[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 only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[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 only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[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 only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[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 only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on Total Vaccinated cohort which included all subjects with the vaccine administration documented and symptom sheet completed only on subjects that reported the specific symptom. Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2011	The overall rationale for this amendment is two-fold. First, the protocol is being amended to implement changes to the protocol of the study's first year (in progress). Second, the amendment also facilitates the use of the protocol for a potential extension of the study to a second year, based on the outcome of a benefit interim analysis planned for the end of the first year.
28 July 2011	The original protocol indicated that the study would conclude at the end of the extended safety follow-up (ESFU) visit. This amended protocol recommends that wherever possible, the ESFU visit (provided it occurs at least six months after the first vaccination) should be scheduled to coincide with the end of the ILI surveillance period so that it will not be necessary to have a separate final contact with subjects at the end of ILI surveillance. However, in the event that subjects in a particular country complete the ESFU visit prior to the end of the ILI surveillance period, this amendment to the protocol adds a final phone contact at the end of the ILI surveillance period to conclude the study. This final phone contact will enable the collection of essential subject data from the subjects for whom the ILI surveillance continues after the ESFU visit and the phone contact will also enable study conclusion for these subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported