



Clinical trial results:

A Phase III, Observer-Blind, Randomized, Non-influenza Vaccine Comparator-Controlled, Parallel-Group, Multi-Country Study in Children Aged 6–35 Months to Assess the Safety and Efficacy of Abbott's Candidate Quadrivalent Influenza Vaccine

Summary

EudraCT number	2016-004904-74
Trial protocol	SK DK EE CZ LT BG IT SI ES FR HR HU RO
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	09 July 2020
First version publication date	09 July 2020

Trial information

Trial identification

Sponsor protocol code	INFQ3003
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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 Director, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate, in children aged 6 to 35 months, the absolute efficacy of quadrivalent influenza vaccine (QIV) in the prevention of symptomatic influenza infection due to any circulating seasonal influenza strain compared with a non-influenza (child) vaccine (NIV), assessed by reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza A and/or B infection.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice and the applicable national regulations to assure 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.

Following the vaccination, subjects were observed for at least 30 minutes to monitor for any immediate adverse reactions (appropriate medical treatment and supervision were readily available in case of an anaphylactic event).

Background therapy: -

Evidence for comparator:

NIVs were selected as the control group for this study based on recommendations outlined in the Guideline on Influenza Vaccines by the European Medicines Agency (EMA/CHMP/VWP/457259/2014). As per the guideline, NIVs were used to avoid the use of placebo in this vulnerable population and to provide a benefit to study participation for all study subjects. The NIVs selected for the control group were vaccines that were approved for use and commonly used in routine medical practice for the respective age ranges.

The selected NIV controls needed to complement the existing national/regional childhood vaccination programs and therefore the eventual usability of each of the NIVs varied by country/region.

Actual start date of recruitment	01 September 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	8 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 160
Country: Number of subjects enrolled	Czech Republic: 92
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Estonia: 569
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Italy: 91
Country: Number of subjects enrolled	Lithuania: 250

Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Philippines: 285
Country: Number of subjects enrolled	Romania: 45
Country: Number of subjects enrolled	Slovakia: 30
Country: Number of subjects enrolled	Slovenia: 6
Country: Number of subjects enrolled	Spain: 224
Country: Number of subjects enrolled	Thailand: 152
Country: Number of subjects enrolled	Vietnam: 21
Worldwide total number of subjects	2007
EEA total number of subjects	1540

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)	1341
Children (2-11 years)	666
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:

The study was conducted at 56 centers across Europe and Asia and comprised at least 3 clinic visits and 3 telephone contacts (TCs) per completed subject. The study included 2 cohorts (Cohort 1 and Cohort 2) and was conducted over 3 influenza seasons (Northern Hemisphere [NH] 2017/2018, NH 2018/2019, and Southern Hemisphere [SH] 2019).

Pre-assignment

Screening details:

Eligible subjects were randomly assigned to vaccination with QIV or a NIV in a 1:1 ratio. Study comprised of a primary immunization period (including Cohort 1 Year 1 and Cohort 2) and a revaccination period (including subset of subjects from Cohort 1 who were exposed to QIV in Year 1). Results data are presented for the primary immunization period.

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:

Observer blind: the subject and their parents/legally acceptable representative (LAR), the Investigator, and those responsible for evaluation of any study endpoint (e.g., safety, reactogenicity, immunogenicity, and efficacy) and for review/analysis of study data were unaware of the treatment assignments. To maintain blinding, the vaccination was performed by authorized medical site study personnel who did not participate in any of the study clinical evaluations.

Arms

Are arms mutually exclusive?	Yes
Arm title	Quadrivalent Influenza Vaccine

Arm description:

Each subject received 2 doses of QIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3) was planned between 6 and 8 months after the first vaccination.

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:

Subjects received 2 doses of 0.5 milliliters (mL) each of QIV administered by intramuscular injection in the deltoid muscle of the upper arm or in the anterolateral thigh.

For the NH QIV (subunit, inactivated), the active drug substance was 15 micrograms (µg) of hemagglutinin (HA) of each of the 4 viral strains recommended for the NH season by the World Health Organization (WHO) and the Committee for Medicinal Products for Human Use as follows:

- Cohort 1 Year 1 (Season NH 2017/2018)
- Cohort 2 NH (Season NH 2018/2019)

For the SH QIV (subunit, inactivated) the active drug substance was 15 µg of HA of each of the 4 viral strains recommended for the SH season by the WHO as follows:

- Cohort 2 SH (Season SH 2019)

Arm title	Non-influenza Vaccine
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Arm description:

Each subject received 2 doses of a NIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3)

was planned between 6 and 8 months after the first vaccination. For each subject enrolled in the NIV control group, only 1 reference product was used.

Arm type	Control vaccine
Investigational medicinal product name	Non-influenza Vaccine
Investigational medicinal product code	
Other name	NIV
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 2 doses of 0.25 to 0.5 mL each of a NIV control administered by intramuscular injection in the deltoid muscle of the upper arm or in the anterolateral thigh.

Depending on the subject's age and the routine childhood vaccination programs in each of the respective countries, the NIV controls used could be:

For infants 6 to 11 months of age:

- Pneumococcal conjugate vaccine or meningococcal group C conjugate vaccine.

For toddlers 12 to 35 months of age:

- Hepatitis A vaccine, tick borne encephalitis vaccine or varicella vaccine.

Dose and administration details apply for subjects randomized to a NIV in both Cohorts 1 and 2.

Number of subjects in period 1	Quadrivalent Influenza Vaccine	Non-influenza Vaccine
Started	1009	998
Vaccinated	1005	995
Completed	986	975
Not completed	23	23
Consent withdrawn by subject	14	9
Administrative	1	1
Adverse event, non-fatal	1	1
Lost to follow-up	5	10
Protocol deviation	2	2

Baseline characteristics

Reporting groups

Reporting group title	Quadrivalent Influenza Vaccine
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Reporting group description:

Each subject received 2 doses of QIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3) was planned between 6 and 8 months after the first vaccination.

Reporting group title	Non-influenza Vaccine
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Reporting group description:

Each subject received 2 doses of a NIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3) was planned between 6 and 8 months after the first vaccination. For each subject enrolled in the NIV control group, only 1 reference product was used.

Reporting group values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine	Total
Number of subjects	1009	998	2007
Age categorical			
Units: Subjects			
>=6 and <11 months	200	195	395
>=12 and <18 months	291	281	572
>=19 and <24 months	216	217	433
>=25 and <35 months	302	305	607
Age continuous			
Units: Months			
arithmetic mean	19.4	19.6	
standard deviation	± 8.1	± 8.3	-
Gender categorical			
Units: Subjects			
Female	517	499	1016
Male	492	499	991
Race			
Units: Subjects			
White	751	733	1484
Asian	244	240	484
Black	5	6	11
Other	9	19	28
Cohort			
Units: Subjects			
Cohort 1	388	387	775
Cohort 2 Northern Hemisphere	386	379	765
Cohort 2 Southern Hemisphere	235	232	467

End points

End points reporting groups

Reporting group title	Quadrivalent Influenza Vaccine
Reporting group description: Each subject received 2 doses of QIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3) was planned between 6 and 8 months after the first vaccination.	
Reporting group title	Non-influenza Vaccine
Reporting group description: Each subject received 2 doses of a NIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3) was planned between 6 and 8 months after the first vaccination. For each subject enrolled in the NIV control group, only 1 reference product was used.	

Primary: First occurrence of RT-PCR-confirmed influenza A and/or B illness of any severity due to any circulating seasonal influenza strain

End point title	First occurrence of RT-PCR-confirmed influenza A and/or B illness of any severity due to any circulating seasonal influenza strain
End point description: The primary endpoint assessed the first occurrence of RT-PCR-confirmed influenza A and/or B illness of any severity due to any circulating seasonal influenza strain occurring between 28 days following the second vaccine administration and the end of the primary immunization influenza surveillance period. The number of subjects with RT-PCR-confirmed influenza A and/or B infection due to any circulating strain is presented for the full analysis (FA) sample. The analysis excluded subjects who did not receive the second vaccination, those who dropped-out or withdrew before 28 days after the second vaccination, and those with first occurrence of RT-PCR-confirmed influenza between the first vaccination and 28 days after the second vaccination.	
End point type	Primary
End point timeframe: Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]) up to TC3 (end of the primary immunization influenza surveillance period).	

End point values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	991	981		
Units: Subjects	59	117		

Statistical analyses

Statistical analysis title	Absolute vaccine efficacy; primary analysis
Statistical analysis description: Absolute vaccine efficacy of QIV compared with NIVs in the prevention of symptomatic influenza infection due to any circulating seasonal influenza strain. Time to first occurrence was measured from Day 28 after second study vaccination. Hazard ratio (HR) was obtained from a Cox Proportional Hazards model. For purpose of the analysis, vaccine efficacy was derived as 1-HR. Model contained age group (6-	

11, 12-18, 19-24, 25-35 and 6-24 months), country and vaccine group (QIV or NIV) as factors.

Comparison groups	Non-influenza Vaccine v Quadrivalent Influenza Vaccine
Number of subjects included in analysis	1972
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Absolute vaccine efficacy of QIV
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.66

Secondary: First occurrence of RT-PCR-confirmed influenza A and/or B illness of any severity due to antigenically-matching influenza strains

End point title	First occurrence of RT-PCR-confirmed influenza A and/or B illness of any severity due to antigenically-matching influenza strains
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End point description:

A secondary endpoint assessed the first occurrence of RT-PCR-confirmed influenza A and/or B illness of any severity due to antigenically-matching influenza strains occurring between 28 days following the second vaccine administration and the end of the primary immunization influenza surveillance period. The number of subjects with RT-PCR-confirmed influenza A and/or B infection due to antigenically-matching strains is presented for the FA sample. The analysis excluded subjects who did not receive the second vaccination, those who dropped-out or withdrew before 28 days after the second vaccination, and those with first occurrence of RT-PCR-confirmed influenza between the first vaccination and 28 days after the second vaccination.

End point type	Secondary
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End point timeframe:

Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]) up to TC3 (end of the primary immunization influenza surveillance period).

End point values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	991	981		
Units: Subjects	19	56		

Statistical analyses

Statistical analysis title	Absolute vaccine efficacy; secondary analysis
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Statistical analysis description:

Absolute vaccine efficacy of QIV compared with NIVs in the prevention of symptomatic influenza infection due to antigenically-matching influenza strains. Time to first occurrence was measured from Day 28 after second study vaccination. The HR was obtained from a Cox Proportional Hazards model. For purpose of the analysis, vaccine efficacy was derived as 1-HR. Model contained age group (6-11, 12-18, 19-24, 25-35 and 6-24 months), country and vaccine group (QIV or NIV) as factors.

Comparison groups	Quadrivalent Influenza Vaccine v Non-influenza Vaccine
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Number of subjects included in analysis	1972
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Absolute vaccine efficacy of QIV
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.81

Secondary: Pre- and post-vaccination geometric mean hemagglutination inhibition (HI) antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Pre- and post-vaccination geometric mean hemagglutination inhibition (HI) antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the geometric mean titer with respect to the HI assay. The pre-first vaccination and post-second vaccination geometric mean HI antibody titers against each of the indicated vaccine strains are presented for the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 or a NIV during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

Pre-vaccination: Visit 1 (Day 1). Post-vaccination: Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

End point values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	343		
Units: Titer				
geometric mean (standard deviation)				
A(H3N2): pre-vaccination (n=346, 337)	12.5 (± 5.8)	12.6 (± 5.8)		
A(H3N2): post-vaccination (n=348, 341)	341.4 (± 6.7)	12.9 (± 5.7)		
A(H1N1): pre-vaccination (n=344, 337)	9.4 (± 3.4)	8.6 (± 3.3)		
A(H1N1): post-vaccination (n=347, 338)	71.1 (± 4.4)	12.0 (± 4.1)		
B/Victoria: pre-vaccination (n=347, 337)	5.6 (± 1.7)	5.2 (± 1.4)		
B/Victoria: post-vaccination (n=348, 341)	11.1 (± 4.0)	5.3 (± 1.5)		
B/Yamagata: pre-vaccination (n=344, 337)	5.0 (± 1.1)	5.1 (± 1.2)		
B/Yamagata: post-vaccination (n=347, 338)	10.8 (± 3.1)	5.6 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pre- and post-vaccination geometric mean virus neutralization (VN) antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Pre- and post-vaccination geometric mean virus neutralization (VN) antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the geometric mean titer with respect to the VN assay. The pre-first vaccination and post-second vaccination geometric mean VN antibody titers against each of the indicated vaccine strains are presented for the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

Pre-vaccination: Visit 1 (Day 1). Post-vaccination: Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

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: The VN and NI assays were only performed for a random subset of subjects who were vaccinated with QIV from Cohort 1. Subjects vaccinated with a NIV are therefore not applicable for reporting of this end point.

End point values	Quadrivalent Influenza Vaccine			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Titer				
geometric mean (standard deviation)				
A(H3N2): pre-vaccination (n=102)	8.5 (± 1.6)			
A(H3N2): post-vaccination (n=102)	22.2 (± 3.7)			
A(H1N1): pre-vaccination (n=102)	7.3 (± 1.2)			
A(H1N1): post-vaccination (n=102)	12.7 (± 2.3)			
B/Victoria: pre-vaccination (n=102)	7.9 (± 1.6)			
B/Victoria: post-vaccination (n=102)	20.0 (± 3.3)			
B/Yamagata: pre-vaccination (n=102)	7.9 (± 1.5)			
B/Yamagata: post-vaccination (n=102)	41.5 (± 2.7)			

Statistical analyses

Secondary: Pre- and post-vaccination geometric mean neuraminidase inhibition (NI) antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Pre- and post-vaccination geometric mean neuraminidase inhibition (NI) antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage ^[2]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the geometric mean titer with respect to the NI assay. The pre-first vaccination and post-second vaccination geometric mean NI antibody titers against each of the indicated vaccine strains are presented for the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

Pre-vaccination: Visit 1 (Day 1). Post-vaccination: Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The VN and NI assays were only performed for a random subset of subjects who were vaccinated with QIV from Cohort 1. Subjects vaccinated with a NIV are therefore not applicable for reporting of this end point.

End point values	Quadrivalent Influenza Vaccine			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Titer				
geometric mean (standard deviation)				
A(H3N2): pre-vaccination (n=102)	7.8 (± 2.5)			
A(H3N2): post-vaccination (n=102)	22.8 (± 5.2)			
A(H1N1): pre-vaccination (n=102)	5.7 (± 1.9)			
A(H1N1): post-vaccination (n=102)	60.1 (± 3.2)			
B/Victoria: pre-vaccination (n=101)	6.4 (± 2.3)			
B/Victoria: post-vaccination (n=102)	39.9 (± 4.0)			
B/Yamagata: pre-vaccination (n=102)	5.4 (± 1.4)			
B/Yamagata: post-vaccination (n=102)	8.4 (± 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post-vaccination geometric mean fold increases in HI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Post-vaccination geometric mean fold increases in HI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the geometric mean fold increase with respect to HI titers. The post-vaccination geometric mean fold increase in HI antibody titers against each of the indicated vaccine strains are presented for the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 or a NIV during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

At Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

End point values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	343		
Units: Titer (fold increase)				
geometric mean (standard deviation)				
A(H3N2) (n=346, 335)	27.4 (± 4.1)	1.0 (± 2.0)		
A(H1N1) (n=344, 332)	7.7 (± 4.7)	1.3 (± 4.1)		
B/Victoria (n=347, 335)	2.0 (± 3.7)	1.0 (± 1.3)		
B/Yamagata (n=344, 332)	2.2 (± 3.1)	1.1 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Post-vaccination geometric mean fold increases in VN antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Post-vaccination geometric mean fold increases in VN antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage ^[3]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the geometric mean fold increase with respect to VN titers. The post-vaccination geometric mean fold increase in VN antibody titers against each of the indicated vaccine strains are presented for the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

At Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

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: The VN and NI assays were only performed for a random subset of subjects who were vaccinated with QIV from Cohort 1. Subjects vaccinated with a NIV are therefore not applicable for reporting of this end point.

End point values	Quadrivalent Influenza Vaccine			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Titer (fold increase)				
geometric mean (standard deviation)				
A(H3N2) (n=102)	2.6 (± 2.8)			
A(H1N1) (n=102)	1.7 (± 2.1)			
B/Victoria (n=102)	2.5 (± 2.6)			
B/Yamagata (n=102)	5.3 (± 2.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post-vaccination geometric mean fold increases in NI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Post-vaccination geometric mean fold increases in NI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage ^[4]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the geometric mean fold increase with respect to NI titers. The post-vaccination geometric mean fold increase in NI antibody titers against each of the indicated vaccine strains are presented for the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

At Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The VN and NI assays were only performed for a random subset of subjects who were vaccinated with QIV from Cohort 1. Subjects vaccinated with a NIV are therefore not applicable for reporting of this end point.

End point values	Quadrivalent Influenza Vaccine			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Titer (fold increase)				
geometric mean (standard deviation)				
A(H3N2) (n=102)	2.9 (± 2.8)			
A(H1N1) (n=102)	10.5 (± 2.7)			
B/Victoria (n=101)	6.2 (± 2.8)			
B/Yamagata (n=102)	1.6 (± 2.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion rates based on HI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Seroconversion rates based on HI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the seroconversion rate with respect to HI titers. Seroconversion was defined as becoming seropositive (titer ≥ 10) if seronegative (titer < 10) at enrollment, or (at least) a 4-fold rise in titer if seropositive (titer ≥ 10) at enrollment. Seroconversion rates for HI are presented as the percentage of seroconverted subjects against each of the indicated vaccine strains. Analysis was performed on the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 or a NIV during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

At Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

End point values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	343		
Units: Percentage of subjects				
number (not applicable)				
A(H3N2) (n=346, 335)	92.5	3.6		
A(H1N1) (n=344, 332)	74.4	21.4		
B/Victoria (n=347, 335)	26.5	1.2		
B/Yamagata (n=344, 332)	35.5	3.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion rates based on VN antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Seroconversion rates based on VN antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage ^[5]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the seroconversion rate with respect to VN titers. Seroconversion was defined as becoming seropositive (titer ≥ 10) if seronegative (titer < 10) at enrollment, or (at least) a 4-fold rise in titer if seropositive (titer ≥ 10) at enrollment. Seroconversion rates for VN are presented as the percentage of seroconverted subjects against each of the indicated vaccine strains. Analysis was performed on the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary			
End point timeframe:				
At Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).				
Notes:				
[5] - 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 VN and NI assays were only performed for a random subset of subjects who were vaccinated with QIV from Cohort 1. Subjects vaccinated with a NIV are therefore not applicable for reporting of this end point.				
End point values	Quadrivalent Influenza Vaccine			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Percentage of subjects				
number (not applicable)				
A(H3N2) (n=102)	71.6			
A(H1N1) (n=102)	51.0			
B/Victoria (n=102)	68.6			
B/Yamagata (n=102)	93.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion rates based on NI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage

End point title	Seroconversion rates based on NI antibody titers against the influenza A and B strains: A(H3N2), A(H1N1), B/Victoria lineage and B/Yamagata lineage ^[6]
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End point description:

Characterization of the immunogenicity of each of the strains in QIV was assessed by deriving the seroconversion rate with respect to NI titers. Seroconversion was defined as becoming seropositive (titer ≥ 10) if seronegative (titer < 10) at enrollment, or (at least) a 4-fold rise in titer if seropositive (titer ≥ 10) at enrollment. Seroconversion rates for NI are presented as the percentage of seroconverted subjects against each of the indicated vaccine strains. Analysis was performed on the immunogenicity sample for subjects in Cohort 1 (i.e., received QIV recommended for the NH season 2017/2018 during the primary immunogenicity period). n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

At Visit 3 (28-33 days after second vaccination [equivalent to 56-66 days after Day 1]).

Notes:

[6] - 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 VN and NI assays were only performed for a random subset of subjects who were vaccinated with QIV from Cohort 1. Subjects vaccinated with a NIV are therefore not applicable for reporting of this end point.

End point values	Quadrivalent Influenza Vaccine			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Percentage of subjects				
number (not applicable)				
A(H3N2) (n=102)	66.7			
A(H1N1) (n=102)	97.1			
B/Victoria (n=101)	93.1			
B/Yamagata (n=102)	34.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with solicited systemic reactions

End point title	Percentage of subjects with solicited systemic reactions
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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). The diary was completed by the parents/LAR, as appropriate. The following systemic reactions were assessed: fever, irritability/fussiness, drowsiness, sweating, diarrhea/vomiting and loss of appetite. The percentage of subjects with solicited systemic reactions during the primary immunization period are presented for the safety sample. n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

Period of 7 days after each of the 2 study vaccinations (first vaccination at Visit 1 [Day 1] and second vaccination at Visit 2 [28-33 days after Day 1]).

End point values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1005	995		
Units: Percentage of subjects				
number (not applicable)				
Fever (n=999, 985)	19.3	18.1		
Irritability/fussiness (n=1000, 985)	30.2	33.6		
Drowsiness (n=1000, 985)	17.5	17.3		
Sweating (n=1000, 985)	12.4	11.5		
Diarrhea/vomiting (n=1000, 985)	19.8	18.0		
Loss of appetite (n=1000, 985)	19.3	21.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with solicited local reactions

End point title	Percentage of subjects with solicited local reactions
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End point description:

A subject diary was used to record pre-specified vaccination site (local) reactions occurring during the first 7 days after vaccination (solicited reactogenicity). The diary was completed by the parents/LAR, as appropriate. The following vaccination site reactions were assessed: erythema, swelling, induration, vaccination site pain and ecchymosis. Percentages of subjects with solicited local reactions during the primary immunization period are presented for the safety sample. n = number of subjects with non-missing data for each parameter analyzed.

End point type	Secondary
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End point timeframe:

Period of 7 days after each of the 2 study vaccinations (first vaccination at Visit 1 [Day 1] and second vaccination at Visit 2 [28-33 days after Day 1]).

End point values	Quadrivalent Influenza Vaccine	Non-influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1005	995		
Units: Percentage of subjects				
number (not applicable)				
Vaccination site erythema (n=1000, 985)	11.6	19.6		
Vaccination site swelling (n=1000, 985)	4.3	7.2		
Vaccination site induration (n=1000, 985)	4.4	10.4		
Vaccination site pain (n=1000, 985)	22.6	27.0		
Vaccination site ecchymosis (n=1000, 985)	4.0	4.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are reported for the primary immunization period from Day 1 up to the final safety follow-up TC. Overall time frame of between 6 and 8 months after first vaccination.

Adverse event reporting additional description:

The safety sample consisted of all subjects who were in the all subjects vaccinated sample and had at least 1 post-vaccination safety observation.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Quadrivalent Influenza Vaccine
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Reporting group description:

Each subject received 2 doses of QIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3) was planned between 6 and 8 months after the first vaccination.

Reporting group title	Non-influenza Vaccine
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Reporting group description:

Each subject received 2 doses of a NIV. The first vaccination was administered on Day 1 (Visit 1), followed by a second vaccination 28 to 33 days after Day 1 (Visit 2). The final safety follow-up (TC3) was planned between 6 and 8 months after the first vaccination. For each subject enrolled in the NIV control group, only 1 reference product was used.

Serious adverse events	Quadrivalent Influenza Vaccine	Non-influenza Vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 1005 (3.68%)	54 / 995 (5.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical poisoning			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Carbohydrate metabolism disorder			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
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 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Niemann-Pick disease			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	5 / 1005 (0.50%)	3 / 995 (0.30%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	7 / 1005 (0.70%)	10 / 995 (1.01%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
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			
Immune thrombocytopenic purpura			

subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 1005 (0.00%)	2 / 995 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
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			
Asthma			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoidal hypertrophy			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
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	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal sinus			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 1005 (0.60%)	6 / 995 (0.60%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 1005 (0.10%)	2 / 995 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	2 / 1005 (0.20%)	3 / 995 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 1005 (0.10%)	3 / 995 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 1005 (0.20%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	8 / 1005 (0.80%)	3 / 995 (0.30%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parasitic gastroenteritis			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 1005 (0.10%)	2 / 995 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 1005 (0.10%)	2 / 995 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 1005 (0.00%)	2 / 995 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 1005 (0.10%)	2 / 995 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis bacterial			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 1005 (0.10%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 1005 (0.10%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus infection			
subjects affected / exposed	1 / 1005 (0.10%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chikungunya virus infection			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpangina			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 1005 (0.10%)	0 / 995 (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	2 / 1005 (0.20%)	5 / 995 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 1005 (0.00%)	1 / 995 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Quadrivalent Influenza Vaccine	Non-influenza Vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	586 / 1005 (58.31%)	616 / 995 (61.91%)	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	412 / 1005 (41.00%)	443 / 995 (44.52%)	
occurrences (all)	657	741	
Pyrexia			
subjects affected / exposed	36 / 1005 (3.58%)	25 / 995 (2.51%)	
occurrences (all)	43	33	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 1005 (1.59%)	21 / 995 (2.11%)	
occurrences (all)	16	22	
Vomiting			
subjects affected / exposed	11 / 1005 (1.09%)	13 / 995 (1.31%)	
occurrences (all)	12	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	42 / 1005 (4.18%)	47 / 995 (4.72%)	
occurrences (all)	47	51	
Rhinorrhoea			
subjects affected / exposed	13 / 1005 (1.29%)	7 / 995 (0.70%)	
occurrences (all)	14	9	

Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	11 / 1005 (1.09%)	8 / 995 (0.80%)	
occurrences (all)	13	8	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	65 / 1005 (6.47%)	74 / 995 (7.44%)	
occurrences (all)	106	96	
Rhinitis			
subjects affected / exposed	57 / 1005 (5.67%)	74 / 995 (7.44%)	
occurrences (all)	66	82	
Nasopharyngitis			
subjects affected / exposed	44 / 1005 (4.38%)	56 / 995 (5.63%)	
occurrences (all)	58	79	
Tonsillitis			
subjects affected / exposed	23 / 1005 (2.29%)	15 / 995 (1.51%)	
occurrences (all)	25	16	
Pharyngitis			
subjects affected / exposed	15 / 1005 (1.49%)	19 / 995 (1.91%)	
occurrences (all)	15	22	
Laryngitis			
subjects affected / exposed	9 / 1005 (0.90%)	12 / 995 (1.21%)	
occurrences (all)	11	12	
Viral upper respiratory tract infection			
subjects affected / exposed	36 / 1005 (3.58%)	35 / 995 (3.52%)	
occurrences (all)	44	42	
Viral infection			
subjects affected / exposed	26 / 1005 (2.59%)	20 / 995 (2.01%)	
occurrences (all)	29	22	
Respiratory tract infection viral			
subjects affected / exposed	18 / 1005 (1.79%)	21 / 995 (2.11%)	
occurrences (all)	21	26	
Otitis media			
subjects affected / exposed	35 / 1005 (3.48%)	45 / 995 (4.52%)	
occurrences (all)	40	57	
Otitis media acute			

subjects affected / exposed	34 / 1005 (3.38%)	33 / 995 (3.32%)	
occurrences (all)	41	40	
Bronchitis			
subjects affected / exposed	58 / 1005 (5.77%)	44 / 995 (4.42%)	
occurrences (all)	67	57	
Pneumonia			
subjects affected / exposed	17 / 1005 (1.69%)	22 / 995 (2.21%)	
occurrences (all)	22	27	
Gastroenteritis			
subjects affected / exposed	48 / 1005 (4.78%)	46 / 995 (4.62%)	
occurrences (all)	54	51	
Conjunctivitis			
subjects affected / exposed	23 / 1005 (2.29%)	30 / 995 (3.02%)	
occurrences (all)	25	36	
Respiratory tract infection			
subjects affected / exposed	20 / 1005 (1.99%)	30 / 995 (3.02%)	
occurrences (all)	30	44	
Hand-foot-and-mouth disease			
subjects affected / exposed	23 / 1005 (2.29%)	18 / 995 (1.81%)	
occurrences (all)	23	18	
Pharyngitis streptococcal			
subjects affected / exposed	7 / 1005 (0.70%)	16 / 995 (1.61%)	
occurrences (all)	10	31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2017	Protocol amendment 1 incorporated the following changes: exclusion criteria changes (2 added and 2 others revised), clarification for the selection of control vaccines for different age groups, clarification of Investigator instructions in case of immediate (serious) adverse reactions, and addition of specific guidance on the reporting of suspected unexpected serious adverse reactions.
21 February 2018	Protocol amendment 2 incorporated the following changes: the planned interim analysis was removed due to lower than planned recruitment of subjects into Cohort 1, number of countries and sites was expanded to enable recruitment of up to 2,000 subjects in Cohort 2, and clarification regarding adverse events of special interest.
12 July 2018	Protocol amendment 3 incorporated the following changes: enrollment of Cohort 2 was extended into an additional influenza season.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported