



Clinical trial results:

Randomized, Double-Blind and Active-Controlled Study in Children and Adolescents Aged 3–17 Years to Assess the Safety and Immunogenicity of Abbott's Candidate Quadrivalent Influenza Vaccine and its Non-Inferiority versus Trivalent Influenza Vaccine

Summary

EudraCT number	2015-005482-23
Trial protocol	DE FI EE HU LT
Global end of trial date	14 April 2017

Results information

Result version number	v1 (current)
This version publication date	28 October 2017
First version publication date	28 October 2017

Trial information

Trial identification

Sponsor protocol code	INFQ3002
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Abbott Biologicals B.V.
Sponsor organisation address	C.J. van Houtenlaan 36, Weesp, Netherlands, NL-1381 CP
Public contact	Public Affairs Manager, Abbott Products Operations AG, hind.ounis@abbott.com
Scientific contact	Global Clinical Director, Abbott Healthcare Products B.V., serge.vandewitte@abbott.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001782-PIP01-15
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	14 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2017
Global end of trial reached?	Yes
Global end of trial date	14 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate in a population of children and adolescents 3 to 17 years of age the non-inferiority of quadrivalent influenza vaccine (QIV) with respect to post-vaccination geometric mean Hemagglutination Inhibition (HI) antibody titers against the shared strains compared with the trivalent influenza vaccines (TIV) with either the B-strain of the Victoria lineage (TIV[Vic]) or the B-strain of the Yamagata lineage (TIV[Yam]).

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice and the applicable national regulations so as to ensure that the rights, safety, and well-being of the participating study subjects were protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

Background therapy:

Children and adolescents aged ≥ 9 years were considered primed subjects as well as those aged < 9 years who had received \geq two doses of a seasonal influenza vaccine at least one month apart; children aged < 9 years who had not previously received \geq two doses of a seasonal influenza vaccine at least one month apart were considered unprimed. Primed subjects were required to attend two clinic visits, while unprimed subjects were required to attend three clinical visits.

Evidence for comparator:

The candidate vaccine in this study, QIV, was compared against TIV(Vic) and TIV(Yam). For all vaccines, the active drug substance consisted of approximately 15 micrograms (μg) of hemagglutinin (HA) antigen of each of the three or four viral strains recommended by the World Health Organization and Committee for Medicinal Products for Human Use for the strains recommended for the northern hemisphere 2016/2017 season. These comprised:

- an A/California/7/2009 (H1N1)pdm09-like virus; referred to as the A(H1N1) strain.
- an A/Hong Kong/4801/2014 (H3N2)-like virus; referred to as the A(H3N2) strain.
- a B/Brisbane/60/2008-like virus; referred to as the B-Victoria strain.
- a B/Phuket/3073/2013-like virus; referred to as the B-Yamagata strain.

The B/Brisbane/60/2008-like virus (TIV[Vic]) was the recommended B-strain for the marketed TIV formulation (Influvac®).

Actual start date of recruitment	02 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 229
Country: Number of subjects enrolled	Estonia: 127
Country: Number of subjects enrolled	Finland: 450
Country: Number of subjects enrolled	Germany: 80
Country: Number of subjects enrolled	Hungary: 184
Country: Number of subjects enrolled	Lithuania: 130

Worldwide total number of subjects	1200
EEA total number of subjects	1200

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	978
Adolescents (12-17 years)	222
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty eight study centres in six countries (Estonia, Finland, Germany, Hungary, Lithuania, and Poland) screened and enrolled subjects. The first subject entered the study on 02 September 2016 and the last subject completed the last visit on 14 April 2017.

Pre-assignment

Screening details:

A total of 1,223 subjects provided informed consent and were screened for eligibility. Of these, 23 subjects failed screening and 1,200 subjects were vaccinated. Allocation was stratified 2:1 by age group: 3 to 8 years and 9 to 17 years, and in both age groups, subjects were randomly assigned to receive QIV, TIV(Vic) and TIV(Yam) in a 1:1:1 ratio.

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

Blinding implementation details:

All syringes were identical in appearance and packaged in the correct proportions to ensure desired dosages were used and that blinding was maintained.

Arms

Are arms mutually exclusive?	Yes
Arm title	Quadrivalent Influenza Vaccine

Arm description:

Primed subjects received a single dose of QIV on Day 1 and unprimed subjects received two doses of QIV (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.

Arm type	Experimental
Investigational medicinal product name	Quadrivalent Influenza Vaccine
Investigational medicinal product code	
Other name	QIV, Influvac® Tetra
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Primed subjects: single dose of 0.5 milliliters (mL) QIV administered by intramuscular injection on Day 1 (Visit 1).

Unprimed subjects: two single doses of 0.5 mL of QIV administered by intramuscular injection on Day 1 (Visit 1) and on Day 29 (Visit 2).

The HA content of the QIV batch was as follows:

- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) (14.4 µg HA/dose).
- A/Hong Kong/4801/2014 (H3N2)-like strain (A/Hong Kong/4801/2014, X-263B) (18.6 µg HA/dose).
- B/Brisbane/60/2008-like strain (B/Brisbane/60/2008, wild type) (16.2 µg HA/dose).
- B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild type) (17.5 µg HA/dose).

Arm title	Trivalent Influenza Vaccine (Victoria)
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Arm description:

Primed subjects received a single dose of TIV(Vic) on Day 1 and unprimed subjects received two doses of TIV(Vic) (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.

Arm type	Active comparator
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Investigational medicinal product name	Trivalent Influenza Vaccine (Victoria)
Investigational medicinal product code	
Other name	TIV(Vic), Influvac®
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Primed subjects: single dose of 0.5 mL TIV(Vic) administered by intramuscular injection on Day 1 (Visit 1).

Unprimed subjects: two single doses of 0.5 mL of TIV(Vic) administered by intramuscular injection on Day 1 (Visit 1) and on Day 29 (Visit 2).

The HA content of the TIV(Vic) batch was as follows:

- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) (14.7 µg HA/dose).
- A/Hong Kong/4801/2014 (H3N2)-like strain (A/Hong Kong/4801/2014, X-263B) (18.8 µg HA/dose).
- B/Brisbane/60/2008-like strain (B/Brisbane/60/2008, wild type) (15.6 µg HA/dose).

Arm title	Trivalent Influenza Vaccine (Yamagata)
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Arm description:

Primed subjects received a single dose of TIV(Yam) on Day 1 and unprimed subjects received two doses of TIV(Yam) (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.

Arm type	Active comparator
Investigational medicinal product name	Trivalent Influenza Vaccine (Yamagata)
Investigational medicinal product code	
Other name	TIV(Yam)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Primed subjects: single dose of 0.5 mL TIV(Yam) administered by intramuscular injection on Day 1 (Visit 1).

Unprimed subjects: two single doses of 0.5 mL of TIV(Yam) administered by intramuscular injection on Day 1 (Visit 1) and on Day 29 (Visit 2).

The HA content of the TIV(Yam) batch was as follows:

- A/California/7/2009 (H1N1)pdm09-like strain (A/California/7/2009, X-181) (15.2 µg HA/dose).
- A/Hong Kong/4801/2014 (H3N2)-like strain (A/Hong Kong/4801/2014, X-263B) (20.0 µg HA/dose).
- B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild type) (16.1 µg HA/dose).

Number of subjects in period 1	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)
Started	402	404	394
Completed	399	403	393
Not completed	3	1	1
Consent withdrawn by subject	2	-	1
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	Quadrivalent Influenza Vaccine
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Reporting group description:

Primed subjects received a single dose of QIV on Day 1 and unprimed subjects received two doses of QIV (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.

Reporting group title	Trivalent Influenza Vaccine (Victoria)
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Reporting group description:

Primed subjects received a single dose of TIV(Vic) on Day 1 and unprimed subjects received two doses of TIV(Vic) (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.

Reporting group title	Trivalent Influenza Vaccine (Yamagata)
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Reporting group description:

Primed subjects received a single dose of TIV(Yam) on Day 1 and unprimed subjects received two doses of TIV(Yam) (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.

Reporting group values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)
Number of subjects	402	404	394
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	7.4	7.7	7.6
standard deviation	± 4	± 3.9	± 3.9
Gender categorical Units: Subjects			
Female	193	207	179
Male	209	197	215

Reporting group values	Total		
Number of subjects	1200		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	579		
Male	621		

End points

End points reporting groups

Reporting group title	Quadrivalent Influenza Vaccine
Reporting group description: Primed subjects received a single dose of QIV on Day 1 and unprimed subjects received two doses of QIV (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.	
Reporting group title	Trivalent Influenza Vaccine (Victoria)
Reporting group description: Primed subjects received a single dose of TIV(Vic) on Day 1 and unprimed subjects received two doses of TIV(Vic) (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.	
Reporting group title	Trivalent Influenza Vaccine (Yamagata)
Reporting group description: Primed subjects received a single dose of TIV(Yam) on Day 1 and unprimed subjects received two doses of TIV(Yam) (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.	
Subject analysis set title	Trivalent Influenza Vaccine (Pooled)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Primed subjects received a single dose of TIV on Day 1 and unprimed subjects received two doses of TIV (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm. For each A strain, the HI, VN and NI titer data of the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled. Reactogenicity data of the two trivalent formulations was also pooled.	

Primary: Post-vaccination geometric HI antibody titers against A(H1N1) strain

End point title	Post-vaccination geometric HI antibody titers against A(H1N1) strain ^[1]
End point description: Non-inferiority of QIV was assessed with respect to post-vaccination geometric mean HI antibody titers against the shared strains compared with TIV(Vic) and TIV(Yam) groups; results are reported for HI titers against the A(H1N1) strain. Population for analysis was the per-protocol sample, defined through blind data review and comprised of all subjects who were included in the full analysis sample and did not present any major protocol violations.	
End point type	Primary
End point timeframe: The HI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.	
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: For each A strain, the HI titer data of the two trivalent formulations, TIV(Vic) and TIV (Yam), were pooled.	

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	388	774		
Units: titer				
geometric mean (standard deviation)	548.9 (± 3.2)	622.2 (± 3.4)		

Statistical analyses

Statistical analysis title	A(H1N1) strain non-inferiority analysis
Statistical analysis description:	
Non-inferiority was analyzed by calculating for each of the two A-strains and each of the two B-strains a two-sided 95% confidence interval (CI) for adjusted geometric mean ratios (GMRs) for the TIV versus QIV comparison, using an analysis of variance (ANOVA) model for the log transformed titers at Day 29/Day 57 with age group, center and priming status included as covariates in the model.	
Comparison groups	Quadrivalent Influenza Vaccine v Trivalent Influenza Vaccine (Pooled)
Number of subjects included in analysis	1162
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Adjusted GMR
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.3

Notes:

[2] - The non-inferiority margin was set at 1.5. Non-inferiority of QIV to TIV would be concluded if, for all four strains, the upper limit of the 95% CI fell below 1.5.

Primary: Post-vaccination geometric HI antibody titers against A(H3N2) strain

End point title	Post-vaccination geometric HI antibody titers against A(H3N2) strain ^[3]
End point description:	
Non-inferiority of QIV was assessed with respect to post-vaccination geometric mean HI antibody titers against the shared strains compared with TIV(Vic) and TIV(Yam) groups; results are reported for HI titers against the A(H3N2) strain. Population for analysis was the per-protocol sample, defined through blind data review and comprised of all subjects who were included in the full analysis sample and did not present any major protocol violations.	
End point type	Primary

End point timeframe:

The HI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

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: For each A strain, the HI titer data of the two trivalent formulations, TIV(Vic) and TIV (Yam), were pooled.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	388	774		
Units: titer				

geometric mean (standard deviation)	1150.4 (± 3.2)	1193.9 (± 3.4)		
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Statistical analyses

Statistical analysis title	A(H3N2) strain non-inferiority analysis
Statistical analysis description:	
Non-inferiority was analyzed by calculating for each of the two A-strains and each of the two B-strains a two-sided 95% CI for adjusted GMRs for the TIV versus QIV comparison, using an ANOVA model for the log transformed titers at Day 29/Day 57 with age group, center and priming status included as covariates in the model.	
Comparison groups	Quadrivalent Influenza Vaccine v Trivalent Influenza Vaccine (Pooled)
Number of subjects included in analysis	1162
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Adjusted GMR
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.19

Notes:

[4] - The non-inferiority margin was set at 1.5. Non-inferiority of QIV to TIV would be concluded if, for all four strains, the upper limit of the 95% CI fell below 1.5.

Primary: Post-vaccination geometric HI antibody titers against B-Victoria strain

End point title	Post-vaccination geometric HI antibody titers against B-Victoria strain
End point description:	
Non-inferiority of QIV was assessed with respect to post-vaccination geometric mean HI antibody titers against the shared strains compared with TIV(Vic) and TIV(Yam) groups; results are reported for HI titers against the B-Victoria strain. Population for analysis was the per-protocol sample, defined through blind data review and comprised of all subjects who were included in the full analysis sample and did not present any major protocol violations.	
End point type	Primary
End point timeframe:	
The HI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.	

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	393	381	
Units: titer				
geometric mean (standard deviation)	302.6 (± 4.2)	364 (± 4.6)	104.8 (± 6.4)	

Statistical analyses

Statistical analysis title	B-Victoria strain non-inferiority analysis
Statistical analysis description: Non-inferiority was analyzed by calculating for each of the two A-strains and each of the two B-strains a two-sided 95% CI for adjusted GMRs for the TIV versus QIV comparison, using an ANOVA model for the log transformed titers at Day 29/Day 57 with age group, center and priming status included as covariates in the model.	
Comparison groups	Quadrivalent Influenza Vaccine v Trivalent Influenza Vaccine (Victoria)
Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
Method	ANOVA
Parameter estimate	Adjusted GMR
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.46

Notes:

[5] - The non-inferiority margin was set at 1.5. Non-inferiority of QIV to TIV would be concluded if, for all four strains, the upper limit of the 95% CI fell below 1.5.

Primary: Post-vaccination geometric HI antibody titers against B-Yamagata strain

End point title	Post-vaccination geometric HI antibody titers against B-Yamagata strain
End point description: Non-inferiority of QIV was assessed with respect to post-vaccination geometric mean HI antibody titers against the shared strains compared with TIV(Vic) and TIV(Yam) groups; results are reported for HI titers against the B-Yamagata strain. Population for analysis was the per-protocol sample, defined through blind data review and comprised of all subjects who were included in the full analysis sample and did not present any major protocol violations.	
End point type	Primary
End point timeframe: The HI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.	

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	393	381	
Units: titer				
geometric mean (standard deviation)	277.6 (± 3.8)	38.6 (± 6.6)	270.7 (± 4.3)	

Statistical analyses

Statistical analysis title	B-Yamagata strain non-inferiority analysis
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Statistical analysis description:

Non-inferiority was analyzed by calculating for each of the two A-strains and each of the two B-strains a two-sided 95% CI for adjusted GMRs for the TIV versus QIV comparison, using an ANOVA model for the log transformed titers at Day 29/Day 57 with age group, center and priming status included as covariates in the model.

Comparison groups	Quadrivalent Influenza Vaccine v Trivalent Influenza Vaccine (Yamagata)
Number of subjects included in analysis	769
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[6]
Parameter estimate	Adjusted GMR
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.19

Notes:

[6] - The non-inferiority margin was set at 1.5. Non-inferiority of QIV to TIV would be concluded if, for all four strains, the upper limit of the 95% CI fell below 1.5.

Secondary: Post-vaccination geometric HI antibody titers against the alternate lineage B-strain (Victoria lineage)

End point title	Post-vaccination geometric HI antibody titers against the alternate lineage B-strain (Victoria lineage)
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End point description:

Superiority of QIV to TIV(Vic) and TIV(Yam) was assessed with respect to post-vaccination geometric HI antibody titers against the alternate lineage B-strain; results are reported for HI titers against the B-Victoria strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers).

End point type	Secondary
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End point timeframe:

The HI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	396	399	389	
Units: titer				
geometric mean (standard deviation)	306.7 (± 4.2)	361.4 (± 4.6)	104.5 (± 6.4)	

Statistical analyses

Statistical analysis title	B-Victoria strain superiority analysis
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Statistical analysis description:

Superiority was analyzed by calculating for each of the two A-strains and each of the two B-strains a two-sided 95% CI for adjusted GMRs for the TIV versus QIV comparison, using an ANOVA model for the log transformed titers at Day 29/Day 57 with age group, center and priming status included as covariates in the model.

Comparison groups	Trivalent Influenza Vaccine (Yamagata) v Quadrivalent Influenza Vaccine
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted GMR
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.36
upper limit	3.64

Notes:

[7] - Superiority of QIV to TIV against the alternate lineage B-strains would be concluded if for both strains: GMR > 1 and p-value <0.05.

Secondary: Post-vaccination geometric HI antibody titers against the alternate lineage B-strain (Yamagata lineage)

End point title	Post-vaccination geometric HI antibody titers against the alternate lineage B-strain (Yamagata lineage)
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End point description:

Superiority of QIV to TIV(Vic) and TIV(Yam) was assessed with respect to post-vaccination geometric HI antibody titers against the alternate lineage B-strain; results are reported for HI titers against the B-Yamagata strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers).

End point type	Secondary
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End point timeframe:

The HI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	396	399	389	
Units: titer				
geometric mean (standard deviation)	280.8 (± 3.8)	38.3 (± 6.5)	269 (± 4.3)	

Statistical analyses

Statistical analysis title	B-Yamagata strain superiority analysis
Statistical analysis description:	
Superiority was analyzed by calculating for each of the two A-strains and each of the two B-strains a two-sided 95% CI for adjusted GMRs for the TIV versus QIV comparison, using an ANOVA model for the log transformed titers at Day 29/Day 57 with age group, center and priming status included as covariates in the model.	
Comparison groups	Quadrivalent Influenza Vaccine v Trivalent Influenza Vaccine (Victoria)
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted GMR
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.83
upper limit	9.03

Notes:

[8] - Superiority of QIV to TIV against the alternate lineage B-strains would be concluded if for both strains: GMR > 1 and p-value <0.05.

Secondary: Post-vaccination geometric mean fold increases in HI, Virus Neutralization (VN) and Neuraminidase Inhibition (NI) antibody titers against A(H1N1) strain

End point title	Post-vaccination geometric mean fold increases in HI, Virus Neutralization (VN) and Neuraminidase Inhibition (NI) antibody titers against A(H1N1) strain ^[9]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the geometric mean fold increase with respect to HI, VN and NI antibody titers; results are reported for antibody titers against the A(H1N1) strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: For each A strain, the HI, VN and NI titer data of the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	396	786		
Units: titer (fold increase)				
geometric mean (standard deviation)				
HI titers (n=396; 786)	6.6 (± 4.2)	6.9 (± 4.4)		
VN titers (n=59; 118)	2.5 (± 2.2)	2.4 (± 2.1)		
NI titers (n=59; 118)	4.8 (± 3.6)	4.9 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Post-vaccination geometric mean fold increases in HI, VN and NI antibody titers against A(H3N2) strain

End point title	Post-vaccination geometric mean fold increases in HI, VN and NI antibody titers against A(H3N2) strain ^[10]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the geometric mean fold increase with respect to HI, VN and NI antibody titers; results are reported for antibody titers against the A(H3N2) strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

Notes:

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

Justification: For each A strain, the HI, VN and NI titer data of the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	396	786		
Units: titer (fold increase)				
geometric mean (standard deviation)				
HI titers (n=396; 786)	16.2 (± 5.3)	18.6 (± 5.2)		
VN titers (n=59; 118)	3.4 (± 2.3)	3.4 (± 2.4)		

NI titers (n=59; 118)	2.4 (\pm 2.8)	2.2 (\pm 3.2)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Post-vaccination geometric mean fold increases in HI, VN and NI antibody titers against B-Victoria strain

End point title	Post-vaccination geometric mean fold increases in HI, VN and NI antibody titers against B-Victoria strain
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the geometric mean fold increase with respect to HI, VN and NI antibody titers; results are reported for antibody titers against the B-Victoria strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	396	399	387	
Units: titer (fold increase)				
geometric mean (standard deviation)				
HI titers (n=396; 399; 387)	11.9 (\pm 4.7)	10.4 (\pm 4.7)	3.6 (\pm 4.3)	
VN titers (n=59; 59; 59)	5.1 (\pm 2.8)	6.4 (\pm 2.9)	1.9 (\pm 2.5)	
NI titers (n=59; 59; 59)	2.3 (\pm 3.3)	2.1 (\pm 2.2)	2.1 (\pm 2.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Post-vaccination geometric mean fold increases in HI, VN and NI antibody titers against B-Yamagata strain

End point title	Post-vaccination geometric mean fold increases in HI, VN and NI antibody titers against B-Yamagata strain
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the geometric mean fold increase with respect to HI, VN and NI antibody titers; results are reported for

antibody titers against the B-Yamagata strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	396	399	387	
Units: titer (fold increase)				
geometric mean (standard deviation)				
HI titers (n=396; 399; 387)	16.7 (± 5.1)	2.5 (± 3.8)	14.9 (± 5.9)	
VN titers (n=59; 59; 59)	5.8 (± 2.8)	1.8 (± 2)	5.5 (± 2.8)	
NI titers (n=59; 59; 59)	2.3 (± 2.7)	1.5 (± 2.1)	2.3 (± 2.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion rates based on HI, VN and NI antibody titers against A(H1N1) strain

End point title	Seroconversion rates based on HI, VN and NI antibody titers against A(H1N1) strain ^[11]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the seroconversion rates with respect to HI, VN and NI antibody titers. Seroconversion (defined as becoming seropositive if seronegative at enrollment, or [at least] a 4-fold rise in titer if seropositive at enrollment) rates are presented as percentage of subjects and are reported for antibody titers against the A(H1N1) strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

Notes:

[11] - 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: For each A strain, the HI, VN and NI titer data of the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	396	786		
Units: percentage of subjects				
number (not applicable)				
HI titers (n=396; 786)	60.1	60.4		
VN titers (n=59; 118)	66.1	61.9		
NI titers (n=59; 118)	57.6	68.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion rates based on HI, VN and NI antibody titers against A(H3N2) strain

End point title	Seroconversion rates based on HI, VN and NI antibody titers against A(H3N2) strain ^[12]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the seroconversion rates with respect to HI, VN and NI antibody titers. Seroconversion (defined as becoming seropositive if seronegative at enrollment, or [at least] a 4-fold rise in titer if seropositive at enrollment) rates are presented as percentage of subjects and are reported for antibody titers against the A(H3N2) strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

Notes:

[12] - 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: For each A strain, the HI, VN and NI titer data of the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	396	786		
Units: percentage of subjects				
number (not applicable)				
HI titers (n=396; 786)	80.6	81.6		
VN titers (n=59; 118)	76.3	67.8		
NI titers (n=59; 118)	33.9	33.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion rates based on HI, VN and NI antibody titers against B-Victoria strain

End point title	Seroconversion rates based on HI, VN and NI antibody titers against B-Victoria strain
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the seroconversion rates with respect to HI, VN and NI antibody titers. Seroconversion (defined as becoming seropositive if seronegative at enrollment, or [at least] a 4-fold rise in titer if seropositive at enrollment) rates are presented as percentage of subjects and are reported for antibody titers against the B-Victoria strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	396	399	387	
Units: percentage of subjects				
number (not applicable)				
HI titers (n=396; 399; 387)	76.5	72.7	39.5	
VN titers (n=59; 59; 59)	76.3	79.7	25.4	
NI titers (n=59; 59; 59)	39.0	32.2	32.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion rates based on HI, VN and NI antibody titers against B-Yamagata strain

End point title	Seroconversion rates based on HI, VN and NI antibody titers against B-Yamagata strain
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End point description:

Characterization of the immunogenicity of each of the strains in QIV and TIV was assessed by deriving the seroconversion rates with respect to HI, VN and NI antibody titers. Seroconversion (defined as becoming seropositive if seronegative at enrollment, or [at least] a 4-fold rise in titer if seropositive at enrollment) rates are presented as percentage of subjects and are reported for antibody titers against the B-Yamagata strain. Population for analysis was the full analysis sample and comprised of all subjects who were included in the safety sample and had post-vaccination primary efficacy data (i.e., HI titers). Note: VN and NI titers were assessed only for a random subset of subjects (comprising of approximately 15% of the overall randomized population). n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

The HI, VN and NI titers were measured on Day 29 (Visit 2) post-vaccination for primed subjects and on Day 57 (Visit 3) post-vaccination for unprimed subjects.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Victoria)	Trivalent Influenza Vaccine (Yamagata)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	396	399	387	
Units: percentage of subjects				
number (not applicable)				
HI titers (n=396; 399; 387)	79.3	28.1	73.1	
VN titers (n=59; 59; 59)	81.4	33.9	71.2	
NI titers (n=59; 59; 59)	42.4	22.0	37.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (percentage) of subjects with solicited systemic reactions

End point title	Proportion (percentage) of subjects with solicited systemic reactions ^[13]
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End point description:

A subject diary was used to record pre-specified systemic reactions occurring during the first 7 days after vaccination (solicited reactogenicity). Population for analysis was the safety sample and comprised of all subjects who were vaccinated and had at least one post-vaccination safety observation. Solicited systemic reactions were assessed only in children aged 3-5 years for the following categories: Irritability/fussiness, Drowsiness, Diarrhea/vomiting, and Loss of appetite; and only in children aged 6-17 years for: Headache, Fatigue/tiredness, Gastrointestinal symptoms, Myalgia/muscle pain, Arthralgia/joint pain, Malaise, and Shivering; Fever and Sweating were assessed for both age groups. Note: n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

Solicited events were recorded during the first 7 days after vaccination (up to Day 7).

Notes:

[13] - 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: The reactogenicity data of the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	795		
Units: percentage of subjects				
number (not applicable)				
Fever (n=402; 795)	4.2	2.6		

Irritability/fussiness (n=176; 314)	21.0	17.8		
Drowsiness (n=176; 314)	15.9	12.7		
Diarrhea/vomiting (n=176; 314)	6.8	7.3		
Loss of appetite (n=176; 314)	13.1	11.1		
Headache (n=229; 489)	24.0	20.9		
Fatigue/tiredness (n=229; 489)	23.6	22.1		
Gastrointestinal symptoms (n=229; 489)	14.8	10.0		
Myalgia/muscle pain (n=229; 489)	14.8	15.3		
Arthralgia/joint pain (n=229; 489)	6.1	4.9		
Malaise (n=229; 488)	14.8	12.3		
Sweating (n=401; 794)	4.2	3.7		
Shivering (n=229; 489)	4.4	3.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion (percentage) of subjects with solicited local reactions

End point title	Proportion (percentage) of subjects with solicited local reactions ^[14]
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End point description:

A subject diary was used to record pre-specified injection site (local) reactions occurring during the first 7 days after vaccination (solicited reactogenicity). Population for analysis was the safety sample and comprised of all subjects who were vaccinated and had at least one post-vaccination safety observation. Note: n = Number of subjects with non-missing data.

End point type	Secondary
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End point timeframe:

Solicited events were recorded during the first 7 days after vaccination (up to Day 7).

Notes:

[14] - 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: The reactogenicity data of the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled.

End point values	Quadrivalent Influenza Vaccine	Trivalent Influenza Vaccine (Pooled)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	795		
Units: percentage of subjects				
number (not applicable)				
Vaccination site erythema (n=402; 794)	19.4	16.6		
Swelling (n=402; 795)	13.4	10.7		
Induration (n=402; 795)	11.4	10.1		
Vaccination site pain (n=402; 794)	59.0	52.5		
Vaccination site ecchymosis (n=402; 795)	6.5	4.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For serious adverse events (SAEs): Day 1 up to end of safety follow-up period (up to Day 183). For non-serious adverse events (AEs): Day 1 up to Day 29 (primed subjects) or up to Day 57 (unprimed subjects).

Adverse event reporting additional description:

All AEs are reported as treatment-emergent AEs during the immunization period plus safety follow-up period for SAEs and during the immunization period only for non-serious AEs. Population for analysis was the safety sample and comprised of all subjects who were vaccinated and had at least one post-vaccination safety observation.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Trivalent Influenza Vaccine (Pooled)
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Reporting group description:

Primed subjects received a single dose of TIV on Day 1 and unprimed subjects received two doses of TIV (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm. The safety data of the subjects vaccinated with the two trivalent formulations, TIV(Vic) and TIV(Yam), were pooled.

Reporting group title	Quadrivalent Influenza Vaccine
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Reporting group description:

Primed subjects received a single dose of QIV on Day 1 and unprimed subjects received two doses of QIV (Day 1 and Day 29). Each dose contained approximately 15 µg HA antigen per virus strain, given intramuscularly in the deltoid muscle of the upper arm.

Serious adverse events	Trivalent Influenza Vaccine (Pooled)	Quadrivalent Influenza Vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 798 (0.88%)	4 / 402 (1.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ewing's sarcoma			
subjects affected / exposed	0 / 798 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			

subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 798 (0.00%)	1 / 402 (0.25%)	
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	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 798 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			

subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 798 (0.50%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 798 (0.00%)	1 / 402 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 798 (0.13%)	0 / 402 (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	1 / 798 (0.13%)	1 / 402 (0.25%)	
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: 1 %

Non-serious adverse events	Trivalent Influenza Vaccine (Pooled)	Quadrivalent Influenza Vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 798 (14.04%)	48 / 402 (11.94%)	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 798 (1.75%)	4 / 402 (1.00%)	
occurrences (all)	15	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 798 (2.38%)	10 / 402 (2.49%)	
occurrences (all)	21	10	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	13 / 798 (1.63%)	4 / 402 (1.00%)	
occurrences (all)	14	4	
Cough			
subjects affected / exposed	24 / 798 (3.01%)	7 / 402 (1.74%)	
occurrences (all)	25	7	
Rhinorrhoea			
subjects affected / exposed	9 / 798 (1.13%)	0 / 402 (0.00%)	
occurrences (all)	10	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	37 / 798 (4.64%)	19 / 402 (4.73%)	
occurrences (all)	39	20	
Nasopharyngitis			
subjects affected / exposed	20 / 798 (2.51%)	7 / 402 (1.74%)	
occurrences (all)	21	7	
Otitis media			
subjects affected / exposed	5 / 798 (0.63%)	7 / 402 (1.74%)	
occurrences (all)	5	9	
Rhinitis			
subjects affected / exposed	11 / 798 (1.38%)	2 / 402 (0.50%)	
occurrences (all)	11	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2016	<p>The amendment was implemented to include feedback from the protocol review conducted by the centralized Voluntary Harmonization Procedure. Updates comprised:</p> <ul style="list-style-type: none">• The person who was authorized and in the position to break the blinding in case of a serious adverse event (SAE) was specified.• It was clarified that the use of prohibited medications did not affect the contraindications for the second study vaccination in unprimed subjects.• Major protocol deviations, considered for the exclusion of subjects from the per protocol subject sample, were defined and specified.• It was emphasized that all attempts to contact the subject/parent(s)/legally acceptable representative (LAR) of drop-outs after study vaccination had to be documented in the source documents.• The reactogenicity grading scale for local solicited reactions was adapted for use in the pediatric populations.• AE reporting methods were clarified, to state that all AEs, including those not considered related to the study vaccine, were to be reported.• The analysis of safety was updated to state that all solicited local reactions were to be considered as related to the vaccine.• The analysis of efficacy was updated to state that the serology data were to include serological baseline status.• The benefit-risk considerations were updated to state that subjects who received TIV with the alternate B-strain lineage may have less benefit compared with those who received TIV with the recommended B-strain lineage or QIV with both B-strain lineages.• The study assessments and flow chart were updated to state that parents/LARs should have been reminded to inform the study site in case of an SAE not treated at site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported