Clinical trial results:
A Phase III, Stratified, Randomized, Observer Blind, Controlled, Multicenter Clinical Study to Evaluate the Safety, Immunogenicity and Efficacy of an Adjuvanted Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Adjuvanted Comparator Influenza Vaccine in Children 6 to < 72 Months of Age

Summary

EudraCT number	2012-000218-12
Trial protocol	FI IT ES
Global end of trial date	09 September 2016

Results information

Result version number	v1 (current)
This version publication date	26 September 2017
First version publication date	26 September 2017

Trial information

Trial identification

Sponsor protocol code	V118_05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01964989
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seqirus UK Limited
Sponsor organisation address	The Point, 29 Market Street, Maidenhead, United Kingdom, SL6 8AA
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	16 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The relative efficacy of aQIV compared to comparator vaccine as determined by RT-PCR-confirmed influenza

Protection of trial subjects:

This clinical study was designed and was to be implemented and reported in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations (CFR) Title 21, and Japanese Ministry of Health, Labor, and Welfare, Seqirus codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki European Council 2001, US CFR, ICH 1997).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2013
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?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 444
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Finland: 648
Country: Number of subjects enrolled	Italy: 215
Country: Number of subjects enrolled	Canada: 182
Country: Number of subjects enrolled	Philippines: 2273
Country: Number of subjects enrolled	Taiwan: 282
Country: Number of subjects enrolled	Thailand: 2040
Country: Number of subjects enrolled	United States: 4508
Worldwide total number of subjects	10644
EEA total number of subjects	1359

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)	2686
Children (2-11 years)	7958
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:

Subjects were enrolled from 146 sites in 9 countries

Pre-assignment

Screening details:

All enrolled subjects were included in the trial

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	aQIV (≥6 to <72 months)

Arm description:

Vaccine non-naïve and naïve subjects ≥6 to <72 months of age who received aQIV

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	TIV/QIV (≥6 to <72 months)

Arm description:

Vaccine non-naïve and naïve subjects ≥6 to <72 months of age who received TIV/QIV

Arm type	Experimental
Investigational medicinal product name	Inactivated Trivalent/Quadrivalent Influenza Virus Vaccine
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 (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)
Started	5352	5292
Completed	4568	4545
Not completed	784	747
Adverse event, serious fatal	1	3
Consent withdrawn by subject	156	160
Adverse event, non-fatal	-	1
Other	267	252
Lost to follow-up	254	232
Administrative reason	103	95
Protocol deviation	3	4

Baseline characteristics

Reporting groups	
Reporting group title	aQIV (≥6 to <72 months)
Reporting group description:	
Vaccine non-naïve and naïve subjects ≥6 to <72 months of age who received aQIV	
Reporting group title	TIV/QIV (≥6 to <72 months)
Reporting group description:	
Vaccine non-naïve and naïve subjects ≥6 to <72 months of age who received TIV/QIV	

Reporting group values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)	Total
Number of subjects	5352	5292	10644
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)	1322	1364	2686
Children (2-11 years)	4030	3928	7958
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	38.4	38	
standard deviation	± 18.43	± 18.4	-
Gender categorical Units: Subjects			
Female	2643	2590	5233
Male	2709	2702	5411

End points

End points reporting groups

Reporting group title	aQIV (≥6 to <72 months)
Reporting group description:	
Vaccine non-naïve and naïve subjects ≥6 to <72 months of age who received aQIV	
Reporting group title	TIV/QIV (≥6 to <72 months)
Reporting group description:	
Vaccine non-naïve and naïve subjects ≥6 to <72 months of age who received TIV/QIV	
Subject analysis set title	All Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All screened subjects who provided informed consent and provided demographic and/or other baseline screening measurements, were randomized and received a subject ID.	
Subject analysis set title	Full Analysis Set (FAS) - Efficacy
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the Enrolled Set who actually received a study vaccination and were evaluated for efficacy at least 21 days after the last vaccination.	
Subject analysis set title	FAS - Immunogenicity
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS Immunogenicity (or FAS Immunogenicity Homologous): All subjects in the Enrolled Set selected for Immunogenicity Subset during randomization, who received a study vaccination AND provided evaluable serum samples for both before (baseline) and after vaccination to test against vaccine strains	
Subject analysis set title	FAS Immunogenicity Heterologous
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the Enrolled Set selected for Immunogenicity Subset during randomization, who received a study vaccination AND provided evaluable serum samples for both before (baseline) and after vaccination to test against heterologous strains.	
Subject analysis set title	aQIV (≥6 to <24 months) - FAS Efficacy
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects ≥6 to <24 months in the Enrolled Set who actually received aQIV and were evaluated for efficacy at least 21 days after the last vaccination	
Subject analysis set title	TIV/QIV (≥6 to <24 months) - FAS Efficacy
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects ≥6 to <24 months in the Enrolled Set who actually received TIV/QIV and were evaluated for efficacy at least 21 days after the last vaccination	
Subject analysis set title	aQIV (≥6 to <36 months) - FAS Efficacy
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects ≥6 to <36 months in the Enrolled Set who actually received aQIV and were evaluated for efficacy at least 21 days after the last vaccination	
Subject analysis set title	TIV/QIV (≥6 to <36 months) - FAS Efficacy
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects ≥6 to <36 months in the Enrolled Set who actually received TIV/QIV and were evaluated for efficacy at least 21 days after the last vaccination	
Subject analysis set title	aQIV (≥36 to <72 months) - FAS Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects ≥36 to <72 months in the Enrolled Set who actually received aQIV and were evaluated for efficacy at least 21 days after the last vaccination

Subject analysis set title	TIV/QIV (≥36 to <72 months) - FAS Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects ≥36 to <72 months in the Enrolled Set who actually received TIV/QIV and were evaluated for efficacy at least 21 days after the last vaccination

Primary: Efficacy Endpoint: First-Occurrence RT-PCR confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age

End point title	Efficacy Endpoint: First-Occurrence RT-PCR confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age

End point description:

Relative efficacy of aQIV compared to non-adjuvanted comparator (TIV/QIV) was determined by the number of subjects ≥6 to <72 months of age with RT-PCR confirmed occurrence of influenza A and/or B of any influenza strain that occurred at ≥21 days and ≤ 180 days after the last vaccination. Relative vaccine efficacy was calculated as relative vaccine efficacy=1-Hazard Ratio

Efficacy was determined on influenza cases caused by any of the influenza strains related to the two A subtypes and the B lineage(s) common to aQIV and TIV (i.e. A/H1N1, A/H3N2 and B/Yamagata during first influenza season), and common to aQIV and QIV (i.e. A/H1N1, A/H3N2 and both B lineages during second season and through the end of the trial)

End point type	Primary

End point timeframe:

≥21 days and ≤ 180 days after last vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5278	5193		
Units: Subjects	256	252		

Statistical analyses

Statistical analysis title	Relative vaccine efficacy (≥6 to <72 months)

Statistical analysis description:

rVE = (1-HR) is the relative vaccine efficacy of aQIV and HR is defined as hazard ratio between aQIV and non adjuvanted comparator.

Comparison groups	aQIV (≥6 to <72 months) v TIV/QIV (≥6 to <72 months)
Number of subjects included in analysis	10471
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox Proportional Hazard regression
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.81
upper limit	15.41

Secondary: Efficacy Endpoint: First-Occurrence RT-PCR confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months, ≥6 to <24 months, ≥6 to <36 months and ≥36 to <72 months of age

End point title	Efficacy Endpoint: First-Occurrence RT-PCR confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months, ≥6 to <24 months, ≥6 to <36 months and ≥36 to <72 months of age

End point description:

Relative efficacy of aQIV compared to non-adjuvanted comparator (TIV/QIV) was determined by the number of subjects with RT-PCR confirmed occurrence of influenza A and/or B of any influenza strain that occurred at ≥21 days and ≤ 180 days after the last vaccination or until the end of the influenza season, whichever was longer.

Efficacy was determined on influenza cases caused by any of the influenza strains related to the two A subtypes and the B lineage(s) common to aQIV and TIV (i.e. A/H1N1, A/H3N2 and B/Yamagata during first influenza season), and common to aQIV and QIV (i.e. A/H1N1, A/H3N2 and both B lineages during second season and through the end of the trial)

End point type	Secondary

End point timeframe:

≥21 days and ≤ 180 days after last vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)	aQIV (≥6 to <24 months) - FAS Efficacy	TIV/QIV (≥6 to <24 months) - FAS Efficacy
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5278	5193	1299	1339
Units: Subjects				
A/H1N1	7	17	2	5
A/H3N2	200	196	44	66
B/Yamagata	36	36	5	9
B/Victoria	14	9	4	0

End point values	aQIV (≥6 to <36 months) - FAS Efficacy	TIV/QIV (≥6 to <36 months) - FAS Efficacy	aQIV (≥36 to <72 months) - FAS Efficacy	TIV/QIV (≥36 to <72 months) - FAS Efficacy
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2484	2471	2794	2722
Units: Subjects				
A/H1N1	5	8	2	9
A/H3N2	92	99	108	97
B/Yamagata	13	12	23	24
B/Victoria	5	1	9	8

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy Endpoint: First-Occurrence culture confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months, ≥6 to <24 months, ≥6 to <36 months and ≥36 to <72 months of age

End point title	Efficacy Endpoint: First-Occurrence culture confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months, ≥6 to <24 months, ≥6 to <36 months and ≥36 to <72 months of age

End point description:

Relative efficacy of aQIV compared to non-adjuvanted comparator (TIV/QIV) was determined by the number of subjects with culture confirmed occurrence of influenza A and/or B of any influenza strain that occurred at ≥21 days and ≤ 180 days after the last vaccination or until the end of the influenza season, whichever was longer.

Efficacy was determined on influenza cases caused by any of the influenza strains related to the two A subtypes and the B lineage(s) common to aQIV and TIV (i.e. A/H1N1, A/H3N2 and B/Yamagata during first influenza season), and common to aQIV and QIV (i.e. A/H1N1, A/H3N2 and both B lineages during second season and through the end of the trial).

End point type	Secondary

End point timeframe:

≥21 days and ≤ 180 days after last vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)	aQIV (≥6 to <24 months) - FAS Efficacy	TIV/QIV (≥6 to <24 months) - FAS Efficacy
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5278	5193	1299	1339
Units: subjects	140	146	31	48

End point values	aQIV (≥6 to <36 months) - FAS Efficacy	TIV/QIV (≥6 to <36 months) - FAS Efficacy	aQIV (≥36 to <72 months) - FAS Efficacy	TIV/QIV (≥36 to <72 months) - FAS Efficacy
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2484	2471	2794	2722
Units: subjects	64	68	76	78

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy Endpoint: First-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age at ≥7 days and at ≥14 days after first vaccination up to the day of second vaccination in vaccine naïve subjects only

End point title	Efficacy Endpoint: First-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72

	months of age at ≥7 days and at ≥14 days after first vaccination up to the day of second vaccination in vaccine naïve subjects only

End point description:

Relative efficacy of aQIV compared to non-adjuvanted comparator (TIV/QIV) was determined by the number of vaccine naive subjects ≥6 to <72 months of age with RT-PCR confirmed occurrence of influenza A and/or B of any influenza strain that occurred at ≥ 7 days and ≥ 14 days after the first vaccination up to the day of the second vaccination.

Efficacy was determined on influenza cases caused by any of the influenza strains related to the two A subtypes and the B lineage(s) common to aQIV and TIV (i.e. A/H1N1, A/H3N2 and B/Yamagata during first influenza season), and common to aQIV and QIV (i.e. A/H1N1, A/H3N2 and both B lineages during second season and through the end of the trial)

End point type	Secondary

End point timeframe:

≥7 days and at ≥14 days after first vaccination up to day of second vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3559	3535		
Units: Subjects				
≥7 days after first and up to second vaccination	16	35		
≥14 days after first and up to second vaccination	8	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy Endpoint: First-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age occurring at ≥7 days and ≤21 days after last vaccination, in all subjects.

End point title	Efficacy Endpoint: First-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age occurring at ≥7 days and ≤21 days after last vaccination, in all subjects.

End point description:

Relative efficacy of aQIV compared to non-adjuvanted comparator (TIV/QIV) was determined by the number of vaccine naive subjects ≥6 to <72 months of age with RT-PCR confirmed occurrence of influenza A and/or B of any influenza strain that occurred at ≥ 7 days and ≤ 21 after the last vaccination.

Efficacy was determined on influenza cases caused by any of the influenza strains related to the two A subtypes and the B lineage(s) common to aQIV and TIV (i.e. A/H1N1, A/H3N2 and B/Yamagata during first influenza season), and common to aQIV and QIV (i.e. A/H1N1, A/H3N2 and both B lineages during second season and through the end of the trial).

End point type	Secondary

End point timeframe:

≥7 days and ≤21 days after the last vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5286	5208		
Units: Subjects				
≥7 days and ≤21 days after last vaccination	4	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Antibody response 21 days after last vaccination of aQIV and TIV/QIV against vaccine strains according to Center for Biologics Evaluation and Research hemagglutination inhibition (HI) criteria in subjects ≥6 to <72 months of age

End point title	Immunogenicity Endpoint: Antibody response 21 days after last vaccination of aQIV and TIV/QIV against vaccine strains according to Center for Biologics Evaluation and Research hemagglutination inhibition (HI) criteria in subjects ≥6 to <72 months of age

End point description:

The CBER criteria were met if the lower bound of the 2-sided 95% CI for the percent of subjects achieving SC for HI antibody met or exceeded 40% AND the lower bound of the 2-sided 95% CI for the percent of subjects achieving an HI titer ≥1:40 met or exceeded 70%.

Seroconversion is defined as HI ≥1:40 for subjects negative at baseline (ie, HI titer <1:10); or a minimum 4-fold increase in HI titer for subjects positive at baseline (ie, HI titer HI ≥1:10).

Homologous Strains: H1N1=A/California/7/2009-like; H3N2=A/Texas/50/2012; B Yamagata=B/Massachusetts/2/2012; B Victoria=B/Brisbane/60/2008

For B/Victoria results from Season 2 only are presented for both vaccine groups.

End point type	Secondary

End point timeframe:

21 days after last vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1481	1405		
Units: Percentage of subjects				
number (confidence interval 95%)				
A/H1N1, Seroconversion	81.9 (79.7 to 83.9)	73.7 (71.2 to 76.1)		
A/H1N1, HI ≥1:40	99.3 (98.7 to 99.7)	96.3 (95.2 to 97.3)		
A/H3N2, Seroconversion	78.4 (76.1 to 80.6)	73.2 (70.7 to 75.6)		

A/H3N2, HI ≥1:40	99.6 (99.1 to 99.9)	98.2 (97.3 to 98.8)		
B/Yamagata, Seroconversion	86 (84.1 to 87.8)	64.7 (62.1 to 67.3)		
B/Yamagata, HI ≥1:40	93.5 (92 to 94.7)	76.7 (74.3 to 78.9)		
B/Victoria, Seroconversion	91 (88.7 to 93)	77.4 (74.2 to 80.3)		
B/Victoria, HI ≥1:40	96.1 (94.5 to 97.4)	84.8 (82 to 87.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against each of the vaccine strains in terms of ratio of GMT 21 days after the last vaccination in subjects ≥6 to <72 months of age (superiority analysis)

End point title	Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against each of the vaccine strains in terms of ratio of GMT 21 days after the last vaccination in subjects ≥6 to <72 months of age (superiority analysis)

End point description:

GMT Ratio: aQIV (GMT) over TIV/QIV (GMT)

Superiority criterion for the GMT ratio: The lower bound of the two-sided 95% CI on the adjusted ratio of GMTs for HI antibody titer should exceed 1.

Homologous Strains: H1N1=A/California/7/2009-like; H3N2=A/Texas/50/2012; B Yamagata=B/Massachusetts/2/2012; B Victoria=B/Brisbane/60/2008

For B/Victoria results from Season 2 only are presented for both vaccine groups.

End point type	Secondary

End point timeframe:

21 days after the last vaccination

End point values	FAS - Immunogenicity			
Subject group type	Subject analysis set			
Number of subjects analysed	2886[1]			
Units: titer ratios				
geometric mean (confidence interval 95%)				
A/H1N1	1.91 (1.8 to 2)			
A/H3N2	1.71 (1.6 to 1.8)			
B/Yamagata	2.19 (2 to 2.4)			
B/Victoria	2.27 (2 to 2.6)			

Notes:

[1] - aQIV=1481, TIV/QIV=1405

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against each of the vaccine strains in terms of differences in the percentage of subjects with SC 21 days after last vaccination in subjects ≥6 to <72 months of age (superiority analysis)

End point title	Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against each of the vaccine strains in terms of differences in the percentage of subjects with SC 21 days after last vaccination in subjects ≥6 to <72 months of age (superiority analysis)

End point description:

SC Differences= aQIV (%Subjects with SC) - TIV/QIV (%Subjects with SC)

Seroconversion is defined as HI ≥ 1:40 for subjects negative at baseline (ie, HI titer<1:10); or a minimum 4-fold increase in HI titer for subjects positive at baseline (ie, HI tier ≥ 1:10).

Superiority criterion for seroconversion: The lower bound of the two-sided 95% CI on the unadjusted difference of percentages of subjects seroconverted for HI antibody should exceed 0%.

Homologous Strains: H1N1=A/California/7/2009-like; H3N2=A/Texas/50/2012; B Yamagata=B/Massachusetts/2/2012; B Victoria=B/Brisbane/60/2008

For B/Victoria results from Season 2 only are presented for both vaccine groups

End point type	Secondary

End point timeframe:

21 days after the last vaccination

End point values	FAS - Immunogenicity			
Subject group type	Subject analysis set			
Number of subjects analysed	2886[2]			
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1	8.2 (5 to 11.3)			
A/H3N2	5.2 (1.9 to 8.4)			
B/Yamagata	21.3 (18.1 to 24.5)			
B/Victoria	13.6 (10 to 17.3)			

Notes:

[2] - aQIV=1481, TIV/QIV=1405

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against heterologous strains in terms of ratio of GMT 21 days after last vaccination in subjects ≥6 to <72 months of age

End point title	Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against heterologous strains in terms of ratio of GMT

	21 days after last vaccination in subjects ≥6 to <72 months of age

End point description:

GMT Ratio: aQIV (GMT) over TIV/QIV (GMT)

Heterologous Strains: H1N1=A/Brisbane/59/2007-like; H3N2=A/Hong Kong/4801/2014; B Yamagata=B/Phuket/3073/2013-like; B Victoria=B/Malaysia/2506/2004

For B/Victoria results from Season 2 only are presented for both vaccine groups and used in the vaccine comparison analysis.

End point type	Secondary

End point timeframe:

21 days after last vaccination

End point values	FAS Immunogenicity Heterologous			
Subject group type	Subject analysis set			
Number of subjects analysed	592[3]			
Units: titer ratios				
geometric mean (confidence interval 95%)				
A/H1N1	1.14 (1.1 to 1.2)			
A/H3N2	1.94 (1.6 to 2.3)			
B/Yamagata	2.17 (1.8 to 2.6)			
B/Victoria	2.12 (1.6 to 2.7)			

Notes:

[3] - aQIV=297, TIV/QIV=295

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against heterologous strains in terms of differences in percentages of subjects with SC 21 days after last vaccination in subjects ≥6 to <72 months of age

End point title	Immunogenicity Endpoint: HI antibody responses to aQIV vs TIV/QIV against heterologous strains in terms of differences in percentages of subjects with SC 21 days after last vaccination in subjects ≥6 to <72 months of age

End point description:

SC Differences= aQIV (%Subjects with SC) - TIV/QIV (%Subjects with SC)

Seroconversion was defined as: HI titer ≥40 for subjects negative at baseline (ie, HI titer <10); or a minimum 4-fold increase in HI titer for subjects positive at baseline (HI titer ≥10)

Heterologous Strains: H1N1=A/Brisbane/59/2007-like; H3N2=A/Hong Kong/4801/2014; B Yamagata=B/Phuket/3073/2013-like; B Victoria=B/Malaysia/2506/2004

End point type	Secondary

End point timeframe:

21 days after last vaccination

End point values	FAS Immunogenicity Heterologous			
Subject group type	Subject analysis set			
Number of subjects analysed	592[4]			
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1	1.3 (-1.1 to 4.1)			
A/H3N2	12.5 (6 to 19)			
B/Yamagata	22.8 (15.6 to 29.8)			
B/Victoria	14.9 (6.6 to 23.3)			

Notes:

[4] - aQIV=297, TIV/QIV=295

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Number of subjects with solicited local and systemic AEs

End point title	Safety Endpoint: Number of subjects with solicited local and systemic AEs

End point description:

Safety was assessed in terms of number of subjects ≥6 to <72 months of age reporting solicited local and systemic reactions, day 1 to day 7 after vaccination with either aQIV or TIV/QIV

End point type	Secondary

End point timeframe:

7 days following each vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5138	5056		
Units: Number of subjects				
Any	3748	3242		
Local	2651	2188		
Systemic	2714	2174		
Others	1536	907		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Number of subjects with unsolicited AEs

End point title	Safety Endpoint: Number of subjects with unsolicited AEs

End point description:

Safety was assessed in terms of number of subjects ≥6 to <72 months of age reporting unsolicited reactions up to 12 months after last vaccination, Serious Adverse Events (SAEs), AEs leading to New Oncet of Chronic Diseases (NOCD), Adverse Events of Special Interests (AESI), AEs leading to withdrawal from the study or study vaccination after vaccination with either aQIV or TIV/QIV.

End point type	Secondary

End point timeframe:

Up to 12 months after last vaccination

End point values	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5243	5161		
Units: Number of subjects				
Any unsolicited AEs	3576	3543		
Possibly or probably related unsolicited AEs	686	533		
SAEs	234	230		
Possibly or probably related SAEs	6	1		
AEs with an outcome of death	1	3		
AEs leading to premature withdrawal	10	9		
AEs leading to NOCD	87	96		
AESI	5	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs: day 1 to day 7 after each vaccination, unsolicited AEs: day 1 today 22 for vaccine non-naive and day 1 to day 50 for vaccine naive subjects, SAEs: day 1 to day 366 for vaccine non-naïve and day 1 to day 390 for vaccine naïve subjects

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	aQIV (≥6 to <72 months)

Reporting group description:

Vaccine non-naive and naive subjects (≥6 to <72 months old) received one or two doses of adjuvanted quadrivalent influenza virus vaccine

Reporting group title	TIV/QIV (≥6 to <72 months)

Reporting group description:

Vaccine non-naive and naive subjects (≥6 to <72 months old) received one or two doses of non-adjuvanted comparator influenza virus vaccine

Serious adverse events	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)	
Total subjects affected by serious adverse events			
subjects affected / exposed	234 / 5339 (4.38%)	230 / 5273 (4.36%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ependymoma			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	7 / 5339 (0.13%)	8 / 5273 (0.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 5339 (0.02%)	6 / 5273 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site inflammation			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergy to arthopod sting			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			

subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type I hypersensitivity			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Atelectasis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	9 / 5339 (0.17%)	11 / 5273 (0.21%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	4 / 5339 (0.07%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 5339 (0.02%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 5339 (0.02%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 5339 (0.02%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	2 / 5339 (0.04%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	24 / 5339 (0.45%)	19 / 5273 (0.36%)	
occurrences causally related to treatment / all	0 / 24	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal scratch			
subjects affected / exposed	2 / 5339 (0.04%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical burn of gastrointestinal tract			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Craniocerebral injury			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure to toxic agent			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	2 / 5339 (0.04%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Joint dislocation			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 5339 (0.00%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 5339 (0.04%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 5339 (0.00%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue injury			

subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic liver injury			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal injury			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Ankyloglossia congenital			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis congenital			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart disease congenital			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiogenic shock			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Autism			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebral haemorrhage			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis autoimmune			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	13 / 5339 (0.24%)	7 / 5273 (0.13%)	
occurrences causally related to treatment / all	1 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 5339 (0.06%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Status epilepticus			

subjects affected / exposed	2 / 5339 (0.04%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac disease			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 5339 (0.02%)	5 / 5273 (0.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	5 / 5339 (0.09%)	5 / 5273 (0.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-Schonlein purpura			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen sclerosus			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papule			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	3 / 5339 (0.06%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post streptococcal glomerulonephritis			

subjects affected / exposed	2 / 5339 (0.04%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperaldosteronism			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fasciitis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenovirus infection			
subjects affected / exposed	0 / 5339 (0.00%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebiasis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 5339 (0.04%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast abscess			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			

subjects affected / exposed	7 / 5339 (0.13%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	12 / 5339 (0.22%)	13 / 5273 (0.25%)	
occurrences causally related to treatment / all	0 / 12	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 5339 (0.09%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholera			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	3 / 5339 (0.06%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	9 / 5339 (0.17%)	9 / 5273 (0.17%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	0 / 5339 (0.00%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis viral			
subjects affected / exposed	2 / 5339 (0.04%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	23 / 5339 (0.43%)	23 / 5273 (0.44%)	
occurrences causally related to treatment / all	0 / 23	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 5339 (0.00%)	5 / 5273 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 5339 (0.00%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	3 / 5339 (0.06%)	4 / 5273 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			

subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand-foot-and-mouth disease			
subjects affected / exposed	2 / 5339 (0.04%)	4 / 5273 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpangina			
subjects affected / exposed	5 / 5339 (0.09%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis viral			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycoplasma infection			

subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	2 / 5339 (0.04%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	2 / 5339 (0.04%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	4 / 5339 (0.07%)	7 / 5273 (0.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	3 / 5339 (0.06%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	38 / 5339 (0.71%)	28 / 5273 (0.53%)	
occurrences causally related to treatment / all	0 / 38	0 / 28	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia adenoviral			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia chlamydial			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	3 / 5339 (0.06%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	4 / 5339 (0.07%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			

subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	3 / 5339 (0.06%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 5339 (0.02%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 5339 (0.02%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal infection			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal scalded skin syndrome			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	3 / 5339 (0.06%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	5 / 5339 (0.09%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	0 / 5339 (0.00%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 5339 (0.02%)	4 / 5273 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 5339 (0.06%)	7 / 5273 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	4 / 5339 (0.07%)	3 / 5273 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral rash			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sinusitis			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	15 / 5339 (0.28%)	11 / 5273 (0.21%)	
occurrences causally related to treatment / all	0 / 15	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 5339 (0.02%)	0 / 5273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 5339 (0.04%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 5339 (0.00%)	2 / 5273 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	2 / 5339 (0.04%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	3 / 5339 (0.06%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 5339 (0.00%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 5339 (0.02%)	1 / 5273 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	aQIV (≥6 to <72 months)	TIV/QIV (≥6 to <72 months)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4627 / 5339 (86.66%)	4330 / 5273 (82.12%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	1366 / 5339 (25.59%)	1107 / 5273 (20.99%)	
occurrences (all)	1366	1107	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	2690 / 5339 (50.38%)	2664 / 5273 (50.52%)	
occurrences (all)	2690	2664	

Injection site pain			
subjects affected / exposed	2360 / 5339 (44.20%)	1861 / 5273 (35.29%)	
occurrences (all)	2360	1861	
Injection site erythema			
subjects affected / exposed	1226 / 5339 (22.96%)	1031 / 5273 (19.55%)	
occurrences (all)	1226	1031	
Pyrexia			
subjects affected / exposed	1178 / 5339 (22.06%)	778 / 5273 (14.75%)	
occurrences (all)	1178	778	
Injection site induration			
subjects affected / exposed	804 / 5339 (15.06%)	576 / 5273 (10.92%)	
occurrences (all)	804	576	
Injection site haemorrhage			
subjects affected / exposed	407 / 5339 (7.62%)	374 / 5273 (7.09%)	
occurrences (all)	407	374	
Chills			
subjects affected / exposed	356 / 5339 (6.67%)	210 / 5273 (3.98%)	
occurrences (all)	356	210	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	701 / 5339 (13.13%)	677 / 5273 (12.84%)	
occurrences (all)	701	677	
Vomiting			
subjects affected / exposed	634 / 5339 (11.87%)	516 / 5273 (9.79%)	
occurrences (all)	634	516	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	305 / 5339 (5.71%)	312 / 5273 (5.92%)	
occurrences (all)	305	312	
Rhinorrhoea			
subjects affected / exposed	206 / 5339 (3.86%)	225 / 5273 (4.27%)	
occurrences (all)	206	225	
Psychiatric disorders			

Irritability			
subjects affected / exposed	1441 / 5339 (26.99%)	1204 / 5273 (22.83%)	
occurrences (all)	1441	1204	
Eating disorder			
subjects affected / exposed	1163 / 5339 (21.78%)	898 / 5273 (17.03%)	
occurrences (all)	1163	898	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	722 / 5339 (13.52%)	724 / 5273 (13.73%)	
occurrences (all)	722	724	
Nasopharyngitis			
subjects affected / exposed	387 / 5339 (7.25%)	365 / 5273 (6.92%)	
occurrences (all)	387	365	
Otitis media			
subjects affected / exposed	375 / 5339 (7.02%)	352 / 5273 (6.68%)	
occurrences (all)	375	352	
Pneumonia			
subjects affected / exposed	218 / 5339 (4.08%)	241 / 5273 (4.57%)	
occurrences (all)	218	241	
Rhinitis			
subjects affected / exposed	215 / 5339 (4.03%)	221 / 5273 (4.19%)	
occurrences (all)	215	221	
Bronchitis			
subjects affected / exposed	186 / 5339 (3.48%)	201 / 5273 (3.81%)	
occurrences (all)	186	201	
Gastroenteritis			
subjects affected / exposed	156 / 5339 (2.92%)	139 / 5273 (2.64%)	
occurrences (all)	156	139	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2014	- A secondary efficacy objective was added to evaluate the relative efficacy of aQIV compared to non-adjuvanted QIV comparator as determined by the proportion of subjects with first-occurrence confirmed influenza A and/or B of any influenza strain (second season and subsequent season(s) if applicable). - Two secondary immunogenicity objectives were added, to compare immunogenicity of the adjuvanted and non-adjuvanted vaccines in healthy and high risk subjects. - The number of subjects enrolled overall and in the immunogenicity subset was revised and randomization was restricted to the first approximately 4000 enrolled subjects in Season 2. - The wording of the statistical analysis of the primary objective was revised. - End of influenza season was defined as the end of June for NH influenza season and end of December for Southern Hemisphere influenza season. - Subgroups were added and revised for efficacy, immunogenicity and safety analyses.
30 April 2015	- Objectives were added to include RT-PCR-confirmed cases starting from: ≥7 days up to 21 days after the last vaccination in all subjects and ≥7 days up to 180 days after the last vaccination, or end of influenza season, whichever was longer in all subjects. - A Healthcare Utilization and HEO objective was added to evaluate the relative efficacy of aQIV to comparator for prevention of moderate-to-severe influenza cases. - An exploratory objective was added to include confirmed cases reported ≥21 days after last vaccination until study termination.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported