EU Clinical Trials Register

Clinical trial results:

A Phase III, placebo-controlled, observer-blind, randomised, multi-centre study to describe the immunogenicity and safety of GSK Biologicals' Quadrivalent Split Virion Influenza Vaccine 2014/2015 Influsplit™ Tetra (Fluarix™ Tetra) (GSK2321138A) when co-administered with Merck & Co. Inc.'s 23-valent pneumococcal polysaccharide vaccine injected intramuscularly in adults 50 years of age and older at risk for complications from influenza and pneumococcal infections.

Summary

EudraCT number	2014-001118-24
Trial protocol	BE FR
Global end of trial date	04 May 2015

Results information

Result version number	v1 (current)
This version publication date	16 December 2016
First version publication date	16 December 2016

Trial information

Trial identification

Sponsor protocol code	117276

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02218697
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium,
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089-904466, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To demonstrate the non-inferiority of the immune response to Influsplit™ Tetra (Fluarix™ Tetra) in terms of HI antibody titres at Day 28 after Influsplit™ Tetra vaccination, for each influenza virus strain, when co-administered with or administered separately from Pneumovax™ 23.
2) To demonstrate the non-inferiority of the humoral immune response to Pneumovax™ 23 in terms of anti-pneumococcal antibody concentrations at 28 days after administration of the pneumococcal vaccine, for six pneumococcal serotypes (1, 3, 4, 7F, 14, 19A) , when co administered with or administered separately from Influsplit™ Tetra.

Protection of trial subjects:

All subjects were observed closely for at least 30 minutes following the administration of the vaccine(s)/placebo, with appropriate medical treatment readily available in case of anaphylaxis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2014
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	Belgium: 100
Country: Number of subjects enrolled	France: 257
Worldwide total number of subjects	357
EEA total number of subjects	357

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)	0
Adults (18-64 years)	236

From 65 to 84 years	80
85 years and over	41

Subject disposition

Recruitment

Recruitment details:

In the Control Group, 2 subjects withdrew at Day 0. In the Co-Ad Group, 4 subjects withdrew at Day 0, 1 subject withdrew at Day 28 and 1 subject withdrew at Day 56.

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. 1 enrolled subject turned out to be questionable and thus, was removed from the study prior to receiving any vaccination.

Period 1

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

Blinding implementation details:

Data will be collected in an observer-blind manner. The laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Group

Arm description:

Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of placebo at Day 0 and 1 dose of Pneumovax™ 23 vaccine at Day 28.

Arm type	Experimental
Investigational medicinal product name	Influsplit™ Tetra
Investigational medicinal product code	
Other name	Fluarix™ Tetra, Alpharix Tetra™
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in deltoid muscle at Day 0, 1 dose each in Control and Co-Ad groups.

Investigational medicinal product name	Pneumovax™ 23
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in deltoid muscle, 1 dose each in Control (at Day 28) and Co-Ad (at Day 0) groups.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline (NaCl)
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in deltoid muscle, 1 dose each in Control (at Day 0) and Co-Ad (at Day 28) groups.

Arm title	Co-Ad Group

Arm description:

Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of Pneumovax™ 23 vaccine at Day 0 and 1 dose of placebo at Day 28.

Arm type	Experimental
Investigational medicinal product name	Influsplit™ Tetra
Investigational medicinal product code	
Other name	Fluarix™ Tetra, Alpharix Tetra™
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in deltoid muscle at Day 0, 1 dose each in Control and Co-Ad groups.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline (NaCl)
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in deltoid muscle, 1 dose each in Control (at Day 0) and Co-Ad (at Day 28) groups.

Investigational medicinal product name	Pneumovax™ 23
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection in deltoid muscle, 1 dose each in Control (at Day 28) and Co-Ad (at Day 0) groups.

Number of subjects in period 1[1]	Control Group	Co-Ad Group
Started	179	177
Completed	177	171
Not completed	2	6
Consent withdrawn by subject	2	3
Adverse event, non-fatal	-	2
Unwilling to be vaccinated in left arm	-	1

Notes:

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

Justification: 1 enrolled subject turned out to be questionable and thus, was removed from the study prior to receiving any vaccination.

Baseline characteristics

Reporting groups

Reporting group title	Control Group
Reporting group description:	
Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of placebo at Day 0 and 1 dose of Pneumovax™ 23 vaccine at Day 28.	
Reporting group title	Co-Ad Group
Reporting group description:	
Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of Pneumovax™ 23 vaccine at Day 0 and 1 dose of placebo at Day 28.	

Reporting group values	Control Group	Co-Ad Group	Total
Number of subjects	179	177	356
Age categorical			
Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	68.4	68.1	
standard deviation	± 9.4	± 9	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	77	76	153
Male	102	101	203
Race/Ethnicity, Customized			
Units: Subjects			
African Heritage / African American	1	2	3
White - Arabic / North African Heritage	3	1	4
White - Caucasian / European Heritage	175	172	347
Mixed Origin	0	2	2

End points

End points reporting groups

Reporting group title	Control Group
Reporting group description:	
Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of placebo at Day 0 and 1 dose of Pneumovax™ 23 vaccine at Day 28.	
Reporting group title	Co-Ad Group
Reporting group description:	
Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of Pneumovax™ 23 vaccine at Day 0 and 1 dose of placebo at Day 28.	

Primary: Humoral immune response in terms of Haemagglutination Inhibition (HI) antibodies titers against the 4 vaccine strains.

End point title	Humoral immune response in terms of Haemagglutination Inhibition (HI) antibodies titers against the 4 vaccine strains.
End point description:	
HI antibody titres were expressed as geometric mean titers (GMTs) and adjusted GMT ratios (Control Group/Co-Ad Group). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), FluA/Texas/50/2012 (H3N2), Flu B/Brisbane/60/2008 (Victoria) and Flu B/Massachusetts/2/2012 (Yamagata).	
End point type	Primary
End point timeframe:	
At Day 28 post Influsplit™ Tetra vaccination	

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	163		
Units: Titers				
geometric mean (confidence interval 95%)				
H1N1	253.2 (205.3 to 312.1)	235.5 (195 to 284.5)		
H3N2	73.6 (62.1 to 87.1)	78.6 (65.2 to 94.7)		
Victoria	178.7 (154.9 to 206.2)	157.9 (136.4 to 182.9)		
Yamagata	346.5 (302.3 to 397.1)	353.8 (310.5 to 403.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	

The adjusted GMT of HI antibodies for H1N1 strain at Day 28 post Influsplit™ Tetra vaccination, the GMT ratio of Control group/Co-Ad group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and

the pre-vaccination titer as covariate.

Comparison groups	Control Group v Co-Ad Group
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.46

Notes:

[1] - Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio (Control Group / Co-Ad Group) does not exceed 2.0.

The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted GMT ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The adjusted GMT of HI antibodies for H3N2 strain at Day 28 post Influsplit™ Tetra vaccination, the GMT ratio of Control group/Co-Ad group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination titer as covariate.

Comparison groups	Control Group v Co-Ad Group
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.21

Notes:

[2] - Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio (Control Group / Co-Ad Group) does not exceed 2.0.

The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted GMT ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

The adjusted GMT of HI antibodies for Victoria strain at Day 28 post Influsplit™ Tetra vaccination, the GMT ratio of Control group/Co-Ad group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination titer as covariate.

Comparison groups	Control Group v Co-Ad Group

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.4

Notes:

[3] - Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio (Control Group / Co-Ad Group) does not exceed 2.0.

The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted GMT ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

The adjusted GMT of HI antibodies for Yamagata strain at Day 28 post Influsplit™ Tetra vaccination, the GMT ratio of Control group/Co-Ad group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination titer as covariate.

Comparison groups	Control Group v Co-Ad Group
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.16

Notes:

[4] - Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio (Control Group / Co-Ad Group) does not exceed 2.0.

The GMTs were used to calculate the Adjusted GMTs, which in turn were used to calculate the Adjusted GMT ratio with 95% confidence interval.

Primary: Pneumococcal vaccine response in terms of anti-pneumococcal antibody concentrations against 6 pneumococcal serotypes (1, 3, 4, 7F, 14 and 19A).

End point title	Pneumococcal vaccine response in terms of anti-pneumococcal antibody concentrations against 6 pneumococcal serotypes (1, 3, 4, 7F, 14 and 19A).

End point description:

Anti-pneumococcal antibody concentrations were expressed as adjusted geometric mean concentrations (GMCs) and adjusted GMC ratio (Control Group/Co-Ad Group).

End point type	Primary

End point timeframe:

At 28 days after Pneumovax™ 23 vaccination

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	162		
Units: ug per ml				
geometric mean (confidence interval 95%)				
Polysaccharide 01 IgG [N=169,162]	5.5 (4.3 to 7)	4.9 (3.9 to 6.2)		
Polysaccharide 03 IgG [N=169,162]	1.7 (1.4 to 2.1)	1.7 (1.4 to 2)		
Polysaccharide 04 IgG [N=169,161]	2.3 (1.8 to 2.9)	1.7 (1.4 to 2.2)		
Polysaccharide 7F IgG [N=169,162]	9 (6.9 to 11.8)	8.1 (6.2 to 10.6)		
Polysaccharide 14 IgG [N=169,162]	20.2 (16 to 25.6)	14.1 (11.3 to 17.6)		
Polysaccharide 19A IgG [N=169,162]	9.2 (7.1 to 11.9)	7.7 (6.1 to 9.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Anti-pneumococcal antibody concentrations for Polysaccharide 01 serotype at Day 28 post Pneumovax™ 23 vaccination, the GMC ratio of Control Group/Co-Ad Group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titres/concentrations, including the vaccine group as fixed effect and the pre-vaccination titre/concentration as covariate.

Comparison groups	Co-Ad Group v Control Group
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.5

Notes:

[5] - Non-inferiority criterion (for each of six pneumococcal serotypes): UL of the 95% CI for the geometric mean concentration (GMC) ratio (Control group over Co-Ad group) does not exceed 2.0.

The GMCs were used to calculate the Adjusted GMCs, which in turn were used to calculate the Adjusted GMC ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Anti-pneumococcal antibody concentrations for Polysaccharide 03 serotype at Day 28 post Pneumovax™ 23 vaccination, the GMC ratio of Control Group/Co-Ad Group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titres/concentrations, including the vaccine group as fixed effect and the pre-vaccination titre/concentration as covariate.

Comparison groups	Co-Ad Group v Control Group

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.45

Notes:

[6] - Non-inferiority criterion (for each of six pneumococcal serotypes): UL of the 95% CI for the geometric mean concentration (GMC) ratio (Control group over Co-Ad group) does not exceed 2.0.

The GMCs were used to calculate the Adjusted GMCs, which in turn were used to calculate the Adjusted GMC ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Anti-pneumococcal antibody concentrations for Polysaccharide 04 serotype at Day 28 post Pneumovax™ 23 vaccination, the GMC ratio of Control Group/Co-Ad Group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titres/concentrations, including the vaccine group as fixed effect and the pre-vaccination titre/concentration as covariate.

Comparison groups	Co-Ad Group v Control Group
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.62

Notes:

[7] - Non-inferiority criterion (for each of six pneumococcal serotypes): UL of the 95% CI for the geometric mean concentration (GMC) ratio (Control group over Co-Ad group) does not exceed 2.0.

The GMCs were used to calculate the Adjusted GMCs, which in turn were used to calculate the Adjusted GMC ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Anti-pneumococcal antibody concentrations for Polysaccharide 7F serotype at Day 28 post Pneumovax™ 23 vaccination, the GMC ratio of Control Group/Co-Ad Group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titres/concentrations, including the vaccine group as fixed effect and the pre-vaccination titre/concentration as covariate.

Comparison groups	Co-Ad Group v Control Group

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.63

Notes:

[8] - Non-inferiority criterion (for each of six pneumococcal serotypes): UL of the 95% CI for the geometric mean concentration (GMC) ratio (Control group over Co-Ad group) does not exceed 2.0.

The GMCs were used to calculate the Adjusted GMCs, which in turn were used to calculate the Adjusted GMC ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Anti-pneumococcal antibody concentrations for Polysaccharide 14 serotype at Day 28 post Pneumovax™ 23 vaccination, the GMC ratio of Control Group/Co-Ad Group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titres/concentrations, including the vaccine group as fixed effect and the pre-vaccination titre/concentration as covariate.

Comparison groups	Co-Ad Group v Control Group
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.57

Notes:

[9] - Non-inferiority criterion (for each of six pneumococcal serotypes): UL of the 95% CI for the geometric mean concentration (GMC) ratio (Control group over Co-Ad group) does not exceed 2.0.

The GMCs were used to calculate the Adjusted GMCs, which in turn were used to calculate the Adjusted GMC ratio with 95% confidence interval.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Anti-pneumococcal antibody concentrations for Polysaccharide 19A serotype at Day 28 post Pneumovax™ 23 vaccination, the GMC ratio of Control Group/Co-Ad Group and the two sided 95% CI were computed by fitting an ANCOVA model on the logarithm10 transformation of the titres/concentrations, including the vaccine group as fixed effect and the pre-vaccination titre/concentration as covariate.

Comparison groups	Co-Ad Group v Control Group

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Method	ANCOVA
Parameter estimate	Adjusted GMC ratio
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.7

Notes:

[10] - Non-inferiority criterion (for each of six pneumococcal serotypes): UL of the 95% CI for the geometric mean concentration (GMC) ratio (Control group over Co-Ad group) does not exceed 2.0.

The GMCs were used to calculate the Adjusted GMCs, which in turn were used to calculate the Adjusted GMC ratio with 95% confidence interval.

Secondary: Number of subjects reporting solicited local adverse events (AEs) after each dose and across doses (AD).

End point title	Number of subjects reporting solicited local adverse events (AEs) after each dose and across doses (AD).

End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of the specified solicited local symptom regardless of its intensity. Grade 3 pain = significant pain at rest and pain that prevented normal everyday activities. Grade 3 redness and swelling = greater than 50 millimeters (mm) i.e. > 100mm.
9999 = placeholder value for group(s) with results not being applicable/missing.

End point type	Secondary

End point timeframe:

Within 7 days (Days 0 - 6) after each vaccination

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	173		
Units: Subjects				
Any Pain, Dose 1 (Influsplit™ Tetra) [N=177,173]	28	58		
Grade 3 Pain, Dose 1 (Influsplit™ Tetra) [N=177,173]	0	2		
Any Pain, Dose 1 (Placebo) [N=176, NA]	10	99999		
Grade 3 Pain, Dose 1 (Placebo) [N=176, NA]	0	99999		
Any Pain, Dose 1 (Pneumovax™ 23) [N= NA,173]	99999	76		
Grade 3 Pain, Dose 1 (Pneumovax™ 23) [N= NA,173]	99999	6		
Any Redness, Dose 1 (Influsplit™ Tetra)[N=177,173]	3	2		
Grade3 Redness, Dose 1 (Influsplit™ Tetra)[N=177,173	0	0		
Any Redness, Dose 1 (Placebo) [N=176,NA]	3	99999		

Grade 3 Redness, Dose 1 (Placebo) [N=176,NA]	0	99999
Any Redness, Dose 1 (Pneumovax™ 23) [N=NA,173]	99999	8
Grade 3 Redness, Dose 1 (Pneumovax™ 23) [N=NA,173]	99999	0
Any Swelling, Dose1 (Influsplit™ Tetra)[N=177,173]	1	3
Grade3 Swelling,Dose1(Influsplit™ Tetra)[N=177,173	0	0
Any Swelling, Dose 1 (Placebo) [N=176,NA]	1	99999
Grade 3 Swelling, Dose 1 (Placebo) [N=176,NA]	0	99999
Any Swelling, Dose 1 (Pneumovax™ 23) [N=NA,173]	99999	7
Grade 3 Swelling,Dose 1 (Pneumovax™ 23) [N=NA,173]	99999	0
Any Pain, Dose 2 (Influsplit™ Tetra) [N=NA,NA]	99999	99999
Grade 3 Pain, Dose 2 (Influsplit™ Tetra) [N=NA,NA]	99999	99999
Any Pain, Dose 2 (Placebo) [N=NA,171]	99999	8
Grade 3 Pain, Dose 2 (Placebo) [N=NA,171]	99999	0
Any Pain, Dose 2 (Pneumovax™ 23) [N= 177,NA]	63	99999
Grade 3 Pain, Dose 2 (Pneumovax™ 23) [N= 177,NA]	8	99999
Any Redness, Dose 2 (Influsplit™ Tetra)[N=NA,NA]	99999	99999
Grade 3 Redness,Dose 2(Influsplit™ Tetra)[N=NA,NA]	99999	99999
Any Redness, Dose 2 (Placebo) [N=NA,171]	99999	1
Grade 3 Redness, Dose 2 (Placebo) [N=NA,171]	99999	0
Any Redness, Dose 2 (Pneumovax™ 23) [N=177,NA]	8	99999
Grade 3 Redness, Dose 2 (Pneumovax™ 23) [N=177,NA]	1	99999
Any Swelling, Dose 2 (Influsplit™ Tetra)[N=NA,NA]	99999	99999
Grade3 Swelling,Dose 2(Influsplit™ Tetra)[N=NA,NA]	99999	99999
Any Swelling, Dose 2 (Placebo) [N=NA,171]	99999	0
Grade 3 Swelling, Dose 2 (Placebo) [N=NA,171]	99999	0
Any Swelling, Dose 2 (Pneumovax™ 23) [N=177,NA]	5	99999
Grade 3 Swelling, Dose 2 (Pneumovax™ 23)[N=177,NA]	1	99999
Any Pain, AD (Influsplit™ Tetra) [N=177,173]	28	58
Grade 3 Pain, AD (Influsplit™Tetra) [N=177,173]	0	2
Any Pain, AD (Placebo) [N=176,171]	10	8
Grade 3 Pain, AD (Placebo) [N=176,171]	0	0
Any Pain, AD (Pneumovax™ 23) [N=177,173]	63	76

Grade 3 Pain, AD (Pneumovax™ 23) [N=177,173]	8	6		
Any Redness, AD (Influsplit™Tetra) [N=177,173]	3	2		
Grade 3 Redness,AD (Influsplit™ Tetra) [N=177,173]	0	0		
Any Redness AD (Placebo) [N=176,171]	3	1		
Grade 3 Redness, AD (Placebo) [N=176,171]	0	0		
Any Redness, AD (Pneumovax™ 23)[N=177,173]	8	8		
Grade 3 Redness, AD (Pneumovax™23) [N=177,173]	1	0		
Any Swelling, AD (Influsplit™Tetra)[N=177,173]	1	3		
Grade 3 Swelling, AD (Influsplit™Tetra)[N=177,173]	0	0		
Any Swelling, AD (Placebo) [N=176,171]	1	0		
Grade 3 Swelling, AD (Placebo)[N=176,171]	0	0		
Any Swelling, AD (Pneumovax™23) [N=177,173]	5	7		
Grade 3 Swelling, AD (Pneumovax™23) [N=177,173]	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited general adverse events (AEs)

End point title	Number of subjects reporting solicited general adverse events (AEs)

End point description:

Solicited general symptoms assessed were fatigue, gastrointestinal symptoms*, headache, joint pain, muscle aches, shivering, sweating and fever. Any was defined as any solicited general symptom reported irrespective of intensity and relationship to vaccination. Grade 3 was defined as symptoms that prevented normal everyday activities. Related was defined as symptoms assessed by the investigator to have a causal relationship to vaccination. Grade 3 fever was defined as temperature greater than (>)39.0°C. *Gastrointestinal (GI) symptoms included nausea, vomiting, diarrhoea and/or abdominal

End point type	Secondary

End point timeframe:

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

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	175		
Units: Subjects				
Any Fatigue, Dose 1 [N=176,173]	30	39		
Grade 3 Fatigue, Dose 1 [N=176,173]	1	2		
Related Fatigue, Dose 1 [N=176,173]	23	33		
Any GI symptoms, Dose 1 [N=176,173]	16	12		

Grade 3 GI symptoms, Dose 1 [N=176,173]	1	1
Related GI symptoms, Dose 1 [N=176,173]	9	5
Any Headache, Dose 1 [N=176,173]	21	20
Grade 3 Headache, Dose 1 [N=176,173]	0	2
Related Headache, Dose 1 [N=176,173]	13	17
Any Joint pain, Dose 1 [N=176,173]	11	16
Grade 3 Joint pain, Dose 1 [N=176,173]	0	0
Related Joint pain, Dose 1 [N=176,173]	6	14
Any Muscle aches, Dose 1 [N=176,173]	15	20
Grade 3 Muscle aches, Dose 1 [N=176,173]	0	1
Related Muscle aches, Dose 1 [N=176,173]	12	19
Any Shivering, Dose 1 [N=176,173]	6	10
Grade 3 Shivering, Dose 1 [N=176,173]	0	1
Related Shivering, Dose 1 [N=176,173]	5	8
Any Sweating, Dose 1 [N=176,173]	11	16
Grade 3 Sweating, Dose 1 [N=176,173]	0	1
Related Sweating, Dose 1 [N=176,173]	9	10
Any Fever, Dose 1 [N=176,173]	0	2
Grade 3 Fever, Dose 1 [N=176,173]	0	1
Related Fever, Dose 1 [N=176,173]	0	2
Any Fatigue, Dose 2 [N=177,171]	25	12
Grade 3 Fatigue, Dose 2 [N=177,171]	1	0
Related Fatigue, Dose 2 [N=177,171]	22	6
Any GI symptoms, Dose 2 [N=177,171]	11	7
Grade 3 GI symptoms, Dose 2 [N=177,171]	0	1
Related GI symptoms, Dose 2 [N=177,171]	9	2
Any Headache, Dose 2 [N=177,171]	18	10
Grade 3 Headache, Dose 2 [N=177,171]	1	0
Related Headache, Dose 2 [N=177,171]	14	3
Any Joint pain, Dose 2 [N=177,171]	17	11
Grade 3 Joint pain, Dose 2 [N=177,171]	1	0
Related Joint pain, Dose 2 [N=177,171]	12	7
Any Muscle aches, Dose 2 [N=177,171]	21	12
Grade 3 Muscle aches, Dose 2 [N=177,171]	4	0
Related Muscle aches, Dose 2 [N=177,171]	19	6
Any Shivering, Dose 2 [N=177,171]	8	5
Grade 3 Shivering, Dose 2 [N=177,171]	1	0
Related Shivering, Dose 2 [N=177,171]	5	3
Any Sweating, Dose 2 [N=177,171]	10	8
Grade 3 Sweating, Dose 2 [N=177,171]	1	0
Related Sweating, Dose 2 [N=177,171]	5	5
Any Fever, Dose 2 [N=177,171]	1	0
Grade 3 Fever, Dose 2 [N=177,171]	0	0
Related Fever, Dose 2 [N=177,171]	1	0
Any Fatigue, Across Doses [N=178,175]	43	43
Grade 3 Fatigue, Across Doses [N=178,175]	2	2

Related Fatigue, Across Doses [N=178,175]	34	37		
Any GI symptoms, Across Doses [N=178,175]	23	17		
Grade 3 GI symptoms, Across Doses [N=178,175]	1	2		
Related GI symptoms, Across Doses [N=178,175]	15	7		
Any Headache, Across Doses [N=178,175]	30	27		
Grade 3 Headache, Across Doses [N=178,175]	1	2		
Related Headache, Across Doses [N=178,175]	22	20		
Any Joint pain, Across Doses [N=178,175]	25	23		
Grade 3 Joint pain, Across Doses [N=178,175]	1	0		
Related Joint pain, Across Doses [N=178,175]	16	20		
Any Muscle aches, Across Doses [N=178,175]	32	28		
Grade 3 Muscle aches, Across Doses [N=178,175]	4	1		
Related Muscle aches, Across Doses [N=178,175]	28	24		
Any Shivering, Across Doses [N=178,175]	13	14		
Grade 3 Shivering, Across Doses [N=178,175]	1	1		
Related Shivering, Across Doses [N=178,175]	9	10		
Any Sweating, Across Doses [N=178,175]	16	19		
Grade 3 Sweating, Across Doses [N=178,175]	1	1		
Related Sweating, Across Doses [N=178,175]	11	14		
Any Fever, Across Doses [N=178,175]	1	2		
Grade 3 Fever, Across Doses [N=178,175]	0	1		
Related Fever, Across Doses [N=178,175]	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of local adverse events

End point title	Duration of local adverse events
End point description:	
Duration was defined as number of days with any grade of local symptoms.	
End point type	Secondary
End point timeframe:	
During the 7-day (Days 0-6) post-vaccination period	

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	90		
Units: Days				
median (full range (min-max))				
Pain, Dose 1 [N=35,90]	2 (1 to 3)	2 (1 to 3)		
Pain, Dose 2 [N=63,8]	2 (1 to 3)	2 (1 to 3)		
Redness, Dose 1 [N=6,9]	4 (3 to 4)	2 (2 to 3)		
Redness, Dose 2 [N=8,1]	2 (1 to 2.5)	1 (1 to 1)		
Swelling, Dose 1 [N=2,9]	4.5 (4 to 5)	2 (2 to 4)		
Swelling, Dose 2 [N=5,0]	3 (1 to 5)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of solicited general AEs.

End point title	Duration of solicited general AEs.
End point description:	
Duration was defined as number of days with any grade of general symptoms.	
End point type	Secondary
End point timeframe:	
During the 7-day (Days 0-6) post-vaccination period	

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	39		
Units: Days				
median (full range (min-max))				
Fatigue, Dose 1 [N=30,39]	2 (1 to 3)	2 (1 to 3)		
Fatigue, Dose 2 [N=25,12]	3 (2 to 4)	3.5 (1.5 to 6.5)		
Gastrointestinal symptoms, Dose 1 [N=16,12]	2 (1 to 4)	2 (1 to 2)		
Gastrointestinal symptoms, Dose 2 [N=11,7]	3 (2 to 3)	3 (2 to 6)		
Headache, Dose 1 [N=21,20]	1 (1 to 2)	1.5 (1 to 2.5)		
Headache, Dose 2 [N=18,10]	2 (1 to 3)	2 (1 to 3)		
Joint pain, Dose 1 [N=11,16]	2 (1 to 3)	2 (1 to 4)		
Joint pain, Dose 2 [N=17,11]	2 (2 to 3)	2 (1 to 7)		
Muscle aches, Dose 1 [N=15,20]	2 (1 to 3)	3 (1.5 to 4.5)		
Muscle aches, Dose 2 [N=21,12]	2 (1 to 3)	2 (1 to 4)		
Sweating, Dose 1 [N=11,16]	2 (1 to 6)	2 (1 to 3.5)		

Sweating, Dose 2 [N=10,8]	2 (1 to 5)	2 (1.5 to 2)		
Shivering, Dose 1 [N=6,10]	2 (1 to 2)	1 (1 to 2)		
Shivering, Dose 2 [N=8,5]	1 (1 to 2)	3 (1 to 3)		
Fever, Dose 1 [N=0,2]	0 (0 to 0)	1 (1 to 1)		
Fever, Dose 2 [N=1,0]	1 (1 to 1)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting the occurrence of medically attended adverse events (MAEs)

End point title	Number of subjects reporting the occurrence of medically attended adverse events (MAEs)

End point description:

MAEs were defined as adverse events with medically-attended visits that were not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Any was defined as any occurrence of MAE(s) regardless of intensity grade or relationship to vaccination. Related was defined as MAE assessed by the investigator to be causally related to the study vaccination.

End point type	Secondary

End point timeframe:

Throughout the study period (Days 0-180)

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	177		
Units: Subjects				
Any MAE(s)	37	43		
Related MAE(s)	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting the occurrence of potential immune mediated diseases (pIMDs)

End point title	Number of subjects reporting the occurrence of potential immune mediated diseases (pIMDs)

End point description:

Potential immune-mediated diseases (pIMDs) were defined as a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. Any was defined as any occurrence of pIMD(s) regardless of intensity grade or relationship to vaccination. Related was defined as pIMD assessed by the investigator to be causally related to the study vaccination.

End point type	Secondary

End point timeframe:

During the entire study period (Days 0-180)

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	177		
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 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 AE was defined as an 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 and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as occurrence of any unsolicited symptom regardless of intensity grade or relation to vaccination.

End point type	Secondary

End point timeframe:

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

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	177		
Units: Subjects				
Any Unsolicited AEs	35	42		
Grade 3 Unsolicited AEs	5	8		
Related Unsolicited AEs	5	5		

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)

End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

End point type	Secondary

End point timeframe:

Throughout the study period (Days 0-180)

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	177		
Units: Subjects				
Any SAE(s)	11	7		
Related SAE(s)	0	0		
Fatal SAE(s)	0	1		
Related Fatal SAE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects by calculating serum antihaemagglutination (HA) antibody titers against the 4 influenza vaccine strains

End point title	Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects by calculating serum antihaemagglutination (HA) antibody titers against the 4 influenza vaccine strains

End point description:

HI antibody titres were expressed as Geometric mean titers (GMTs). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Brisbane/60/2008 (Victoria) and Flu B/Massachusetts/02/2012 (Yamagata).

End point type	Secondary

End point timeframe:

At Day 0 and Day 28

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	163		
Units: Titers				
geometric mean (confidence interval 95%)				
H1N1, Day 0 [N=171,162]	32.4 (26.3 to 39.9)	253.2 (205.3 to 312.1)		

H1N1, Day 28 [N=170,163]	34 (27.8 to 41.7)	235.5 (195 to 284.5)		
H3N2, Day 0 [N=171,162]	20.8 (17.5 to 24.9)	21.8 (18.2 to 26.2)		
H3N2, Day 28 [N=170,162]	73.6 (62.1 to 87.1)	78.6 (65.2 to 94.7)		
Victoria, Day 0 [N=171,162]	48.7 (41.6 to 57.1)	51.5 (43.9 to 60.3)		
Victoria, Day 28 [N=170,162]	178.7 (154.9 to 206.2)	157.9 (136.4 to 182.9)		
Yamagata, Day 0 [N=171,162]	120.7 (104.3 to 139.8)	119.9 (103 to 139.5)		
Yamagata, Day 28 [N=170,162]	346.5 (302.3 to 397.1)	353.8 (310.5 to 403.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains.

End point title	Number of subjects who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains.

End point description:

A seroprotected subject was defined as a vaccinated subject with a serum HI titer greater than or equal to (≥) 1:40 that usually is accepted as indicating protection in adults. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Brisbane/60/2008 (Victoria) and Flu B/Massachusetts/2/2012 (Yamagata).

End point type	Secondary

End point timeframe:

At Day 0 and Day 28

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	163		
Units: Subjects				
H1N1, Day 0 [N=171,162]	83	77		
H1N1, Day 28 [N=170,163]	160	157		
H3N2, Day 0 [N=171,162]	57	50		
H3N2, Day 28 [N=170,162]	131	128		
Victoria, Day 0 [N=171,162]	106	113		
Victoria, Day 28 [N=170,162]	167	154		
Yamagata, Day 0 [N=171,162]	159	146		
Yamagata, Day 28 [N=170,162]	169	162		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains.

End point title	Number of seroconverted subjects for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains.

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 (≥) 1:40, or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Brisbane/60/2008 (Victoria) and Flu B/Massachusetts/02/2012 (Yamagata).

End point type	Secondary

End point timeframe:

At Day 28

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	162		
Units: Subjects				
H1N1	110	101		
H3N2	62	61		
Victoria	73	55		
Yamagata	60	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains.

End point title	Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains.

End point description:

MGI was defined as the fold increase in serum haemagglutination inhibition (HI) GMTs post-vaccination compared to pre-vaccination (Day 0). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Brisbane/60/2008 (Victoria) and Flu B/Massachusetts/02/2012 (Yamagata).

End point type	Secondary

End point timeframe:

At Day 28

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	162		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1	7.7 (6.1 to 9.7)	6.9 (5.5 to 8.6)		
H3N2	3.5 (3 to 4.2)	3.6 (3 to 4.4)		
Victoria	3.6 (3.1 to 4.3)	3.1 (2.6 to 3.6)		
Yamagata	2.8 (2.5 to 3.3)	3 (2.5 to 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-pneumococcal antibody concentrations for the following serotypes: 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C , 19A, 19F and 23F

End point title	Number of subjects with anti-pneumococcal antibody concentrations for the following serotypes: 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C , 19A, 19F and 23F

End point description:

The pneumococcal antigen testing was performed, as determined by ELISA cut-offs of ≥0.05 µg/mL and a seroprotection cut-off of ≥ 0.2 µg/m l. PRE = Pre -vaccination i.e . at Day 0 for Co-Ad Group and at Day 28 for Control Group. POST = Post-vaccination i.e . at Day 28 for C o-Ad Group and at Day 56 for Control Group.

End point type	Secondary

End point timeframe:

At Days 0 (Co-Ad group only), 28 (both groups), and 56 (Control group only)

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	163		
Units: Subjects				
POLYSACCHARIDE 01 AB.IGG (≥ 0.05 MG/ML) (PRE)	162	152		
POLYSACCHARIDE 01 AB.IGG (≥ 0.05 MG/ML) (POST)	169	162		
POLYSACCHARIDE 01 AB.IGG (≥ 0.2 MG/ML) (PRE)	112	118		
POLYSACCHARIDE 01 AB.IGG (≥ 0.2 MG/ML) (POST)	167	159		
POLYSACCHARIDE 03 AB.IGG (≥ 0.05 MG/ML) (PRE)	158	149		
POLYSACCHARIDE 03 AB.IGG (≥ 0.05 MG/ML) (POST)	167	161		
POLYSACCHARIDE 03 AB.IGG (≥ 0.2 MG/ML) (PRE)	114	121		
POLYSACCHARIDE 03 AB.IGG (≥ 0.2 MG/ML) (POST)	158	153		
POLYSACCHARIDE 04 AB.IGG (≥ 0.05 MG/ML) (PRE)	138	129		

POLYSACCHARIDE 04 AB.IGG (≥ 0.05 MG/ML) (POST)	167	158		
POLYSACCHARIDE 04 AB.IGG (≥ 0.2 MG/ML) (PRE)	77	82		
POLYSACCHARIDE 04 AB.IGG (≥ 0.2 MG/ML) (POST)	158	149		
POLYSACCHARIDE 05 AB.IGG5 (≥ 0.05 MG/ML) (PRE)	165	159		
POLYSACCHARIDE 05 AB.IGG5 (≥ 0.05 MG/ML) (POST)	169	162		
POLYSACCHARIDE 05 AB.IGG5 (≥ 0.2 MG/ML) (PRE)	130	115		
POLYSACCHARIDE 05 AB.IGG5 (≥ 0.2 MG/ML) (POST)	163	155		
POLYSACCHARIDE 6B AB.IGG (≥ 0.05 MG/ML) (PRE)	158	149		
POLYSACCHARIDE 6B AB.IGG (≥ 0.05 MG/ML) (POST)	164	160		
POLYSACCHARIDE 6B A B.IGG (≥ 0.2 MG/ML) (PRE)	106	110		
POLYSACCHARIDE 6B AB.IGG (≥ 0.2 MG/ML) (POST)	157	147		
POLYSACCHARIDE 7F AB.IGG (≥ 0.05 MG/ML) (PRE)	159	154		
POLYSACCHARIDE 7F AB.IGG (≥ 0.05 MG/ML) (POST)	169	162		
POLYSACCHARIDE 7F AB.IGG (≥ 0.2 MG/ML) (PRE)	127	130		
POLYSACCHARIDE 7F AB.IGG (≥ 0.2 MG/ML) (POST)	165	161		
POLYSACCHARIDE 9V AB.IGG (≥ 0.05 MG/ML) (PRE)	165	150		
POLYSACCHARIDE 9V AB.IGG (≥ 0.05 MG/ML) (POST)	168	160		
POLYSACCHARIDE 9V AB.IGG (≥ 0.2 MG/ML) (PRE)	123	117		
POLYSACCHARIDE 9V AB.IGG (≥ 0.2 MG/ML) (POST)	166	157		
POLYSACCHARIDE 14 AB.IGG (≥ 0.05 MG/ML) (PRE)	170	163		
POLYSACCHARIDE 14 AB.IGG (≥ 0.05 MG/ML) (POST)	169	162		
POLYSACCHARIDE 14 AB.IGG (≥ 0.2 MG/ML) (PRE)	168	160		
POLYSACCHARIDE 14 AB.IGG (≥ 0.2 MG/ML) (POST)	168	162		
POLYSACCHARIDE 18C AB.IGG (≥ 0.05 MG/ML) (PRE)	166	161		
POLYSACCHARIDE 18C A B.IGG (≥ 0.05 MG/ML) (POST)	169	162		
POLYSACCHARIDE 18C AB.IGG (≥ 0.2 MG/ML) (PRE)	154	148		
POLYSACCHARIDE 18C AB.IGG (≥ 0.2 MG/ML) (POST)	168	159		
POLYSACCHARIDE 19A AB.IGG (≥ 0.05 MG/ML) (PRE)	168	160		
POLYSACCHARIDE 19A AB.IGG (≥ 0.05 MG/ML) (POST)	169	161		
POLYSACCHARIDE 19A AB.IGG (≥ 0.2 MG/ML) (PRE)	146	148		
POLYSACCHARIDE 19A AB.IGG (≥ 0.2 MG/ML) (POST)	165	158		

POLYSACCHARIDE 19F AB.IGG (≥ 0.05 MG/ML) (PRE)	169	160		
POLYSACCHARIDE 19F AB.IGG (≥ 0.05 MG/ML) (POST)	169	162		
POLYSACCHARIDE 19F AB.IGG (≥ 0.2 MG/ML) (PRE)	151	152		
POLYSACCHARIDE 19F AB.IGG (≥ 0.2 MG/ML) (POST)	169	161		
POLYSACCHARIDE 23F AB.IGG (≥ 0.05 MG/ML) (PRE)	151	151		
POLYSACCHARIDE 23F AB.IGG (≥ 0.05 MG/ML) (POST)	165	159		
POLYSACCHARIDE 23F AB.IGG (≥ 0.2 MG/ML) (PRE)	112	125		
POLYSACCHARIDE 23F AB.IGG (≥ 0.2 MG/ML) (POST)	155	147		

Statistical analyses

No statistical analyses for this end point

Secondary: Pneumococcal vaccine response in terms of anti-pneumococcal antibody concentrations a gainst 6 pneumococcal serotype s (1, 3, 4, 7F, 14 a nd 19A).

End point title	Pneumococcal vaccine response in terms of anti-pneumococcal antibody concentrations a gainst 6 pneumococcal serotype s (1, 3, 4, 7F, 14 a nd 19A).

End point description:

Anti-pneumococcal antibody concentrations we re expressed as adjusted geometric mean concentrations (GMC s).
PRE= Pre -vaccination i.e . a t Day 0 for C o-Ad Group and at Day 28 for Control Group. PO ST = Post-vaccination i.e . at Day 28 for Co-Ad Group and at Day 56 for Control Group.

End point type	Secondary

End point timeframe:

At Days 0 (C o-Ad group only), 28 (both groups), and 56 (Control group only)

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	163		
Units: Titers				
geometric mean (confidence interval 95%)				
POLYSACCHARIDE 01 AB.IGG (PRE)	0.4 (0.3 to 0.5)	0.4 (0.3 to 0.5)		
POLYSACCHARIDE 01 AB.IGG (POST)	5.5 (4.3 to 7)	4.9 (3.9 to 6.2)		
POLYSACCHARIDE 03 AB.IGG (PRE)	0.4 (0.3 to 0.5)	0.5 (0.4 to 0.6)		
POLYSACCHARIDE 03 AB.IGG (POST)	1.7 (1.4 to 2.1)	1.7 (1.4 to 2)		
POLYSACCHARIDE 04 AB.IGG (PRE)	0.2 (0.2 to 0.3)	0.2 (0.2 to 0.2)		
POLYSACCHARIDE 04 AB.IGG (POST)	2.3 (1.8 to 2.9)	1.7 (1.4 to 2.2)		
POLYSACCHARIDE 05 AB.IGG5 (PRE)	0.6 (0.5 to 0.7)	0.5 (0.4 to 0.6)		
POLYSACCHARIDE 05 AB.IGG5 (POST)	7.8 (5.9 to 10.4)	5.7 (4.3 to 7.5)		
POLYSACCHARIDE 6B AB.IGG (PRE)	0.4 (0.3 to 0.6)	0.4 (0.3 to 0.6)		

POLYSACCHARIDE 6B AB.IGG (POST)	3.9 (2.9 to 5.1)	3.1 (2.3 to 4.1)
POLYSACCHARIDE 7F AB.IGG (PRE)	0.6 (0.5 to 0.8)	0.7 (0.6 to 0.9)
POLYSACCHARIDE 7F AB.IGG (POST)	9 (6.9 to 11.8)	8.1 (6.2 to 10.6)
POLYSACCHA RIDE 9V AB.IGG (PRE)	0.5 (0.4 to 0.7)	0.5 (0.4 to 0.6)
POLYSACCHARIDE 9V AB.IGG (POST)	5.9 (4.8 to 7.4)	4.4 (3.6 to 5.5)
POLYSACCHA RIDE 14 AB.IGG (PRE)	3.7 (3.1 to 4.6)	2.9 (2.4 to 3.5)
POLYSACCHARIDE 14 AB.IGG (POST)	20.2 (16 to 25.6)	14.1 (11.3 to 17.6)
POLYSACCHARIDE 18C AB.IGG (PRE)	1.4 (1.1 to 1.7)	1.2 (1 to 1.5)
POLYSACCHARIDE 18C AB.IGG (POST)	13.5 (10.7 to 16.8)	11.1 (9 to 13.6)
POLYSACCHARIDE 19A AB.IGG (PRE)	1.3 (1 to 1.6)	1.5 (1.2 to 1.9)
POLYSACCHARIDE 19A AB.IGG (POST)	9.2 (7.1 to 11.9)	7.7 (6.1 to 9.8)
POLYSACCHARIDE 19F AB.IGG (PRE)	1.3 (1.1 to 1.7)	1.4 (1.2 to 1.8)
POLYSACCHARIDE 19F AB.IGG (POST)	11.9 (9.3 to 15.2)	10.6 (8.4 to 13.6)
POLYSACCHARIDE 23F AB.IGG (PRE)	0.4 (0.3 to 0.6)	0.5 (0.4 to 0.7)
POLYSACCHARIDE 23F AB.IGG (POST)	3.1 (2.3 to 4.1)	2.9 (2.2 to 3.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects whose N antibody titers were at least 2 or 4-fold higher than their pre-vaccination titer by anti-pneumococcal serotype subjects.

End point title	Number of subjects whose N antibody titers were at least 2 or 4-fold higher than their pre-vaccination titer by anti-pneumococcal serotype subjects.

End point description:

Fold antibody concentration increases post-vaccination/pre-vaccination ≥ 2 and ≥ 4. The anti-pneumococcal serotypes assessed were 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

End point type	Secondary

End point timeframe:

At 28 days post-vaccination with Pneumovax™ 23

End point values	Control Group	Co-Ad Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	163		
Units: Subjects				
Polysaccharide 01 Ab.IgG (≥ 2)	149	144		
Polysaccharide 01 Ab.IgG (≥ 4)	134	126		
Polysaccharide 03 Ab.IgG (≥ 2)	121	97		
Polysaccharide 03 Ab.IgG (≥ 4)	80	65		
Polysaccharide 04 Ab.IgG (≥ 2)	149	137		
Polysaccharide 04 Ab.IgG (≥ 4)	127	112		
Polysaccharide 05 Ab.IgG5 (≥ 2)	156	138		
Polysaccharide 05 Ab.IgG5 (≥ 4)	127	114		

Polysaccharide 14 Ab.IgG (≥ 2)	123	102		
Polysaccharide 14 Ab.IgG (≥ 4)	90	82		
Polysaccharide 18C Ab.IgG (≥ 2)	149	133		
Polysaccharide 18C Ab.IgG (≥ 4)	123	116		
Polysaccharide 19A Ab.IgG (≥ 2)	133	123		
Polysaccharide 19A Ab.IgG (≥ 4)	111	87		
Polysaccharide 19F Ab.IgG (≥ 2)	146	141		
Polysaccharide 19F Ab.IgG (≥ 4)	111	109		
Polysaccharide 23F Ab.IgG (≥ 2)	133	122		
Polysaccharide 23F Ab.IgG (≥ 4)	108	94		
Polysaccharide 6B Ab.IgG (≥ 2)	141	127		
Polysaccharide 6B Ab.IgG (≥ 4)	113	109		
Polysaccharide 7F Ab.IgG (≥ 2)	155	144		
Polysaccharide 7F Ab.IgG (≥ 4)	138	119		
Polysaccharide 9V Ab.IgG (≥ 2)	146	140		
Polysaccharide 9V Ab.IgG (≥ 4)	131	121		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events: During the entire study period (Day 0 to 180); Solicited local and general symptoms: During the 7-day (Days 0-6) post-vaccination period; Unsolicited adverse events: During the 28-day (Days 0-27) post-vaccination period.

Adverse event reporting additional description:

For the systematically assessed other (non-serious) adverse events, the number of participants at risk included those from Total Vaccinated cohort who had the symptom sheet completed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Control Group

Reporting group description:

Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of placebo at Day 0 and 1 dose of Pneumovax™ 23 vaccine at Day 28.

Reporting group title	Co-Ad Group

Reporting group description:

Subjects received 1 dose of Influsplit™ Tetra vaccine and 1 dose of Pneumovax™ 23 vaccine at Day 0 and 1 dose of placebo at Day 28.

Serious adverse events	Control Group	Co-Ad Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 179 (6.15%)	7 / 177 (3.95%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer metastatic			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer stage ii			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the oral cavity			

subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Calcinosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (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			
Pneumonia aspiration			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Wrist fracture				
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Congenital, familial and genetic disorders				
Intestinal malrotation				
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Arrhythmia				
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac failure				
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardio-respiratory arrest				
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Coronary artery stenosis				
subjects affected / exposed	2 / 179 (1.12%)	0 / 177 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Myocardial infarction				
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (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			
Carotid artery stenosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral thrombosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 179 (0.56%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 179 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control Group	Co-Ad Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 179 (65.36%)	127 / 177 (71.75%)	
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 179 (17.32%)	27 / 177 (15.25%)	
occurrences (all)	41	30	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	13 / 179 (7.26%)	14 / 177 (7.91%)	
occurrences (all)	14	15	
Fatigue			
subjects affected / exposed	43 / 179 (24.02%)	43 / 177 (24.29%)	
occurrences (all)	55	51	
Pain			
subjects affected / exposed	76 / 179 (42.46%)	92 / 177 (51.98%)	
occurrences (all)	98	98	
Swelling			
subjects affected / exposed	6 / 179 (3.35%)	9 / 177 (5.08%)	
occurrences (all)	7	9	

Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	23 / 179 (12.85%)	17 / 177 (9.60%)	
occurrences (all)	27	19	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	13 / 179 (7.26%)	10 / 177 (5.65%)	
occurrences (all)	14	10	
Hyperhidrosis			
subjects affected / exposed	16 / 179 (8.94%)	19 / 177 (10.73%)	
occurrences (all)	21	24	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 179 (13.97%)	25 / 177 (14.12%)	
occurrences (all)	28	30	
Myalgia			
subjects affected / exposed	32 / 179 (17.88%)	28 / 177 (15.82%)	
occurrences (all)	36	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2014	The Agence nationale de sécurité du medicament et des produits de santé (ANSM) of France requires the following criterion be added to Section 6.5 Contraindications to subsequent vaccination "Hypersensitivity or allergy to any of the components of the vaccines". Adverse events being considered for inclusion as potential risks in the Risk Management Plan (RMP) for FLU D-QIV are to be closely monitored during the study. Instructions for follow-up and reporting have been added to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported