



Clinical trial results:

A Phase IV, open label, randomized, monocentric study to evaluate immunogenicity and safety of GSK Biologicals' seasonal (2010-2011) influenza vaccine FluarixTM in adolescents previously vaccinated with GSK Biologicals' H1N1 vaccine (PandemrixTM).

Summary

EudraCT number	2010-020331-39
Trial protocol	FI
Global end of trial date	07 July 2011

Results information

Result version number	v2
This version publication date	05 May 2016
First version publication date	07 March 2015
Version creation reason	• Correction of full data set Data (typos) were corrected in Protection of trial subjects section and some of the endpoints.

Trial information

Trial identification

Sponsor protocol code	114452
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01190215
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue Fleming 20, Wavre, Belgium, 1300
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 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	29 September 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2011
Global end of trial reached?	Yes
Global end of trial date	07 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate HI immune response against the H1N1 strain 28 days following vaccination with TIV vaccine (Fluarix) in subjects previously vaccinated with 1 dose of H1N1 adjuvanted vaccine (Pandemrix) in the TIV Group.

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Only eligible subjects that had no contraindications to any components of the vaccines were vaccinated. Subjects were followed-up until Month 6 after each/last vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 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	Finland: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	0
Adolescents (12-17 years)	77
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

Period 1 title	Up to Day 28
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fluarix Group

Arm description:

Subjects previously vaccinated with Pandemrix vaccine received 1 dose of Fluarix vaccine. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

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

Dosage and administration details:

One Intramuscular injection

Arm title	Havrix Group
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Arm description:

Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Arm type	Active comparator
Investigational medicinal product name	Biological: Havrix TM Junior
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Two Intramuscular injections

Number of subjects in period 1	Fluarix Group	Havrix Group
Started	38	39
Completed	38	39

Period 2

Period 2 title	Up to Month 6
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fluarix Group

Arm description:

Subjects previously vaccinated with Pandemrix vaccine received 1 dose of Fluarix vaccine. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Arm type	Experimental
Investigational medicinal product name	Biological: FluarixTM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects previously vaccinated with Pandemrix vaccine received 1 dose of Fluarix vaccine. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Investigational medicinal product name	Biological: HavrixTM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Arm title	Havrix Group
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Arm description:

Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Arm type	Experimental
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Investigational medicinal product name	Biological: Havrix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Number of subjects in period 2	Fluarix Group	Havrix Group
Started	38	39
Completed	36	39
Not completed	2	0
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Fluarix Group
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Reporting group description:

Subjects previously vaccinated with Pandemrix vaccine received 1 dose of Fluarix vaccine. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Reporting group title	Havrix Group
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Reporting group description:

Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Reporting group values	Fluarix Group	Havrix Group	Total
Number of subjects	38	39	77
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	14.6	14.7	
standard deviation	± 2.22	± 2.28	-
Gender categorical Units: Subjects			
Female	22	19	41
Male	16	20	36

End points

End points reporting groups

Reporting group title	Fluarix Group
Reporting group description: Subjects previously vaccinated with Pandemrix vaccine received 1 dose of Fluarix vaccine. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.	
Reporting group title	Havrix Group
Reporting group description: Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.	
Reporting group title	Fluarix Group
Reporting group description: Subjects previously vaccinated with Pandemrix vaccine received 1 dose of Fluarix vaccine. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.	
Reporting group title	Havrix Group
Reporting group description: Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.	

Primary: Geometric mean antibody titres for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain.

End point title	Geometric mean antibody titres for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain. ^[1]
End point description: Fluarix vaccine strain was Flu A/California/7/2009 (H1N1). Day 28 data were presented only for the Fluarix Group. Titres were expressed as geometric mean antibody titre.	
End point type	Primary
End point timeframe: At Day 0 and Day 28	

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 scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Titres				
geometric mean (confidence interval 95%)				
Flu A/Cal/7/09 H1N1 [Day 0]	150.1 (105.8 to 213)	150.3 (106 to 213.3)		
Flu A/Cal/7/09 H1N1 [Day 28]	646.8 (534.6 to 782.6)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of seropositive subjects for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain.

End point title	Number of seropositive subjects for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain. ^[2]
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End point description:

Fluarix vaccine strain was Flu A/California/7/2009 (H1N1). Seropositivity was assessed for subjects with an antibody titre assay cut-off value equal to or above 1:10. Day 28 data was presented only for the Fluarix Group.

End point type	Primary
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End point timeframe:

At Day 0 and Day 28

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Subjects				
Flu A/Cal/7/09 H1N1 [Day 0]	33	39		
Flu A/Cal/7/09 H1N1 [Day 28]	33	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of seroconverted subjects for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain.

End point title	Number of seroconverted subjects for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain. ^{[3][4]}
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End point description:

Fluarix vaccine strain was Flu A/California/7/2009 (H1N1). A seroconverted subject was a subject who had either a pre-vaccination (Day 0) titre less than ($<$) 1:10 and a post-vaccination titre greater than or equal to ($\geq$) 1:40 or a pre-vaccination titre $\geq$ 1:10 and at least a 4-fold increase in post-vaccination titre. Day 28 data were presented for the Fluarix Group only.

End point type	Primary
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End point timeframe:

At Day 28

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Day 28 data were presented for the Fluarix Group only.

End point values	Fluarix Group			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Subjects				
Flu A/California/7/2009	16			

Statistical analyses

No statistical analyses for this end point

Primary: Number of seroprotected subjects for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain.

End point title	Number of seroprotected subjects for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain. ^[5]
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End point description:

Fluarix vaccine strain was Flu A/California/7/2009 (H1N1). A seroprotected subject was a subject with a serum HI titre $\geq 1:40$ that usually is accepted as indicating protection. Day 28 data were presented for the Fluarix Group only.

End point type	Primary
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End point timeframe:

At Day 0 and Day 28

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 scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Subjects				
Flu A/Cal/7/09 H1N1 [Day 0]	31	36		
Flu A/Cal/7/09 H1N1 [Day 28]	33	0		

Statistical analyses

No statistical analyses for this end point

Primary: Mean geometric increase (MG I) for haemagglutination inhibition (HI) antibodies against Fluarix vaccine containing H1N1 strain.

End point title	Mean geometric increase (MG I) for haemagglutination
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End point description:

Fluarix vaccine strain was Flu A/California/7/2009 (H1N1). MGI is defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titre to the pre-vaccination (Day 0) reciprocal HI titre. Day 28 data were presented for the Fluarix Group only.

End point type Primary

End point timeframe:

At Day 28

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Day 28 data were presented for the Fluarix Group only.

End point values	Fluarix Group			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Ratio				
geometric mean (confidence interval 95%)				
Flu A/Cal/7/09 H1N1	4.3 (2.9 to 6.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean antibody titres for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title Geometric mean antibody titres for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. Day 28 data were presented for the Fluarix Group only. Titres were expressed as geometric mean antibody titres (GMTs). Only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group.

End point type Secondary

End point timeframe:

At Day 0 and Day 28

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Titres				
geometric mean (confidence interval 95%)				
Flu A/Cal/7/09 H1N1 [Day 0]	150.1 (105.8 to 213)	150.3 (106 to 213.3)		

Flu A/Cal/7/09 H1N1 [Day 28]	646.8 (534.6 to 782.6)	0 (0 to 0)		
Flu B/Bri/60/08 Victoria [Day 0]	22.2 (14.7 to 33.5)	21 (14.8 to 30)		
Flu B/Bri/60/08 Victoria [Day 28]	320.1 (216.8 to 472.6)	0 (0 to 0)		
Flu A/Vic/210/09 H3N2 [Day 0]	20 (13 to 30.8)	279.2 (202.1 to 385.8)		
Flu A/Vic/210/09 H3N2 [Day 28]	20.3 (13.9 to 29.8)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean antibody titres for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Geometric mean antibody titres for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. Only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group. Titres were expressed as geometric mean antibody titres (GMTs).

End point type	Secondary
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End point timeframe:

At Day 0 and at Month 6

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Titres				
geometric mean (confidence interval 95%)				
Flu B/Bri/60/08 Victoria [Day 0]	22.9 (15.6 to 33.8)	0 (0 to 0)		
Flu B/Bri/60/08 Victoria [Month 6]	242.4 (173.9 to 337.8)	0 (0 to 0)		
Flu A/Cal/7/09 H1N1 [Day 0]	169.7 (116.2 to 247.8)	152.7 (105.6 to 220.8)		
Flu A/Cal/7/09 H1N1 [Month 6]	346.4 (273.4 to 438.8)	131.4 (92.5 to 186.6)		
Flu A/Vic/210/09 H3N2 [Day 0]	17.9 (12.7 to 25.3)	0 (0 to 0)		
Flu A/Vic/210/09 H3N2 [Month 6]	160.1 (118.1 to 217)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Number of seropositive subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. Seropositivity was assessed for subjects with an antibody titre assay cut-off value equal to or above 1:10. Day 28 data were presented for the Fluarix Group only.

End point type	Secondary
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End point timeframe:

At Day 0 and Day 28

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Subjects				
Flu A/Cal/7/09 H1N1 [Day 0]	33	39		
Flu A/Cal/7/09 H1N1 [Day 28]	33	0		
Flu B/Bri/60/08 Victoria [Day 0]	26	31		
Flu B/Bri/60/08 Victoria [Day 28]	33	0		
Flu A/Vic/210/09 H3N2 [Day 0]	24	28		
Flu A/Vic/210/09 H3N2 [Day 28]	33	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Number of seropositive subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. Seropositivity was assessed for subjects with an antibody titre assay cut-off equal to or above 1:10. Only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group.

End point type	Secondary
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End point timeframe:

At Day 0 and at Month 6

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Subjects				
Flu B/Bri/60/08 Victoria [Day 0]	29	0		
Flu B/Bri/60/08 Victoria [Month 6]	35	0		
Flu A/Cal/7/09 H1N1 [Day 0]	35	37		
Flu A/Cal/7/09 H1N1 [Month 6]	35	37		
Flu A/Vic/210/09 H3N2 [Day 0]	25	0		
Flu A/Vic/210/09 H3N2 [Month 6]	35	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Number of seroconverted subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains. ^[8]
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. A seroconverted subject was a subject who had either a pre-vaccination (Day 0) titre less than ($<$) 1:10 and a post-vaccination titre greater than or equal to ($\geq$) 1:40 or a pre-vaccination titre $\geq$ 1:10 and at least a 4-fold increase in post-vaccination titre. Day 28 data were presented for the Fluarix Group only.

End point type	Secondary
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End point timeframe:

At Day 28

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Day 28 data were presented for the Fluarix Group only.

End point values	Fluarix Group			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Subjects				
Flu A/Cal/7/09 H1N1	16			
Flu B/Bri/60/08 Victoria	28			
Flu A/Vic/210/09 H3N2	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Number of seroconverted subjects for haemagglutination
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. A seroconverted subject was a subject who had either a pre-vaccination (Day 0) titre < 1:10 and a post-vaccination titre ≥ 1:40 or a pre-vaccination titre ≥ 1:10 and at least a 4-fold increase in post-vaccination titre. Only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group.

End point type	Secondary
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End point timeframe:

At Month 6

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Subjects				
Flu B/Bri/60/08 Victoria	29	0		
Flu A/Cal/7/09 H1N1	8	2		
Flu A/Vic/210/09 H3N2	30	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Number of seroprotected subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. A seroprotected subject was a subject with a serum HI titre ≥ 1:40 that usually is accepted as indicating protection. Day 28 data were presented for the Fluarix Group only.

End point type	Secondary
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End point timeframe:

At Day 0 and Day 28

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Subjects				
Flu A/Cal/7/09 H1N1 [Day 0]	31	36		
Flu A/Cal/7/09 H1N1 [Day 28]	33	0		
Flu B/Bri/60/08 Victoria [Day 0]	13	11		
Flu B/Bri/60/08 Victoria [Day 28]	33	0		
Flu A/Vic/210/09 H3N2 [Day 0]	12	16		
Flu A/Vic/210/09 H3N2 [Day 28]	33	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Number of seroprotected subjects for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. A seroprotected subject was a subject with a serum HI titre $\geq 1:40$ that usually is accepted as indicating protection. Only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group.

End point type	Secondary
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End point timeframe:

At Day 0 and Month 6

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Subjects				
Flu B/Bri/60/08 Victoria [Day 0]	13	0		
Flu B/Bri/60/08 Victoria [Month 6]	33	0		
Flu A/Cal/7/09 H1N1 [Day 0]	33	34		
Flu A/Cal/7/09 H1N1 [Month 6]	35	34		
Flu A/Vic/210/09 H3N2 [Day 0]	13	0		
Flu A/Vic/210/09 H3N2 [Month 6]	34	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains. ^[9]
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. MGI is defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titre to the pre-vaccination (Day 0) reciprocal HI titre. Day 28 data were presented for the Fluarix Group only.

End point type	Secondary
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End point timeframe:

At Day 28

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Day 28 data were presented for the Fluarix Group only.

End point values	Fluarix Group			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Ratio				
geometric mean (confidence interval 95%)				
Flu A/Cal/7/09 H1N1	4.3 (2.9 to 6.4)			
Flu B/Bri/60/08 Victoria	14.4 (9.4 to 22)			
Flu A/Vic/210/09 H3N2	14 (9.3 to 21.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.

End point title	Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibodies against all Fluarix vaccine strains.
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008. MGI is defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titre to the pre-vaccination (Day 0) reciprocal HI titre. Only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group.

End point type	Secondary
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End point timeframe:

At Month 6

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Ratio				
geometric mean (confidence interval 95%)				
Flu B/Bri/60/08 Victoria	10.6 (7.5 to 14.9)	0 (0 to 0)		
Flu A/Cal/7/09 H1N1	2 (1.6 to 2.7)	0.9 (0.7 to 1.1)		
Flu A/Vic/210/09 H3N2	8.9 (6.6 to 12)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean antibody titres for neutralising antibodies against all Fluarix vaccine strains.

End point title	Geometric mean antibody titres for neutralising antibodies against all Fluarix vaccine strains.
End point description: Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Perth/16/09(H3N2) and B/Brisbane/60/2008. Day 28 data were presented for the Fluarix Group only. Titres were expressed as geometric mean antibody titres (GMTs).	
End point type	Secondary
End point timeframe: At Day 0 and at Day 28	

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	39		
Units: Titre				
geometric mean (confidence interval 95%)				
Flu B/Bri/60/08 Victoria [Day 0]	26 (20.2 to 33.6)	24.5 (18.9 to 31.9)		
Flu B/Bri/60/08 Victoria [Day 28]	257.9 (158.5 to 419.5)	0 (0 to 0)		
Flu A/Cal/7/09 H1N1 [Day 0]	119.7 (95.2 to 150.5)	137.7 (108 to 175.5)		
Flu A/Cal/7/09 H1N1 [Day 28]	1512.4 (1077.9 to 2122.1)	0 (0 to 0)		
Flu A/Per/16/09 H3N2 [Day 0]	69.8 (50.5 to 96.5)	72.6 (55.2 to 95.5)		
Flu A/Per/16/09 H3N2 [Day 28]	614.5 (371.4 to 1016.7)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean antibody titres for neutralising antibodies against all Fluarix vaccine strains.

End point title	Geometric mean antibody titres for neutralising antibodies against all Fluarix vaccine strains.
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End point description:

Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Perth/16/09 (H3N2) and B/Brisbane/60/2008. Titres were expressed as geometric mean antibody titres (GMTs). Only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group.

End point type	Secondary
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End point timeframe:

At Day 0 and at Month 6

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Titre				
geometric mean (confidence interval 95%)				
Flu B/Bri/60/08 Victoria [Day 0]	25.1 (19.7 to 32.1)	0 (0 to 0)		
Flu B/Bri/60/08 Victoria [Month 6]	199.5 (145.8 to 273)	0 (0 to 0)		
Flu A/Cal/7/09 H1N1 [Day 0]	119.4 (94.5 to 150.8)	138.3 (107.5 to 178)		
Flu A/Cal/7/09 H1N1 [Month 6]	390.6 (291.4 to 523.8)	115.3 (82.4 to 161.4)		
Flu A/Per/16/09 H3N2 [Day 0]	62.5 (49.5 to 78.8)	0 (0 to 0)		
Flu A/Per/16/09 H3N2 [Month 6]	266.8 (173.6 to 410.1)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for neutralising antibodies against all Fluarix vaccine strains.

End point title	Number of seroconverted subjects for neutralising antibodies against all Fluarix vaccine strains. ^[10]
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End point description:

A seroconverted subject for neutralising antibodies was a subject with a minimum 4-fold increase in titre at post-vaccination. Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Perth/16/09 (H3N2) and B/Brisbane/60/2008. Day 28 data were presented for the Fluarix Group only.

End point type	Secondary
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End point timeframe:

At Day 28

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Day 28 data were presented for the Fluarix Group only.

End point values	Fluarix Group			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Subjects				
Flu B/Bri/60/08 Victoria	25			
Flu A/Cal/7/09 H1N1	29			
Flu A/Per/16/09 H3N2	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for neutralising antibodies against all Fluarix vaccine strains.

End point title	Number of seroconverted subjects for neutralising antibodies against all Fluarix vaccine strains.
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End point description:

A seroconverted subject for neutralising antibodies was a subject with a minimum 4-fold increase in titre at post-vaccination. Fluarix vaccine strains were Flu A/California/7/2009 (H1N1), A/Perth/16/09 (H3N2) and B/Brisbane/60/2008. At Month 6, only data for the Flu A/California/7/2009 (H1N1) strain were presented for the Havrix Group.

End point type	Secondary
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End point timeframe:

At Month 6

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Subjects				
Flu B/Bri/60/08 Victoria	28	0		
Flu A/Cal/7/09 H1N1	13	2		
Flu A/Per/16/09 H3N2	17	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and Grade 3 solicited local symptoms.

End point title	Number of subjects reporting any and Grade 3 solicited local symptoms.
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End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of any solicited local symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling above 50 millimetres.

End point type	Secondary
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End point timeframe:

Within 7 days (Day 0 – Day 6) after vaccination

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
Any pain	35	24		
Grade 3 pain	2	0		
Any redness	6	5		
Grade 3 redness	0	0		
Any swelling	5	0		
Grade 3 swelling	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and Grade 3 solicited general symptoms.

End point title	Number of subjects reporting any and Grade 3 solicited general symptoms.
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End point description:

Solicited general symptoms assessed were arthralgia, fatigue, gastrointestinal symptoms, headache, myalgia, shivering, sweating, temperature (temperature = axillary temperature equal to or above 37.5 degrees Celsius). Any = occurrence of any solicited general symptom regardless of intensity grade or relation to vaccination. Grade 3 symptom = general symptom that prevented normal activity. Grade 3 temperature = axillary temperature above 39.0 degrees Celsius.

End point type	Secondary
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End point timeframe:

Within 7 days (Day 0 – Day 6) after vaccination

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
Any arthralgia	4	5		
Grade 3 arthralgia	0	0		
Any fatigue	25	24		
Grade 3 fatigue	1	1		
Any gastrointestinal symptoms	8	3		
Grade 3 gastrointestinal symptoms	2	0		
Any headache	24	16		
Grade 3 headache	1	0		

Any myalgia	16	16		
Grade 3 myalgia	0	1		
Any shivering	18	9		
Grade 3 shivering	0	0		
Any sweating	9	4		
Grade 3 sweating	0	0		
Any temperature $\geq 37.5^{\circ}\text{C}$	4	1		
Grade 3 temperature $> 39.0^{\circ}\text{C}$	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with any solicited local symptoms.

End point title	Number of days with any solicited local symptoms.
End point description: Solicited local symptoms assessed were pain, redness and swelling. Inter-quartile range assessed was the 25th percentile and the 75th percentile.	
End point type	Secondary
End point timeframe: Within 7 days (Day 0 – Day 6) after vaccination	

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Days				
median (inter-quartile range (Q1-Q3))				
Pain	2 (1 to 3)	2 (1 to 2.5)		
Redness	2 (1 to 2)	1 (1 to 2)		
Swelling	2 (2 to 3)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with grade 3 solicited local symptoms.

End point title	Number of days with grade 3 solicited local symptoms.
End point description: Solicited local symptoms assessed were pain and swelling. Grade 3 redness/swelling = redness/swelling above 50 millimetres. Inter-quartile range assessed was the 25th percentile and the 75th percentile.	
End point type	Secondary
End point timeframe: Within 7 days (Day 0 – Day 6) after vaccination	

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Days				
median (inter-quartile range (Q1-Q3))				
Pain	1 (1 to 1)	0 (0 to 0)		
Swelling	1 (1 to 1)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with any solicited general symptoms.

End point title	Number of days with any solicited general symptoms.
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End point description:

Solicited general symptoms assessed were arthralgia, fatigue, gastrointestinal symptoms, headache, myalgia, shivering, sweating, temperature (temperature = axillary temperature equal to or above 37.5 degrees Celsius). Inter-quartile range assessed was the 25th percentile and the 75th percentile.

End point type	Secondary
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End point timeframe:

Within 7 days (Day 0 – Day 6) after vaccination

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Days				
median (inter-quartile range (Q1-Q3))				
Arthralgia	2 (1.5 to 4)	1 (1 to 2)		
Fatigue	2 (1 to 4)	2 (1 to 3)		
Gastrointestinal	1 (1 to 2)	1 (1 to 3)		
Headache	2 (1 to 3)	1 (1 to 2)		
Myalgia	2 (1.5 to 3.5)	2 (1 to 3)		
Sweating	1 (1 to 1)	2 (2 to 2.5)		
Shivering	2 (1 to 4)	1 (1 to 1)		
Temperature	1 (1 to 1.5)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with grade 3 solicited general symptoms.

End point title	Number of days with grade 3 solicited general symptoms.
End point description:	
Solicited general symptoms assessed were fatigue, gastrointestinal symptoms, headache and myalgia. Grade 3 symptom = general symptom that prevented normal activity. Inter-quartile range assessed was the 25th percentile and the 75th percentile.	
End point type	Secondary
End point timeframe:	
Within 7 days (Day 0 – Day 6) after vaccination	

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Days				
median (inter-quartile range (Q1-Q3))				
Fatigue	1 (1 to 1)	1 (1 to 1)		
Gastrointestinal	1 (1 to 1)	0 (0 to 0)		
Headache	1 (1 to 1)	0 (0 to 0)		
Myalgia	0 (0 to 0)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects reporting any, grade 3 and related unsolicited adverse events (AEs).
End point description:	
An unsolicited adverse event is any adverse event (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) 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. Grade 3 = event that prevented normal, everyday activities. Related = event assessed by the investigator as causally related to the study vaccination.	
End point type	Secondary
End point timeframe:	
Within 28 days (Day 0 – Day 27) after vaccination	

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
Any	12	11		
Grade 3	1	2		

Related to vaccination	4	1		
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting medically-attended events (MAEs).

End point title	Number of subjects reporting medically-attended events (MAEs).
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End point description:

For each solicited and unsolicited symptom the subject experienced, the subject was asked if they received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel for any reason.

End point type	Secondary
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End point timeframe:

Within the 28-day (Days 0-27) post-vaccination period

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
MAEs Number	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting medically-attended events (MAEs).

End point title	Number of subjects reporting medically-attended events (MAEs).
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End point description:

For each solicited and unsolicited symptom the subject experienced, the subject was asked if they received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel for any reason.

End point type	Secondary
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End point timeframe:

During the entire study period (Up to Month 6)

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
MAE(s) Number	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting adverse events of specific interest (AESIs)/potential immune mediated diseases (pIMDs).

End point title	Number of subjects reporting adverse events of specific interest (AESIs)/potential immune mediated diseases (pIMDs).
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End point description:

Potential Immune-Mediated Diseases (pIMDs) or Adverse events of specific interest (AESI), are a subset of AEs that include both clearly autoimmune diseases and also other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology.

End point type	Secondary
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End point timeframe:

During the entire study period (Up to Month 6)

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
AESIs/pIMDs Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting adverse events of special interest.

End point title	Number of subjects reporting adverse events of special interest.
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End point description:

Adverse events of special interest for safety monitoring includes both convulsion and anaphylaxis.

End point type	Secondary
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End point timeframe:

During the entire study period (Up to Month 6)

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
AEs of special interest Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs).

End point title	Number of subjects reporting serious adverse events (SAEs).
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End point description:

SAEs assessed include medical occurrences that results in death, are life threatening, require hospitalization or prolongation of hospitalization, results in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subjects.

End point type	Secondary
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End point timeframe:

Within the 28-day (Days 0-27) post-vaccination period

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
Any SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs).

End point title	Number of subjects reporting serious adverse events (SAEs).
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End point description:

SAEs assessed include medical occurrences that results in death, are life threatening, require hospitalization or prolongation of hospitalization, results in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subjects.

End point type	Secondary
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End point timeframe:

During the entire study period (Up to Month 6)

End point values	Fluarix Group	Havrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
Any SAE(s)	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events were assessed up to Day 28 and during the entire study period, up to Month 6. Systematically and non-systematically assessed frequent adverse events were assessed during the 7 day and 28 day post-vaccination period respectively.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Havrix Group
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Reporting group description:

Subjects previously vaccinated with Pandemrix vaccine received 1 first dose of Havrix vaccine (subjects aged above 15 years) or Havrix-Junior vaccine (subjects aged 15 years and below). A second dose was given outside the study setting, at Month 6. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Reporting group title	Fluarix Group
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Reporting group description:

Subjects previously vaccinated with Pandemrix vaccine received 1 dose of Fluarix vaccine. All vaccines were administered in the deltoid region of the non-dominant arm on Day 0.

Serious adverse events	Havrix Group	Fluarix Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	
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	Havrix Group	Fluarix Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 39 (61.54%)	35 / 38 (92.11%)	
Nervous system disorders			
Headache (AE)			

subjects affected / exposed	2 / 39 (5.13%)	1 / 38 (2.63%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 39 (61.54%)	35 / 38 (92.11%)	
occurrences (all)	24	35	
Redness			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 39 (12.82%)	6 / 38 (15.79%)	
occurrences (all)	5	6	
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 39 (0.00%)	5 / 38 (13.16%)	
occurrences (all)	0	5	
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 39 (12.82%)	4 / 38 (10.53%)	
occurrences (all)	5	4	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 39 (61.54%)	25 / 38 (65.79%)	
occurrences (all)	24	25	
Gastrointestinal symptoms			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 39 (7.69%)	8 / 38 (21.05%)	
occurrences (all)	3	8	
Headache (Solicited Symptom)			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 39 (41.03%)	24 / 38 (63.16%)	
occurrences (all)	16	24	
Myalgia			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	16 / 39 (41.03%) 16	16 / 38 (42.11%) 16	
Shivering alternative assessment type: Systematic subjects affected / exposed occurrences (all)	9 / 39 (23.08%) 9	18 / 38 (47.37%) 18	
Sweating alternative assessment type: Systematic subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4	9 / 38 (23.68%) 9	
Temperature alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	4 / 38 (10.53%) 4	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	1 / 38 (2.63%) 1	
Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	3 / 38 (7.89%) 3	

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