Clinical trial results:
A Phase III, Randomized, Observer Blind, Multicenter Study to Evaluate the Safety and Immunogenicity of Repeated Exposure to Either the Same or Alternate Type of Vaccine, Adjuvanted or Non-adjuvanted Quadrivalent Subunit Influenza Virus Vaccine (aQIV or QIV), Administered to Subjects Previously Vaccinated in Trial V118_05

Summary

EudraCT number	2015-002973-39
Trial protocol	FI
Global end of trial date	09 May 2017

Results information

Result version number	v1 (current)
This version publication date	13 March 2019
First version publication date	13 March 2019

Trial information

Trial identification

Sponsor protocol code	V118_05E3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02583256
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seqirus UK Limited
Sponsor organisation address	100 New Bridge Street, London, United Kingdom, EC4V 6JA
Public contact	Clinical Trial Disclosure Manager, Seqirus, seqirus.clinicaltrials@seqirus.com
Scientific contact	Clinical Trial Disclosure Manager, Seqirus, seqirus.clinicaltrials@seqirus.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001715-PIP01-14
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	24 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Immunogenicity Objective(s)

- To demonstrate non-inferiority of Haemagglutination Inhibition (HI) antibody responses to aQIV vs QIV vaccine against each of the 4 homologous strains in terms of Geometric Mean Titer ratio (GMT-ratio) 21 days after vaccination in children who have previously received vaccination with aQIV in parent trial V118_05 (A vs. B). Once the above primary objective is successfully tested the following primary objective will be tested.

- To demonstrate superiority of HI antibody responses to aQIV vs QIV vaccine for at least two out of four homologous strains in terms of GMT-ratio 21 days after vaccination in children who have previously received vaccination with aQIV in parent trial V118_05 (treatment arms A vs B).

Protection of trial subjects:

This clinical study was designed and was implemented and reported in accordance with the International Council for Harmonisation Guideline for Good Clinical Practice (GCP), with applicable local regulations including European Directive 2001/20/EC2, US Code of Federal Regulations Title 213, and Japanese Ministry of Health, Labor, and Welfare, Sponsor codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki4 (European Council 2001, US Code of Federal Regulations, International Council for Harmonisation 2016).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 155
Country: Number of subjects enrolled	Philippines: 846
Country: Number of subjects enrolled	Thailand: 600
Worldwide total number of subjects	1601
EEA total number of subjects	155

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)	54
Children (2-11 years)	1547
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 17 sites in total; 9 sites in Finland, 4 sites in the Philippines and 4 sites in Thailand.

Pre-assignment

Screening details:

All enrolled subjects were included in the study.

Period 1

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

Blinding implementation details:

The study was observer blind. Dedicated unblinded staff was involved in the vaccine administration which allowed the subject (and parent) and the responsible investigator to remain blinded to the treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	aQIV/aQIV

Arm description:

Subjects previously vaccinated with aQIV followed one year later with aQIV.
aQIV = adjuvanted Quadrivalent Influenza Vaccine

Arm type	Experimental
Investigational medicinal product name	Adjuvanted Quadrivalent Influenza Vaccine (aQIV) - surface antigen, inactivated, adjuvanted with MF59
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.5ml (0.25 mL for subjects <36 months)

Arm title	aQIV/QIV

Arm description:

Subjects previously vaccinated with aQIV followed one year later with QIV
QIV = Nonadjuvanted Quadrivalent Influenza Vaccine

Arm type	Experimental
Investigational medicinal product name	Quadrivalent Influenza Vaccine (nonadjuvanted)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.5ml (0.25 mL for subjects <36 months)

Arm title	QIV/aQIV

Arm description:

Subjects previously vaccinated with QIV followed one year later with aQIV
aQIV = adjuvanted Quadrivalent Influenza Vaccine

Arm type	Experimental
Investigational medicinal product name	Adjuvanted Quadrivalent Influenza Vaccine (aQIV) - surface antigen, inactivated, adjuvanted with MF59
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.5ml (0.25 mL for subjects <36 months)

Arm title	QIV/QIV

Arm description:

Subjects previously vaccinated with QIV followed one year later with QIV
QIV: Quadrivalent Influenza Vaccine

Arm type	Active comparator
Investigational medicinal product name	Quadrivalent Influenza Vaccine (nonadjuvanted)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.5ml (0.25 mL for subjects <36 months)

Number of subjects in period 1	aQIV/aQIV	aQIV/QIV	QIV/aQIV
Started	403	403	402
Completed	400	401	400
Not completed	3	2	2
Consent withdrawn by subject	-	1	1
Administrative	2	-	1
Lost to follow-up	1	1	-

Number of subjects in period 1	QIV/QIV
Started	393
Completed	390
Not completed	3
Consent withdrawn by subject	-
Administrative	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	aQIV/aQIV
Reporting group description:	
Subjects previously vaccinated with aQIV followed one year later with aQIV. aQIV = adjuvanted Quadrivalent Influenza Vaccine	
Reporting group title	aQIV/QIV
Reporting group description:	
Subjects previously vaccinated with aQIV followed one year later with QIV QIV = Nonadjuvanted Quadrivalent Influenza Vaccine	
Reporting group title	QIV/aQIV
Reporting group description:	
Subjects previously vaccinated with QIV followed one year later with aQIV aQIV = adjuvanted Quadrivalent Influenza Vaccine	
Reporting group title	QIV/QIV
Reporting group description:	
Subjects previously vaccinated with QIV followed one year later with QIV QIV: Quadrivalent Influenza Vaccine	

Reporting group values	aQIV/aQIV	aQIV/QIV	QIV/aQIV
Number of subjects	403	403	402
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	12	10	17
Children (2-11 years)	391	393	385
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
arithmetic mean	54.4	52.3	53.3
standard deviation	± 17.12	± 17.02	± 17.30
Gender categorical Units: Subjects			
Female	197	189	206
Male	206	214	196
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	402	403	402
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaskan Native	0	0	0

Asian	364	364	362
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	38	36	37
Other	1	3	3
Region of Enrollment			
Units: Subjects			
Finland	39	39	39
Philippines	210	211	213
Thailand	154	153	150
Risk Status			
Subjects with underlying conditions that posed high risk of influenza complications (at risk/not at risk)			
Units: Subjects			
At risk	10	20	18
Not at risk	393	383	384

Reporting group values	QIV/QIV	Total	
Number of subjects	393	1601	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	15	54	
Children (2-11 years)	378	1547	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: months			
arithmetic mean	53.0		
standard deviation	± 16.91	-	
Gender categorical			
Units: Subjects			
Female	178	770	
Male	215	831	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	392	1599	
Unknown or Not Reported	1	1	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaskan Native	0	0	
Asian	355	1445	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	35	146	

Other	3	10	
Region of Enrollment Units: Subjects			
Finland	38	155	
Philippines	212	846	
Thailand	143	600	
Risk Status			
Subjects with underlying conditions that posed high risk of influenza complications (at risk/not at risk)			
Units: Subjects			
At risk	13	61	
Not at risk	380	1540	

End points

End points reporting groups

Reporting group title	aQIV/aQIV
Reporting group description:	
Subjects previously vaccinated with aQIV followed one year later with aQIV. aQIV = adjuvanted Quadrivalent Influenza Vaccine	
Reporting group title	aQIV/QIV
Reporting group description:	
Subjects previously vaccinated with aQIV followed one year later with QIV QIV = Nonadjuvanted Quadrivalent Influenza Vaccine	
Reporting group title	QIV/aQIV
Reporting group description:	
Subjects previously vaccinated with QIV followed one year later with aQIV aQIV = adjuvanted Quadrivalent Influenza Vaccine	
Reporting group title	QIV/QIV
Reporting group description:	
Subjects previously vaccinated with QIV followed one year later with QIV QIV: Quadrivalent Influenza Vaccine	

Primary: Geometric mean titers (GMT) and GMT ratio as determined by HI assay on Day 22 against homologous strains (aQIV-primed comparison) - Noninferiority analysis

End point title	Geometric mean titers (GMT) and GMT ratio as determined by HI assay on Day 22 against homologous strains (aQIV-primed comparison) - Noninferiority analysis[1]

End point description:

GMT and 95% CI were analyzed for Day 22 against homologous strains using ANCOVA with study specific covariates.

Noninferiority criterion for the GMTr: Lower bound of two-sided 95% CI on the ratio of Arm A/Arm B HI GMT should not fall below 0.667.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The immunogenicity per protocol set (PPS) consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2

End point type	Primary

End point timeframe:

Day 22

Notes:

[1] - 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: This endpoint reports results and statistics for the aQIV-primed groups: aQIV/aQIV and aQIV/QIV

End point values	aQIV/aQIV	aQIV/QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	398		
Units: geometric mean titer				
number (confidence interval 95%)				
A/H1N1	1219.00 (1137.35 to 1306.52)	1020.89 (953.22 to 1093.36)		
A/H3N2	2355.52 (2226.19 to 2492.35)	2529.83 (2392.90 to 2674.59)		
B/Yamagata	276.23 (252.73 to 301.92)	232.82 (213.25 to 254.19)		
B/Victoria	388.35 (355.33 to 424.44)	328.42 (300.76 to 358.63)		

Statistical analyses

Statistical analysis title	A/H1N1, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain A/ H1N1.

Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Statistical analysis title	A/H3N2, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain A/H3N2.

Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/aQIV v aQIV/QIV

Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1

Statistical analysis title	B/Yamagata, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain B/Yamagata.

Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/QIV v aQIV/aQIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Statistical analysis title	B/Victoria, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain B/Victoria.

Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Primary: GMT and GMT ratio on as determined by HI assay Day 22 against homologous strains (aQIV-primed comparison) - Superiority Analysis

End point title	GMT and GMT ratio on as determined by HI assay Day 22 against homologous strains (aQIV-primed comparison) - Superiority Analysis[2]

End point description:

GMT and 95% CI were analyzed for Day 22 against homologous strains using ANCOVA with study specific covariates.

Superiority criterion for the GMTr: Lower bound of two-sided 95% CI on the ratio of Arm A/Arm B HI GMT should exceed 1.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The immunogenicity full analysis set (FAS) consisting of all subjects who received a study vaccination and provided immunogenicity data at both Visit 1 (baseline) and at least one post-vaccination visit.

End point type	Primary

End point timeframe:

Day 22

Notes:

[2] - 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: This endpoint reports results and statistics for the aQIV-primed groups: aQIV/aQIV and aQIV/QIV

End point values	aQIV/aQIV	aQIV/QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	403		
Units: geometric mean titer				
number (confidence interval 95%)				
A/H1N1	1218.91 (1137.02 to 1306.70)	1023.37 (955.72 to 1095.81)		
A/H3N2	2345.71 (2216.84 to 2482.07)	2521.60 (2385.43 to 2665.56)		
B/Yamagata	274.75 (251.09 to 300.65)	230.51 (210.97 to 251.86)		
B/Victoria	387.35 (354.15 to 423.66)	326.68 (299.10 to 356.81)		

Statistical analyses

Statistical analysis title	A/H1N1, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain A/ H1N1.

Superiority criterion for the GMT ratio: Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should exceed 1

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	GMT ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Statistical analysis title	A/H3N2, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain A/H3N2.

Superiority criterion for the GMT ratio: Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should exceed 1

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	GMT ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1

Statistical analysis title	B/Yamagata, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain B/Yamagata.

Superiority criterion for the GMT ratio: Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should exceed 1

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	GMT ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Statistical analysis title	B/Victoria, aQIV-aQIV and aQIV-QIV

Statistical analysis description:

Comparison performed for strain B/Victoria.

Superiority criterion for the GMT ratio: Lower bound of two-sided 95% CI on the ratio of aQIV-aQIV/aQIV-QIV HI GMT should exceed 1

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	GMT ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Secondary: Postvaccination HI GMTs and GMT ratio on Day 22 against Homologous Strains (QIV-primed Comparison)

End point title	Postvaccination HI GMTs and GMT ratio on Day 22 against Homologous Strains (QIV-primed Comparison)[3]

End point description:

GMT and 95% CI were analyzed for Day 22 against homologous strains using ANCOVA with study specific covariates.

Noninferiority criterion for the GMTr: Lower bound of two-sided 95% CI on the ratio of Arm A/Arm B HI GMT should not fall below 0.667.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The immunogenicity per protocol set (PPS) consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2

End point type	Secondary

End point timeframe:

Day 22

Notes:

[3] - 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: This endpoint reports results and statistics for the QIV-primed groups: QIV/aQIV and QIV/QIV

End point values	QIV/aQIV	QIV/QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	389		
Units: geometric mean titer				
number (confidence interval 95%)				
A/H1N1	1206.20 (1123.80 to 1294.65)	866.51 (807.30 to 930.06)		
A/H3N2	2369.95 (2236.39 to 2511.48)	2229.48 (2103.42 to 2363.10)		
B/Yamagata	221.54 (202.12 to 242.82)	156.01 (142.32 to 171.02)		
B/Victoria	330.94 (302.38 to 362.21)	244.03 (222.84 to 267.24)		

Statistical analyses

Statistical analysis title	A/H1N1, QIV-aQIV and QIV-QIV

Statistical analysis description:

Comparison performed for strain A/H1N1.

Lower bound of two-sided 95% CI on the ratio of QIV-aQIV/QIV-QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	1.51

Statistical analysis title	A/H3N2, QIV-aQIV and QIV-QIV

Statistical analysis description:

Comparison performed for strain A/H3N2.

Lower bound of two-sided 95% CI on the ratio of QIV-aQIV/QIV-QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV

Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.14

Statistical analysis title	B/Yamagata QIV-aQIV and QIV-QIV

Statistical analysis description:

Comparison performed for strain B/Yamagata.

Lower bound of two-sided 95% CI on the ratio of QIV-aQIV/QIV-QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	1.58

Statistical analysis title	B/Victoria QIV-aQIV and QIV-QIV

Statistical analysis description:

Comparison performed for strain B/Victoria strain.

Lower bound of two-sided 95% CI on the ratio of QIV-aQIV/QIV-QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	1.51

Secondary: Postvaccination HI GMTs and GMTrs on Day 181 against homologous strains (aQIV-primed and QIV-primed comparison)

End point title	Postvaccination HI GMTs and GMTrs on Day 181 against homologous strains (aQIV-primed and QIV-primed comparison)

End point description:

GMT and 95% CI were analyzed for Day 22 against homologous strains using ANCOVA with study specific covariates.

Noninferiority criterion for the GMTr: Lower bound of two-sided 95% CI on the ratio of Arm A/Arm B HI GMT should not fall below 0.667.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The immunogenicity per protocol set (PPS) consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2

End point type	Secondary

End point timeframe:

Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	398	397	389
Units: geometric mean titer				
number (confidence interval 95%)				
A/H1N1	489.45 (449.93 to 532.45)	411.72 (378.83 to 447.46)	429.06 (393.73 to 467.57)	307.36 (282.02 to 334.98)
A/H3N2	1432.38 (1310.04 to 1546.52)	1438.40 (1325.53 to 1560.89)	1233.84 (1133.08 to 1343.56)	1222.21 (1121.92 to 1331.46)
B/Yamagata	97.01 (88.67 to 106.13)	86.43 (79.09 to 94.45)	73.37 (66.88 to 80.49)	56.57 (51.56 to 62.08)
B/Victoria	128.32 (115.17 to 142.97)	115.26 (103.57 to 128.26)	104.93 (94.02 to 117.10)	79.76 (71.41 to 89.09)

Statistical analyses

Statistical analysis title	A/H1N1, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain A/H1N1.

Lower bound of two-sided 95% CI on the ratio of aQIV/aQIV:aQIV/QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/aQIV v aQIV/QIV

Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.32

Statistical analysis title	A/H3N2, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain A/H3N2

Lower bound of two-sided 95% CI on the ratio of aQIV/aQIV:aQIV/QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.09

Statistical analysis title	B/Yamagata, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain B/Yamagata.

Lower bound of two-sided 95% CI on the ratio of QIV/aQIV:aQIV/QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.25

Statistical analysis title	B/Victoria, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain B/Victoria.

Lower bound of two-sided 95% CI on the ratio of aQIV/aQIV:aQIV/QIV HI GMT should not fall below 0.667.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.27

Statistical analysis title	A/H1N1, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain A/H1N1.

Lower bound of two-sided 95% CI on the ratio of QIV/aQIV:QIV/QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	1.5

Statistical analysis title	A/H3N2, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain A/H3N2.

Lower bound of two-sided 95% CI on the ratio of QIV/aQIV:QIV/QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV

Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.1

Statistical analysis title	B/Yamagata, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain B/Yamagata.

Lower bound of two-sided 95% CI on the ratio of QIV/aQIV:QIV/QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.4

Statistical analysis title	B/Victoria, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain B/Victoria.

Lower bound of two-sided 95% CI on the ratio of QIV/aQIV:QIV/QIV HI GMT should not fall below 0.667.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.5

Secondary: Postvaccination Seroconversion Rate (SCR) on Day 22 for the Homologous Strains (aQIV-primed and QIV-primed Comparison)

End point title	Postvaccination Seroconversion Rate (SCR) on Day 22 for the Homologous Strains (aQIV-primed and QIV-primed Comparison)

End point description:

The percentage of subjects achieving seroconversion at Day 22 after vaccination is reported for homologous strains. Seroconversion was defined in subjects seronegative at baseline (i.e. HI titer <1:10 on Day 1) as postvaccination HI titer ≥1:40 and defined in subjects seropositive at baseline (i.e. HI titer ≥1:10 on Day 1) as a minimum of a 4-fold increase in post-vaccination HI titer.

Noninferiority criterion for the GMTr: Lower bound of two-sided 95% CI on the ratio of Arm A/Arm B HI GMT should not fall below 0.667.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The immunogenicity per protocol set (PPS) consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2

End point type	Secondary

End point timeframe:

Day 22

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	398	397	389
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1	62.69 (57.75 to 67.43)	60.86 (55.86 to 65.69)	72.04 (67.35 to 76.40)	62.37 (57.34 to 67.21)
A/H3N2	68.91 (64.13 to 73.40)	68.01 (63.17 to 72.57)	72.80 (68.13 to 77.12)	76.74 (72.21 to 80.86)
B/Yamagata	76.37 (71.91 to 80.44)	72.04 (67.35 to 76.40)	79.44 (75.11 to 83.32)	66.49 (61.51 to 71.21)
B/Victoria	77.36 (72.95 to 81.36)	74.75 (70.17 to 78.95)	77.92 (73.49 to 81.92)	69.55 (64.66 to 74.14)

Statistical analyses

Statistical analysis title	A/H1N1, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain A/H1N1.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	aQIV/aQIV v aQIV/QIV

Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	8.6

Statistical analysis title	A/H3N2, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain A/H3N2.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	7.3

Statistical analysis title	B/Yamagata, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain B/Yamagata.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	10.4

Statistical analysis title	B/Victoria, aQIV/aQIV and aQIV/QIV

Statistical analysis description:

Comparison performed for strain B/Victoria.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	aQIV/aQIV v aQIV/QIV
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	8.5

Statistical analysis title	A/H1N1, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain A/H1N1.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	SCR difference
Point estimate	9.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.11
upper limit	16.17

Statistical analysis title	A/H3N2, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain A/H3N2.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	QIV/aQIV v QIV/QIV

Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	SCR difference
Point estimate	-3.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.02
upper limit	2.15

Statistical analysis title	B/Yamagata, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain B/Yamagata.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	SCR difference
Point estimate	12.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.73
upper limit	19.12

Statistical analysis title	B/Victoria, QIV/aQIV and QIV/QIV

Statistical analysis description:

Comparison performed for strain B/Victoria.

The lower bound of two-sided 95% CI on the difference between SCR should not be below -10%.

Comparison groups	QIV/aQIV v QIV/QIV
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	SCR difference
Point estimate	8.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.17
upper limit	14.54

Secondary: Postvaccination HI Geometric Mean Ratio (GMR) against Homologous Strains

End point title	Postvaccination HI Geometric Mean Ratio (GMR) against Homologous Strains

End point description:

The GMR is the geometric mean of the fold increase in HI titer from Day 1 to Day 22 or Day 181. GMR and 95% CI were analyzed for the homologous strains using ANCOVA with study specific covariates.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The immunogenicity per protocol set (PPS) consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2

End point type	Secondary

End point timeframe:

Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	398	397	389
Units: geometric mean ratio				
number (confidence interval 95%)				
A/H1N1 (Day 22/Day 1)	7.69 (7.17 to 8.24)	6.44 (6.01 to 6.90)	7.61 (7.09 to 8.17)	5.47 (5.09 to 5.87)
A/H1N1 (Day 181/Day 1)	3.11 (2.86 to 3.38)	2.61 (2.40 to 2.84)	2.72 (2.50 to 2.97)	1.95 (1.79 to 2.13)
A/H3N2 (Day 22/Day 1)	9.02 (8.53 to 9.55)	9.69 (9.17 to 10.25)	9.08 (8.57 to 9.62)	8.54 (8.06 to 9.05)
A/H3N2 (Day 181/Day 1)	5.44 (5.01 to 5.91)	5.50 (5.07 to 5.97)	4.72 (4.33 to 5.14)	4.67 (4.29 to 5.09)
B/Yamagata (Day 22/Day 1)	7.81 (7.14 to 8.54)	6.58 (6.03 to 7.19)	6.26 (5.71 to 6.86)	4.41 (4.02 to 4.83)
B/Yamagata (Day 181/Day 1)	2.74 (2.50 to 3.00)	2.44 (2.23 to 2.67)	2.07 (1.89 to 2.27)	1.60 (1.46 to 1.75)
B/Victoria (Day 22/Day 1)	7.86 (7.19 to 8.59)	6.64 (6.09 to 7.26)	6.70 (6.12 to 7.33)	4.94 (4.51 to 5.41)
B/Victoria (Day 181/Day 1)	2.59 (2.33 to 2.89)	2.33 (2.09 to 2.59)	2.12 (1.90 to 2.36)	1.61 (1.44 to 1.80)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HI Titer ≥1:40 on Day 22 and Day 181 against Homologous Strains

End point title	Percentage of Subjects With HI Titer ≥1:40 on Day 22 and Day 181 against Homologous Strains

End point description:

The percentage of subjects achieving HI titer ≥1:40 at Day 22 and Day 181 after vaccination is reported for homologous strains.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	398	397	389
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1 (Day 22)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	99.7 (98.6 to 100.0)
A/H1N1 (Day 181)	100.0 (99.1 to 100.0)	99.2 (97.8 to 99.8)	99.2 (97.8 to 99.8)	95.9 (93.4 to 97.6)
A/H3N2 (Day 22)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)
A/H3N2 (Day 181)	99.8 (98.6 to 100.0)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	98.7 (97.0 to 99.6)
B/Yamagata (Day 22)	98.5 (96.8 to 99.5)	98.7 (97.1 to 99.6)	98.5 (96.7 to 99.4)	96.6 (94.3 to 98.2)
B/Yamagata (Day 181)	94.3 (91.5 to 96.3)	93.9 (91.1 to 96.1)	83.9 (79.9 to 87.4)	76.1 (71.5 to 80.3)
B/Victoria (Day 22)	99.9 (98.6 to 100.0)	100.0 (99.1 to 100.0)	99.5 (98.2 to 99.9)	97.9 (95.9 to 99.1)
B/Victoria (Day 181)	95.3 (92.7 to 97.1)	93.9 (91.1 to 96.1)	86.7 (83.0 to 89.9)	76.9 (72.2 to 80.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HI Titer ≥1:110, ≥1:151, ≥1:215, ≥1:330 and ≥1:629 on Day 22 for the Homologous Strains

End point title	Percentage of Subjects With HI Titer ≥1:110, ≥1:151, ≥1:215, ≥1:330 and ≥1:629 on Day 22 for the Homologous Strains

End point description:

The percentage of subjects achieving HI Titers ≥1:110, ≥1:151, ≥1:215, ≥1:330 and ≥1:629 at Day 22 after vaccination is reported for homologous strains.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:
Day 22

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	398	397	389
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1 ≥1: 110	100.00 (99.1 to 100.0)	100.0 (99.1 to 100.0)	99.7 (98.6 to 100.0)	97.7 (95.6 to 98.9)
A/H1N1 ≥1:151	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	99.5 (98.2 to 99.9)	97.4 (95.3 to 98.8)
A/H1N1 ≥1:215	99.8 (98.6 to 100.0)	99.2 (97.8 to 99.8)	97.5 (95.4 to 98.8)	93.8 (90.9 to 96.0)
A/H1N1 ≥1:330	97.3 (95.2 to 98.6)	93.7 (90.8 to 95.9)	93.2 (90.3 to 95.5)	82.5 (78.3 to 86.1)
A/H1N1 ≥1:629	94.8 (92.1 to 96.7)	87.6 (84.0 to 90.7)	87.9 (84.3 to 91.0)	74.2 (69.6 to 78.5)
A/H3N2 ≥1:110	99.8 (98.6 to 100.0)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	99.5 (98.1 to 99.9)
A/H3N2 ≥1:151	99.8 (98.6 to 100.0)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	99.5 (98.1 to 99.9)
A/H3N2 ≥1:215	99.5 (98.2 to 99.9)	100.0 (99.1 to 100.0)	100.0 (99.1 to 100.0)	97.7 (95.6 to 98.9)
A/H3N2 ≥1:330	99.3 (97.8 to 99.8)	99.7 (98.6 to 100.0)	99.5 (98.2 to 99.9)	95.9 (93.4 to 97.6)
A/H3N2 ≥1:629	99.0 (97.5 to 99.7)	99.7 (98.6 to 100.0)	99.2 (97.8 to 99.8)	95.1 (92.4 to 97.0)
B/Yamagata ≥1:110	90.8 (87.5 to 93.4)	88.4 (84.8 to 91.4)	82.7 (78.6 to 86.3)	68.3 (63.4 to 73.0)
B/Yamagata ≥1:151	87.6 (83.9 to 90.6)	81.6 (77.4 to 85.3)	75.9 (71.4 to 80.0)	59.9 (54.8 to 64.9)
B/Yamagata ≥1:215	69.9 (65.2 to 74.3)	64.2 (59.3 to 69.0)	53.3 (48.2 to 58.3)	38.5 (33.6 to 43.6)
B/Yamagata ≥1:330	44.0 (39.1 to 49.0)	34.3 (29.6 to 39.2)	25.1 (20.9 to 29.7)	14.9 (11.5 to 18.9)
B/Yamagata ≥1:629	27.9 (23.5 to 32.5)	20.9 (17.0 to 25.2)	14.2 (10.9 to 18.1)	7.3 (4.9 to 10.4)
B/Victoria ≥1:110	93.0 (90.1 to 95.3)	89.9 (86.5 to 92.7)	86.0 (82.8 to 89.8)	76.1 (71.5 to 80.3)
B/Victoria ≥1:151	91.3 (88.1 to 93.9)	87.9 (84.3 to 90.9)	83.0 (78.9 to 86.6)	70.6 (65.8 to 75.1)
B/Victoria ≥1:215	79.6 (75.3 to 83.4)	73.4 (69.1 to 78.0)	67.5 (62.6 to 72.1)	53.0 (47.9 to 58.1)
B/Victoria ≥1:330	58.7 (53.7 to 63.6)	48.7 (43.8 to 53.8)	41.9 (37.0 to 46.9)	32.0 (27.4 to 37.0)
B/Victoria ≥1:629	45.3 (40.3 to 50.3)	37.6 (32.8 to 42.6)	34.3 (29.6 to 39.2)	24.1 (19.9 to 28.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Postvaccination HI GMTs on Day 1, Day 22, and Day 181 against Heterologous Strains

End point title	Postvaccination HI GMTs on Day 1, Day 22, and Day 181 against Heterologous Strains

End point description:

GMT and 95% CI were analyzed for Day 22 for the heterologous strains using ANCOVA with study specific covariates.

The two heterologous strains selected for HI testing in this study were the H3N2 strain, A/HongKong/4801/2014 (X-263B), and the B/ Victoria lineage strain, B/Malaysia/2506/2004.

The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 1, Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	57	59	58
Units: geometric mean titer				
number (confidence interval 95%)				
A/H3N2 (Day 1)	97.7 (59.4 to 160.6)	156.6 (96.1 to 255.1)	40.9 (25.3 to 66.0)	91.6 (55.6 to 150.8)
A/H3N2 (Day 22)	2436.1 (2058.0 to 2883.6)	2415.2 (2049.9 to 2845.5)	2225.1 (1872.6 to 2643.8)	2097.2 (1769.7 to 2485.2)
A/H3N2 (Day 181)	898.1 (707.5 to 1139.9)	917.6 (728.2 to 1156.3)	953.2 (746.7 to 1216.6)	791.7 (621.5 to 1008.3)
B/Victoria (Day 1)	33.4 (24.6 to 45.3)	23.8 (17.6 to 32.2)	15.8 (11.8 to 21.2)	15.9 (11.7 to 21.6)
B/Victoria (Day 22)	327.1 (255.7 to 418.4)	248.4 (195.3 to 316.0)	283.2 (222.8 to 359.8)	204.8 (159.6 to 262.8)
B/Victoria (Day 181)	107.1 (79.3 to 144.6)	85.6 (63.9 to 114.7)	77.5 (57.9 to 103.9)	56.0 (41.2 to 76.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Postvaccination HI GMRs for Day 22/Day 1 and Day 181/Day 1 for the Heterologous Strains

End point title	Postvaccination HI GMRs for Day 22/Day 1 and Day 181/Day 1 for the Heterologous Strains

End point description:

The GMR is the geometric mean of the fold increase in HI titer from Day 1 to Day 22 or Day 181. GMR and 95% CI were analyzed for the heterologous strains using ANCOVA with study specific covariates.

The two heterologous strains selected for HI testing in this study were the H3N2 strain, A/Hong Kong/4801/2014 (X-263B), and the B Victoria lineage strain, B/Malaysia/2506/2004.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination

and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	57	59	58
Units: geometric mean ratio				
number (confidence interval 95%)				
A/H3N2 (Day 22/Day 1)	14.67 (12.4 to 17.4)	14.55 (12.3 to 17.1)	13.40 (11.3 to 15.9)	12.63 (10.7 to 15.0)
A/H3N2 (Day 181/Day 1)	5.31 (4.2 to 6.7)	5.42 (4.3 to 6.8)	5.63 (4.4 to 7.2)	4.68 (3.7 to 6.0)
B/Victoria (Day 22/Day 1)	13.40 (10.5 to 17.1)	10.18 (8.0 to 13.0)	11.60 (9.1 to 14.7)	8.39 (6.5 to 10.8)
B/Victoria (Day 181/Day 1)	4.38 (3.2 to 5.9)	3.50 (2.6 to 4.7)	3.17 (2.4 to 4.3)	2.29 (1.7 to 3.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HI Titer ≥1:40 and Seroconversion on Day 22 and Day 181 against Heterologous Strain

End point title	Percentage of Subjects With HI Titer ≥1:40 and Seroconversion on Day 22 and Day 181 against Heterologous Strain

End point description:

The percentage of subjects achieving HI titer ≥1:40 at Day 22 and Day 181 after vaccination and the percentage of subject who experienced seroconversion is reported for homologous strains. Seroconversion was defined in subjects seronegative at baseline (i.e. HI titer <1:10 on Day 1) as post-vaccination HI titer ≥1:40 and defined in subjects seropositive at baseline (i.e. HI titer ≥1:10 on Day 1) as a minimum of a 4-fold increase in post-vaccination HI titer.

The two heterologous strains selected for HI testing in this study were the H3N2 strain, A/Hong Kong/4801/2014 (X-263B), and the B/ Victoria lineage strain, B/Malaysia/2506/2004.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	57	59	58
Units: percentage of subjects				
number (confidence interval 95%)				
HI ≥1:40 A/H3N2 (Day 22)	100.00 (94.0 to 100.00)	100.00 (93.7 to 100.00)	100.00 (93.9 to 100.00)	100.00 (93.8 to 100.00)
HI ≥1:40 A/H3N2 (Day 181)	100.00 (93.8 to 100.00)	100.00 (93.68 to 100.00)	100.00 (93.8 to 100)	98.2 (90.4 to 100)
SCR A/H3N2 (Day 22)	78.3 (65.8 to 87.9)	73.7 (60.3 to 84.5)	83.1 (71.0 to 91.6)	69.0 (55.5 to 80.5)
HI ≥1:40 B/Victoria (Day 22)	98.3 (91.1 to 100.00)	100.00 (93.6 to 100.00)	96.6 (88.3 to 99.6)	98.3 (90.8 to 100)
HI ≥1:40 B/Victoria (Day 181)	91.4 (81.0 to 97.1)	83.6 (71.2 to 92.2)	74.1 (61.0 to 84.7)	64.3 (50.4 to 76.6)
SCR B/Victoria (Day 22)	75.0 (62.1 to 85.3)	82.1 (69.6 to 91.1)	81.4 (69.1 to 90.3)	77.6 (64.7 to 87.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Postvaccination Microneutralization (MN) GMTs on Day 1, Day 22, and Day 181 against Homologous Strains

End point title	Postvaccination Microneutralization (MN) GMTs on Day 1, Day 22, and Day 181 against Homologous Strains

End point description:

To further characterize immune response, MN GMT and 95% CI were analyzed for Day 1, Day 22, and Day 181 for the homologous strains.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 1, Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	60	60	60
Units: geometric mean titer				
number (confidence interval 95%)				
A/H1N1 (Day 1)	264.36 (173.8 to 402.1)	198.13 (127.8 to 307.0)	104.28 (67.0 to 162.3)	140.38 (90.0 to 219.1)
A/H1N1 (Day 22)	2253.81 (1713.5 to 2964.5)	2295.46 (1729.5 to 3046.7)	2992.29 (2238.5 to 3999.9)	1543.54 (1156.5 to 2060.1)
A/H1N1 (Day 181)	727.04 (568.6 to 929.6)	725.35 (560.7 to 938.4)	686.98 (527.2 to 895.2)	412.34 (317.2 to 536.0)

A/H3N2 (Day 1)	160.88 (103.6 to 249.7)	113.74 (71.9 to 180.0)	133.25 (83.8 to 211.8)	97.47 (61.1 to 155.6)
A/H3N2 (Day 22)	5532.06 (4441.7 to 6890.0)	6649.94 (5275.3 to 8382.7)	5019.51 (3978.6 to 6332.8)	4696.37 (3699.4 to 5962.1)
A/H3N2 (Day 181)	2069.22 (1488.8 to 2875.9)	2127.88 (1500.4 to 3017.8)	2138.80 (1505.0 to 3039.5)	1696.57 (1178.4 to 2442.5)
B/Yamagata (Day 1)	29.82 (22.2 to 40.1)	37.99 (27.9 to 51.7)	21.57 (15.8 to 29.5)	21.07 (15.4 to 28.9)
B/Yamagata (Day 22)	388.29 (299.1 to 504.0)	301.39 (229.0 to 396.7)	247.31 (187.6 to 326.0)	197.51 (149.3 to 261.4)
B/Yamagata (Day 181)	107.05 (81.4 to 140.8)	103.59 (77.5 to 138.5)	82.90 (61.9 to 111.0)	56.03 (41.5 to 75.6)
B/Victoria (Day 1)	43.66 (33.1 to 57.6)	43.13 (32.3 to 57.6)	27.96 (20.9 to 37.4)	33.14 (24.7 to 44.4)
B/Victoria (Day 22)	355.63 (271.8 to 465.4)	346.99 (262.6 to 458.5)	338.49 (255.0 to 449.4)	193.09 (145.5 to 256.3)
B/Victoria (Day 181)	124.31 (95.3 to 162.1)	106.08 (80.2 to 140.3)	95.87 (72.1 to 127.5)	60.54 (45.4 to 80.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Postvaccination MN GMR for Day 22/Day 1 and Day 181/Day 1 against Homologous Strains

End point title	Postvaccination MN GMR for Day 22/Day 1 and Day 181/Day 1 against Homologous Strains

End point description:

The GMR is the geometric mean of the fold increase in MN titer from Day 1 to Day 22 or Day 181. GMR and 95% CI were analyzed for the homologous strains using ANCOVA with study specific covariates.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 22/Day 1 and Day 181/Day 1

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	60	60	60
Units: geometric mean ratio				
number (confidence interval 95%)				
A/H1N1 (Day 22/Day 1)	11.85 (9.0 to 15.6)	12.07 (9.1 to 16.0)	15.73 (11.8 to 21.0)	8.11 (6.1 to 10.8)
A/H1N1 (Day 181/Day 1)	3.67 (2.9 to 4.7)	3.66 (2.8 to 4.7)	3.47 (2.7 to 4.5)	2.08 (1.6 to 2.7)

A/H3N2 (Day 22/Day 1)	28.19 (22.6 to 35.1)	33.88 (26.9 to 42.7)	25.57 (20.3 to 32.3)	23.93 (18.8 to 30.4)
A/H3N2 (Day 181/Day 1)	10.63 (7.6 to 14.8)	10.93 (7.7 to 15.5)	10.99 (7.7 to 15.6)	8.72 (6.1 to 12.5)
B/Yamagata (Day 22/Day 1)	14.11 (10.9 to 18.3)	10.95 (8.3 to 14.4)	8.99 (6.8 to 11.8)	7.18 (5.4 to 9.5)
B/Yamagata (Day 181/Day 1)	3.97 (3.0 to 5.2)	3.84 (2.9 to 5.1)	3.07 (2.3 to 4.1)	2.08 (1.5 to 2.8)
B/Victoria (Day 22/Day 1)	9.43 (7.2 to 12.3)	9.20 (7.0 to 12.2)	8.97 (6.8 to 11.9)	5.12 (3.9 to 6.8)
B/Victoria (Day 181/Day 1)	3.25 (2.5 to 4.2)	2.77 (2.1 to 3.7)	2.51 (1.9 to 3.3)	1.58 (1.2 to 2.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Postvaccination Anti-neuraminidase (NA) GMTs on Day 1, Day 22, and Day 181 for the Homologous Strains

End point title	Postvaccination Anti-neuraminidase (NA) GMTs on Day 1, Day 22, and Day 181 for the Homologous Strains

End point description:

To further characterize immune response, adjusted anti-NA GMT and 95% CI were analyzed for Day 1, Day 22,
and Day 181 for the homologous strains.

Strains tested: N1 (PR8 H6N1 California/07/2009), N2 (PR8 H6N2 Switzerl/9715293/2013); B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 1, Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	62	59	60
Units: geometric mean titer				
number (confidence interval 95%)				
N1 (Day 1)	1174.69 (767.8 to 1797.3)	1209.21 (815.7 to 1792.6)	230.09 (154.7 to 342.2)	182.80 (122.7 to 272.2)
N1 (Day 22)	3403.72 (2821.4 to 4106.2)	3161.01 (2654.7 to 3763.9)	3588.43 (2994.0 to 4300.9)	2410.65 (2001.2 to 2903.9)
N1 (Day 181)	2477.65 (1958.9 to 3133.7)	1649.89 (1324.9 to 2054.5)	2018.32 (1610.4 to 2529.5)	870.73 (691.0 to 1097.2)
N2 (Day 1)	204.59 (121.3 to 345.2)	289.86 (178.6 to 470.4)	86.08 (52.8 to 140.3)	86.34 (52.9 to 140.9)

N2 (Day 22)	915.19 (753.5 to 1111.6)	1050.44 (876.7 to 1258.7)	1242.36 (1031.4 to 1496.5)	980.87 (813.8 to 1182.2)
N2 (Day 181)	505.91 (375.2 to 682.2)	565.69 (426.7 to 749.9)	516.51 (388.6 to 686.4)	369.04 (277.5 to 490.8)
B/Yamagata (Day 1)	290.06 (202.3 to 415.8)	282.17 (201.7 to 394.8)	148.35 (106.0 to 207.6)	126.07 (90.0 to 176.6)
B/Yamagata (Day 22)	1288.67 (1094.6 to 1517.2)	1250.88 (1074.3 to 1456.5)	1275.06 (1093.5 to 1486.7)	883.66 (756.1 to 1032.7)
B/Yamagata (Day 181)	727.17 (560.2 to 943.9)	596.62 (467.2 to 762.0)	511.73 (400.7 to 653.5)	391.23 (305.3 to 501.3)
B/Victoria (Day 1)	497.11 (344.3 to 717.7)	548.92 (390.7 to 771.2)	306.48 (217.6 to 431.7)	237.96 (168.7 to 335.6)
B/Victoria (Day 22)	3175.99 (2736.5 to 3686.0)	3336.65 (2906.2 to 3830.8)	3331.87 (2894.6 to 3835.2)	2418.50 (2094.6 to 2792.74)
B/Victoria (Day 181)	1424.38 (1108.1 to 1831.0)	1587.86 (1256.5 to 2006.6)	1443.37 (1140.1 to 1827.3)	1030.77 (810.3 to 1311.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Postvaccination Anti-NA GMR for Day 22/Day 1 and Day 181/Day 1 against Homologous Strains

End point title	Postvaccination Anti-NA GMR for Day 22/Day 1 and Day 181/Day 1 against Homologous Strains

End point description:

The GMR is the geometric mean of the fold increase in anti-NA titer from Day 1 to Day 22 or Day 181. GMR and 95% CI were analyzed for the homologous strains using ANCOVA with study specific covariates.

Strains tested: N1 (PR8 H6N1 California/07/2009), N2 (PR8 H6N2 Switzerl/9715293/2013); B/Victoria Brisbane/60/2008;
B/Yamagata Phuket/3073/2013.

End point type	Secondary

End point timeframe:

Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	62	59	60
Units: geometric mean ratio				
number (confidence interval 95%)				
N1 (Day 22/Day 1)	5.40 (4.5 to 6.5)	5.02 (4.2 to 6.0)	5.70 (4.8 to 6.8)	3.83 (3.2 to 4.6)
N1 (Day 181/Day 1)	3.95 (3.1 to 5.0)	2.63 (2.1 to 3.3)	3.22 (2.6 to 4.0)	1.39 (1.1 to 1.8)
N2 (Day 22/Day 1)	4.51 (3.7 to 5.5)	5.18 (4.3 to 6.2)	6.13 (5.1 to 7.4)	4.84 (4.0 to 5.8)

N2 (Day 181/Day 1)	2.45 (1.8 to 3.3)	2.74 (2.1 to 3.6)	2.50 (1.9 to 3.3)	1.79 (1.3 to 2.4)
B/Yamagata (Day 22/Day 1)	5.75 (4.9 to 6.8)	5.59 (4.8 to 6.5)	5.69 (4.9 to 6.6)	3.95 (3.4 to 4.6)
B/Yamagata (Day 181/Day 1)	3.29 (2.5 to 4.3)	2.70 (2.1 to 3.4)	2.32 (1.81 to 3.0)	1.77 (1.4 to 2.3)
B/Victoria (Day 22/Day 1)	6.81 (5.9 to 7.9)	7.15 (6.2 to 8.2)	7.14 (6.2 to 8.2)	5.18 (4.5 to 6.0)
B/Victoria (Day 181/Day 1)	3.05 (2.4 to 3.9)	3.40 (2.7 to 4.3)	3.09 (2.4 to 3.9)	2.21 (1.7 to 2.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Solicited AEs

End point title	Percentage of Subjects with Solicited AEs

End point description:

Safety was assessed in terms of percentage of subjects reporting solicited AEs up to 7 days after vaccination.

End point type	Secondary

End point timeframe:

Day 1 to Day 7 after vaccination

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	403	402	393
Units: percentage of subjects				
number (not applicable)				
Any Solicited AEs	64.76	50.12	53.48	40.71
Local Solicited AEs	44.67	37.97	36.82	29.52
Systemic Solicited AEs	39.21	24.81	30.85	18.83
Other (antipyretic/analgesic use)	27.54	10.17	16.92	10.43

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Unsolicited AEs

End point title	Percentage of Subjects with Unsolicited AEs

End point description:

Safety of revaccination was assessed in terms of percentage of subjects reporting unsolicited AEs up to 12 months after last vaccination.

Analysis Population: The unsolicited safety set consisting of all subjects who received a study vaccination with documented safety assessments for unsolicited AE data (including those where it was reported/confirmed that no events had occurred).

End point type	Secondary

End point timeframe:

Day 1 to Day 22 after vaccination

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	403	402	393
Units: percentage of subjects				
number (not applicable)				
Unsolicited AEs	54.09	55.33	55.97	52.16
Related Unsolicited AEs	6.20	3.97	5.72	3.82

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Serious Adverse Events (SAE), AEs Leading to Withdrawal, New Onset of Chronic Disease (NOCD), Adverse Event of Special Interest (AESI) and Medically Attended AEs

End point title	Percentage of subjects with Serious Adverse Events (SAE), AEs Leading to Withdrawal, New Onset of Chronic Disease (NOCD), Adverse Event of Special Interest (AESI) and Medically Attended AEs

End point description:

Safety of revaccination was assessed in terms of percentage of subjects reporting SAEs, AEs leading to withdrawal, NOCD, AESI and medically attended AE up to 12 months after last vaccination.

Analysis Population: The unsolicited safety set consisting of all subjects who received a study vaccination with documented safety assessments for unsolicited AE data (including those where it was reported/confirmed that no events had occurred).

End point type	Secondary

End point timeframe:

Day 1 to Day 366

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	403	402	393
Units: percentage of subjects				
number (not applicable)				
SAE	2.48	2.73	1.74	2.04
AE leading to withdrawal	0	0	0	0
NOCD	0.50	0	0	0
AESI	0	0	0	0.25
Medically Attended AE	51.61	54.34	53.98	48.60

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Diagnosis of Failure to Thrive or Short Stature

End point title	Percentage of Subjects With Diagnosis of Failure to Thrive or Short Stature

End point description:

Safety of revaccination was assessed in terms of percentage of subjects reporting diagnosis of failure to thrive or short stature up to 12 months after last vaccination.

Analysis Population: The unsolicited safety set consisting of all subjects who received a study vaccination with documented safety assessments for unsolicited AE data (including those where it was reported/confirmed that no events had occurred).

End point type	Secondary

End point timeframe:

Day 1 to Day 366

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	403	402	393
Units: percentage of subjects				
number (not applicable)				
Diagnosis of Failure to Thrive or Short Stature	0.25	0.74	0.25	0.76

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Percentage of Subjects With Otitis Media, or Pneumonia, or Influenza-like Illness

End point title	Safety Endpoint: Percentage of Subjects With Otitis Media, or Pneumonia, or Influenza-like Illness

End point description:

Safety of revaccination was assessed in terms of percentage of subjects reporting otitis media, or pneumonia, or influenza-like illness up to 12 months after last vaccination.

Analysis Population: The unsolicited safety set consisting of all subjects who received a study vaccination with documented safety assessments for unsolicited AE data (including those where it was reported/confirmed that no events had occurred).

End point type	Secondary

End point timeframe:

Day 1 to Day 366

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	403	403	402	393
Units: percentage of subjects				
number (not applicable)				
otitis media, any event	3.23	3.47	3.73	2.80
pneumonia, any event	1.49	1.49	0.75	1.78
influenza-like illness	7.94	10.17	9.20	7.89

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Percentage of subjects with MN Titer ≥1:20, ≥1:40, ≥1:80, ≥1:160, ≥1:320 and ≥1:640 on Day 22 and Day 181 against homologous strains

End point title	Immunogenicity Endpoint: Percentage of subjects with MN Titer ≥1:20, ≥1:40, ≥1:80, ≥1:160, ≥1:320 and ≥1:640 on Day 22 and Day 181 against homologous strains

End point description:

The percentage of subjects achieving MN titer ≥1:20, ≥1:40, ≥1:80 ≥1:160, ≥1:320 and ≥1:640 at Day 22 and Day 181 after vaccination is reported against homologous strains.

Strains tested: A/H1N1 California/07/2009; A/H3N2 Switzerland/9715293/2013; B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	59	60	59
Units: percentage of subjects				
number (confidence interval 95%)				
A/ H1N1, ≥1:20 (Day 22)	100.00 (93.94 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)
A/ H1N1, ≥1:40 (Day 22)	98.31 (90.91 to 99.96)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)
A/H1N1, ≥1:80 (Day 22)	98.31 (90.91 to 99.96)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	98.31 (90.91 to 99.96)

A/H1N1, ≥1:160 (Day 22)	98.31 (90.91 to 99.96)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	94.92 (85.85 to 98.94)
A/H1N1, ≥1:320 (Day 22)	96.61 (88.29 to 99.59)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	94.92 (85.85 to 98.94)
A/H1N1, ≥1:640 (Day 22)	96.61 (88.29 to 99.59)	98.31 (90.91 to 99.96)	91.67 (81.61 to 97.24)	81.36 (69.09 to 90.31)
A/H1N1, ≥1:20 (Day 181)	100.00 (94.04 to 100.00)	100.00 (93.84 to 100.00)	100.00 (93.84 to 100.00)	98.28 (90.76 to 99.96)
A/H1N1, ≥1:40 (Day 181)	100.00 (94.04 to 100.00)	100.00 (93.84 to 100.00)	100.00 (93.84 to 100.00)	96.55 (88.09 to 99.58)
A/H1N1, ≥1:80 (Day 181)	100.00 (94.04 to 100.00)	100.00 (93.84 to 100.00)	100.00 (93.84 to 100.00)	93.10 (83.27 to 98.09)
A/H1N1, ≥1:160 (Day 181)	96.67 (88.47 to 99.59)	98.28 (90.76 to 99.96)	94.83 (85.62 to 98.92)	81.03 (68.59 to 90.13)
A/H1N1, ≥1:320 (Day 181)	91.67 (81.61 to 97.24)	91.38 (81.02 to 97.14)	84.48 (72.58 to 92.65)	63.79 (50.12 to 76.01)
A/H1N1, ≥1:640 (Day 181)	80.00 (67.67 to 89.22)	63.79 (50.12 to 76.01)	55.17 (41.54 to 68.26)	48.28 (34.95 to 61.78)
A/H3N2, ≥1:20 (Day 22)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	98.28 (90.76 to 99.96)
A/H3N2, ≥1:40 (Day 22)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	98.28 (90.76 to 99.96)
A/H3N2, ≥1:80 (Day 22)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	98.28 (90.76 to 99.96)
A/H3N2, ≥1:160 (Day 22)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	98.28 (90.76 to 99.96)
A/H3N2, ≥1:320 (Day 22)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	96.55 (88.09 to 99.58)
A/H3N2, ≥1:640 (Day 22)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	94.83 (85.62 to 98.92)
A/H3N2, ≥1:20 (Day 181)	100.00 (94.04 to 100.00)	98.28 (90.76 to 99.96)	100.00 (93.84 to 100.00)	98.21 (90.45 to 99.95)
A/H3N2, ≥1:40 (Day 181)	100.00 (94.04 to 100.00)	98.28 (90.76 to 99.96)	100.00 (93.84 to 100.00)	96.43 (87.69 to 99.56)
A/H3N2, ≥1:80 (Day 181)	100.00 (94.04 to 100.00)	98.28 (90.76 to 99.96)	100.00 (93.84 to 100.00)	91.07 (80.38 to 97.04)
A/H3N2, ≥1:160 (Day 181)	96.67 (88.47 to 99.59)	98.28 (90.76 to 99.96)	96.55 (88.09 to 99.58)	89.29 (78.12 to 95.97)
A/H3N2, ≥1:320 (Day 181)	91.67 (81.61 to 97.24)	94.83 (85.62 to 98.92)	93.10 (83.27 to 98.09)	85.71 (73.78 to 93.62)
A/H3N2, ≥1:640 (Day 181)	86.67 (75.41 to 94.06)	86.21 (74.62 to 93.85)	84.48 (72.58 to 92.65)	83.93 (71.67 to 92.38)
B/Yamagata, ≥1:20 (Day 22)	100.00 (94.04 to 100.00)	100.00 (93.94 to 100.00)	96.67 (88.47 to 99.59)	96.55 (88.09 to 99.58)
B/Yamagata, ≥1:40 (Day 22)	98.33 (91.06 to 99.96)	98.31 (90.91 to 99.96)	96.67 (88.47 to 99.59)	93.10 (83.27 to 98.09)
B/Yamagata, ≥1:80 (Day 22)	95.00 (86.08 to 98.96)	96.61 (88.29 to 99.59)	95.00 (86.08 to 98.96)	89.66 (78.83 to 96.11)
B/Yamagata, ≥1:160 (Day 22)	91.67 (81.61 to 97.24)	86.44 (75.02 to 93.96)	78.33 (65.80 to 87.93)	70.69 (57.27 to 81.91)
B/Yamagata, ≥1:320 (Day 22)	75.00 (62.14 to 85.28)	72.88 (59.73 to 83.64)	65.00 (51.60 to 76.87)	50.00 (36.58 to 63.42)
B/Yamagata, ≥1:640 (Day 22)	58.33 (44.88 to 70.93)	47.46 (34.30 to 60.88)	31.67 (20.26 to 44.96)	24.14 (13.87 to 37.17)
B/Yamagata, ≥1:20 (Day 181)	98.33 (91.06 to 99.96)	96.55 (88.09 to 99.58)	93.10 (83.27 to 98.09)	80.36 (67.57 to 89.77)
B/Yamagata, ≥1:40 (Day 181)	93.33 (83.80 to 98.15)	93.10 (83.27 to 98.09)	79.31 (66.65 to 88.83)	71.43 (57.79 to 82.70)
B/Yamagata, ≥1:80 (Day 181)	71.67 (58.56 to 82.55)	72.41 (59.10 to 83.34)	56.90 (43.23 to 69.84)	46.43 (32.99 to 60.26)
B/Yamagata, ≥1:160 (Day 181)	45.00 (32.12 to 58.39)	48.28 (34.95 to 61.78)	32.76 (21.01 to 46.34)	17.86 (8.91 to 30.40)

B/Yamagata, ≥1:320 (Day 181)	25.00 (14.72 to 37.86)	24.14 (13.87 to 37.17)	15.52 (7.35 to 27.42)	7.14 (1.98 to 17.29)
B/Yamagata, ≥1:640 (Day 181)	3.33 (0.41 to 11.53)	8.62 (2.86 to 18.98)	5.17 (1.08 to 14.38)	3.57 (0.44 to 12.31)
B/Victoria, ≥1:20 (Day 22)	98.31 (90.91 to 99.96)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)	98.31 (90.91 to 99.96)
B/Victoria, ≥1:40 (Day 22)	94.92 (85.85 to 98.94)	100.00 (93.94 to 100.00)	96.67 (88.47 to 99.59)	93.22 (83.54 to 98.12)
B/Victoria, ≥1:80 (Day 22)	91.53 (81.32 to 97.19)	96.61 (88.29 to 99.59)	90.00 (79.49 to 96.24)	84.75 (73.01 to 92.78)
B/Victoria, ≥1:160 (Day 22)	86.44 (75.02 to 93.96)	86.44 (75.02 to 93.96)	81.67 (69.56 to 90.48)	69.49 (56.13 to 80.81)
B/Victoria, ≥1:320 (Day 22)	74.58 (61.56 to 85.02)	67.80 (54.36 to 79.38)	58.33 (44.88 to 70.93)	35.59 (23.55 to 49.13)
B/Victoria, ≥1:640 (Day 22)	49.15 (35.89 to 62.50)	42.37 (29.61 to 55.93)	33.33 (21.69 to 46.69)	22.03 (12.29 to 34.73)
B/Victoria, ≥1:20 (Day 181)	100.00 (94.04 to 100.00)	100.00 (93.84 to 100.00)	98.28 (90.76 to 99.96)	96.43 (87.69 to 99.56)
B/Victoria, ≥1:40 (Day 181)	86.67 (75.41 to 94.06)	87.93 (76.70 to 95.01)	74.14 (60.96 to 84.74)	60.71 (46.75 to 73.50)
B/Victoria, ≥1:80 (Day 181)	78.33 (65.80 to 87.93)	63.79 (50.12 to 76.01)	44.83 (31.74 to 58.46)	41.07 (28.10 to 55.02)
B/Victoria, ≥1:160 (Day 181)	58.33 (44.88 to 70.93)	43.10 (30.16 to 56.77)	27.59 (16.66 to 40.90)	23.21 (12.98 to 36.42)
B/Victoria, ≥1:320 (Day 181)	31.67 (20.26 to 44.96)	20.69 (11.17 to 33.35)	18.97 (9.87 to 31.41)	8.93 (2.96 to 19.62)
B/Victoria, ≥1:640 (Day 181)	8.33 (2.76 to 18.39)	15.52 (7.35 to 27.42)	12.07 (4.99 to 23.30)	5.36 (1.12 to 14.87)

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Percentage of subjects achieving anti-NA titers ≥1:20, ≥1:40, ≥1:80, ≥1:160, ≥1:320 and ≥1:640 on Days 22 and 181 against homologous strains

End point title	Immunogenicity Endpoint: Percentage of subjects achieving anti-NA titers ≥1:20, ≥1:40, ≥1:80, ≥1:160, ≥1:320 and ≥1:640 on Days 22 and 181 against homologous strains

End point description:

The percentage of subjects achieving anti-NA titers ≥1:20, ≥1:40, ≥1:80, ≥1:160, ≥1:320 and ≥1:640 on Days 22 and 181 after vaccination is reported against homologous strains.

Strains tested: N1 (PR8 H6N1 California/07/2009), N2 (PR8 H6N2 Switzerl/9715293/2013); B/Victoria Brisbane/60/2008; B/Yamagata Phuket/3073/2013.

Analysis Population: The Immunogenicity PPS consisting of all subjects who received a study vaccination and provided immunogenicity data, and who correctly received the study vaccine, had no major protocol deviations, and did not develop RT-PCR-confirmed influenza infection between baseline and Visit 2.

End point type	Secondary

End point timeframe:

Day 22, Day 181

End point values	aQIV/aQIV	aQIV/QIV	QIV/aQIV	QIV/QIV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	62	59	60
Units: percentage of subjects				
number (confidence interval 95%)				
N1, ≥1:20 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
N1, ≥1:40 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	98.33 (91.06 to 99.96)
N1, ≥1:80 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	98.33 (91.06 to 99.96)
N1, ≥1:160 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	93.33 (83.80 to 98.15)
N1, ≥1:320 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	88.33 (77.43 to 95.18)
N1,≥1:640 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	98.31 (90.91 to 99.96)	85.00 (73.43 to 92.90)
N1, ≥1:20 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.84 to 100.00)	93.33 (83.80 to 98.15)
N1, ≥1:40 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.84 to 100.00)	91.67 (81.61 to 97.24)
N1, ≥1:80 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.84 to 100.00)	86.67 (75.41 to 94.06)
N1, ≥1:160 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	96.55 (88.09 to 99.58)	81.67 (69.56 to 90.48)
N1, ≥1:320 (Day 181)	100.00 (93.51 to 100.00)	96.72 (88.65 to 99.60)	93.10 (83.27 to 98.09)	70.00 (56.79 to 81.15)
N1, ≥1:640 (Day 181)	100.00 (93.51 to 100.00)	93.44 (84.05 to 98.18)	72.41 (59.10 to 83.34)	51.67 (38.39 to 64.77)
N2, ≥1:20 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
N2, ≥1:40 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
N2, ≥1:80 (Day 22)	98.21 (90.45 to 99.95)	100.00 (94.22 to 100.00)	98.31 (90.91 to 99.96)	96.67 (88.47 to 99.59)
N2, ≥1:160 (Day 22)	98.21 (90.45 to 99.95)	100.00 (94.22 to 100.00)	98.31 (90.91 to 99.96)	90.00 (79.49 to 96.24)
N2, ≥1:320 (Day 22)	94.64 (85.13 to 98.88)	96.77 (88.83 to 99.61)	94.92 (85.85 to 98.94)	85.00 (73.43 to 92.90)
N2, ≥1:640 (Day 22)	85.71 (73.78 to 93.62)	88.71 (78.11 to 95.34)	79.66 (67.17 to 89.02)	68.33 (55.04 to 79.74)
N2, ≥1:20 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.04 to 100.00)	100.00 (93.84 to 100.00)	90.00 (79.49 to 96.24)
N2, ≥1:40 (Day 181)	98.18 (90.28 to 99.95)	98.33 (91.06 to 99.96)	89.66 (78.83 to 96.11)	88.33 (77.43 to 95.18)
N2, ≥1:80 (Day 181)	94.55 (84.88 to 98.86)	98.33 (91.06 to 99.96)	86.21 (74.62 to 93.85)	80.00 (67.67 to 89.22)
N2, ≥1:160 (Day 181)	85.45 (73.34 to 93.50)	95.00 (86.08 to 98.96)	81.03 (68.59 to 90.13)	70.00 (56.79 to 81.15)
N2, ≥1:320 (Day 181)	80.00 (67.03 to 89.57)	85.00 (73.43 to 92.90)	67.24 (53.66 to 78.99)	61.67 (48.21 to 73.93)
N2, ≥1:640 (Day 181)	70.91 (57.10 to 82.37)	81.67 (69.56 to 90.48)	55.17 (41.54 to 68.26)	50.00 (36.81 to 63.19)
B/Yamagata, ≥1:20 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
B/Yamagata, ≥1:40 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
B/Yamagata, ≥1:80 (Day 22)	98.21 (90.45 to 99.95)	100.00 (94.13 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
B/Yamagata, ≥1:160 (Day 22)	98.21 (90.45 to 99.95)	100.00 (94.13 to 100.00)	100.00 (93.94 to 100.00)	98.33 (91.06 to 99.96)

B/Yamagata, ≥1:320 (Day 22)	98.21 (90.45 to 99.95)	100.00 (94.13 to 100.00)	96.61 (88.29 to 99.59)	88.33 (77.43 to 95.18)
B/Yamagata, ≥1:640 (Day 22)	91.07 (80.38 to 97.04)	91.80 (81.90 to 97.28)	89.83 (79.17 to 96.18)	66.67 (53.31 to 78.31)
B/Yamagata, ≥1:20 (Day 181)	100.00 (93.51 to 100.00)	98.33 (91.06 to 99.96)	100.00 (93.84 to 100.00)	100.00 (94.04 to 100.00)
B/Yamagata, ≥1:40 (Day 181)	100.00 (93.51 to 100.00)	98.33 (91.06 to 99.96)	98.28 (90.76 to 99.96)	96.67 (88.47 to 99.59)
B/Yamagata, ≥1:80 (Day 181)	100.00 (93.51 to 100.00)	98.33 (91.06 to 99.96)	96.55 (88.09 to 99.58)	90.00 (79.49 to 96.24)
B/Yamagata, ≥1:160 (Day 181)	98.18 (90.28 to 99.95)	96.67 (88.47 to 99.59)	91.38 (81.02 to 97.14)	81.67 (69.56 to 90.48)
B/Yamagata, ≥1:320 (Day 181)	92.73 (82.41 to 97.98)	86.67 (75.41 to 94.06)	84.48 (72.58 to 92.65)	65.00 (51.60 to 76.87)
B/Yamagata, ≥1:640 (Day 181)	72.73 (59.04 to 83.86)	61.67 (48.21 to 73.93)	51.72 (38.22 to 65.05)	40.00 (27.56 to 53.46)
B/Victoria, ≥1:20 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
B/Victoria, ≥1:40 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
B/Victoria, ≥1:80 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
B/Victoria, ≥1:160 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	100.00 (94.04 to 100.00)
B/Victoria, ≥1:320 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	98.33 (91.06 to 99.96)
B/Victoria, ≥1:640 (Day 22)	100.00 (93.62 to 100.00)	100.00 (94.22 to 100.00)	100.00 (93.94 to 100.00)	91.67 (81.61 to 97.24)
B/Victoria, ≥1:20 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.84 to 100.00)	100.00 (94.04 to 100.00)
B/Victoria, ≥1:40 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.84 to 100.00)	100.00 (94.04 to 100.00)
B/Victoria, ≥1:80 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	100.00 (93.84 to 100.00)	100.00 (94.04 to 100.00)
B/Victoria, ≥1:160 (Day 181)	100.00 (93.51 to 100.00)	100.00 (94.13 to 100.00)	96.55 (88.09 to 99.58)	96.67 (88.47 to 99.59)
B/Victoria, ≥1:320 (Day 181)	94.55 (84.88 to 98.86)	100.00 (94.13 to 100.00)	96.55 (88.09 to 99.58)	83.33 (71.48 to 91.71)
B/Victoria, ≥1:640 (Day 181)	89.09 (77.75 to 95.89)	95.08 (86.29 to 98.97)	81.03 (68.59 to 90.13)	70.00 (56.79 to 81.15)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Day 366

Adverse event reporting additional description:

The overall safety set included all subjects who were in the solicited safety set and/or in the unsolicited safety set.
Assessment of revaccination safety included:
SAEs collected between Day 1 to Day 366 Non-serious AEs included solicited AEs collected between Day 1 to Day 7 after last vaccination, and unsolicited AEs collected between Day 1 to

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	aQIV-aQIV

Reporting group description:

Subjects previously vaccinated with aQIV followed by one year later by aQIV.
aQIV = adjuvanted Quadrivalent Influenza Vaccine

Reporting group title	aQIV-QIV

Reporting group description:

Subjects previously vaccinated with aQIV followed one year by QIV
QIV: Nonadjuvanted Quadrivalent Influenza Vaccine

Reporting group title	QIV-aQIV

Reporting group description:

Subjects previously vaccinated with QIV followed one year later by aQIV
aQIV: adjuvanted Quadrivalent Influenza Vaccine

Reporting group title	QIV-QIV

Reporting group description:

Subjects previously vaccinated with QIV followed one year later QIV
QIV: Quadrivalent Influenza Vaccine

Serious adverse events	aQIV-aQIV	aQIV-QIV	QIV-aQIV
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 403 (2.48%)	11 / 403 (2.73%)	7 / 402 (1.74%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 403 (0.25%)	1 / 403 (0.25%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			

subjects affected / exposed	0 / 403 (0.00%)	1 / 403 (0.25%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	1 / 403 (0.25%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	0 / 403 (0.00%)	1 / 403 (0.25%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Spina bifida occulta			
subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 403 (0.25%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			

subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 403 (0.25%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 403 (0.50%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Amoebic dysentery			
subjects affected / exposed	1 / 403 (0.25%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			

subjects affected / exposed	0 / 403 (0.00%)	1 / 403 (0.25%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 403 (0.25%)	1 / 402 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 403 (0.25%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
External ear cellulitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 403 (0.25%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 403 (0.00%)	4 / 403 (0.99%)	4 / 402 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpangina			
subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	1 / 402 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 403 (0.25%)	1 / 403 (0.25%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 403 (0.00%)	1 / 403 (0.25%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			

subjects affected / exposed	0 / 403 (0.00%)	0 / 403 (0.00%)	1 / 402 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 403 (0.00%)	0 / 402 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	QIV-QIV		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 393 (2.04%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 393 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			
subjects affected / exposed	0 / 393 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound secretion			
subjects affected / exposed	0 / 393 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Spina bifida occulta			

subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	0 / 393 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenitis			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 393 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Aphthous ulcer			

subjects affected / exposed	1 / 393 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	0 / 393 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 393 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Amoebic dysentery				
subjects affected / exposed	0 / 393 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendiceal abscess				
subjects affected / exposed	0 / 393 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 393 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dengue fever				
subjects affected / exposed	0 / 393 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
External ear cellulitis				
subjects affected / exposed	0 / 393 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpangina			
subjects affected / exposed	0 / 393 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 393 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 393 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	aQIV-aQIV	aQIV-QIV	QIV-aQIV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	289 / 403 (71.71%)	269 / 403 (66.75%)	274 / 402 (68.16%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	79 / 403 (19.60%)	45 / 403 (11.17%)	55 / 402 (13.68%)
occurrences (all)	154	89	111
General disorders and administration site conditions			

Influenza like illness			
subjects affected / exposed	32 / 403 (7.94%)	41 / 403 (10.17%)	37 / 402 (9.20%)
occurrences (all)	36	43	38
Injection site erythema			
subjects affected / exposed	81 / 403 (20.10%)	57 / 403 (14.14%)	51 / 402 (12.69%)
occurrences (all)	157	114	94
Injection site induration			
subjects affected / exposed	62 / 403 (15.38%)	55 / 403 (13.65%)	38 / 402 (9.45%)
occurrences (all)	117	111	62
Injection site pain			
subjects affected / exposed	163 / 403 (40.45%)	137 / 403 (34.00%)	134 / 402 (33.33%)
occurrences (all)	300	245	254
Pyrexia			
subjects affected / exposed	96 / 403 (23.82%)	46 / 403 (11.41%)	72 / 402 (17.91%)
occurrences (all)	135	80	104
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 403 (5.46%)	8 / 403 (1.99%)	14 / 402 (3.48%)
occurrences (all)	38	14	29
Vomiting			
subjects affected / exposed	29 / 403 (7.20%)	15 / 403 (3.72%)	19 / 402 (4.73%)
occurrences (all)	37	26	33
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	66 / 403 (16.38%)	28 / 403 (6.95%)	52 / 402 (12.94%)
occurrences (all)	147	64	121
Irritability			
subjects affected / exposed	60 / 403 (14.89%)	44 / 403 (10.92%)	50 / 402 (12.44%)
occurrences (all)	126	79	98
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	21 / 403 (5.21%)	19 / 403 (4.71%)	26 / 402 (6.47%)
occurrences (all)	24	23	30
Upper respiratory tract infection			
subjects affected / exposed	78 / 403 (19.35%)	100 / 403 (24.81%)	99 / 402 (24.63%)
occurrences (all)	107	139	138

Non-serious adverse events	QIV-QIV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	229 / 393 (58.27%)		
Nervous system disorders			
Somnolence			
subjects affected / exposed	25 / 393 (6.36%)		
occurrences (all)	51		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	31 / 393 (7.89%)		
occurrences (all)	34		
Injection site erythema			
subjects affected / exposed	39 / 393 (9.92%)		
occurrences (all)	69		
Injection site induration			
subjects affected / exposed	24 / 393 (6.11%)		
occurrences (all)	38		
Injection site pain			
subjects affected / exposed	120 / 393 (30.53%)		
occurrences (all)	191		
Pyrexia			
subjects affected / exposed	51 / 393 (12.98%)		
occurrences (all)	77		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 393 (4.07%)		
occurrences (all)	30		
Vomiting			
subjects affected / exposed	13 / 393 (3.31%)		
occurrences (all)	20		
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	24 / 393 (6.11%)		
occurrences (all)	65		
Irritability			
subjects affected / exposed	36 / 393 (9.16%)		
occurrences (all)	73		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 16 / 393 (4.07%) 16 73 / 393 (18.58%) 91		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2016	• During the conduct of the study there was a transition in the Sponsor responsibilities from Novartis to Seqirus. • The study protocol was aligned with the final SAP. • A secondary immunogenicity objective was added to further characterize the immune response using MN assay on Days 22 and 181 in a subset of subjects. • Additional immunogenicity analysis was included to characterize immune response against heterologous influenza strains in a subset of subjects.
08 February 2017	• Immune response evaluation using anti-NA assay in a subset of subjects for each vaccine group was added as secondary objective (as per Pediatric Investigation Plan commitment to the European Medicines Agency Paediatric Committee). • Inclusion of additional safety evaluations such as occurrence of all-cause mortality, hospitalizations, ILI syndrome, all–cause pneumonia, and otitis media. • In order to align the analysis with the parent study V118_05, an additional subgroup analysis by age group (<24 and ≥24 months of age) was added. • The maximal duration of laboratory samples storage (up to 15 years) was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported