



Clinical trial results:

A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects 2 years to <18 Years of Age

Summary

EudraCT number	2016-002883-15
Trial protocol	LT EE ES FI PL
Global end of trial date	30 September 2019

Results information

Result version number	v1 (current)
This version publication date	10 April 2020
First version publication date	10 April 2020

Trial information

Trial identification

Sponsor protocol code	V130_12
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03165617
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seqirus UK Limited
Sponsor organisation address	The Point, 29 Market Street Level 3, Maidenhead, Berkshire, United Kingdom, SL6 8AA
Public contact	Clinical Trial Disclosure Manager , Seqirus , Seqirus.Clinicaltrials@seqirus.com
Scientific contact	Clinical Trial Disclosure Manager , Seqirus, Seqirus.Clinicaltrials@seqirus.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 January 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Primary Efficacy Objective(s):

To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in subjects ≥ 2 years to < 18 years of age.

In case of successful demonstration of the primary efficacy objective:

- Co-Primary Efficacy Objective(s):

To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in subjects ≥ 3 years to < 18 years of age.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

The V130_12 followed both EU (CHMP) and US (FDA) guidelines to use noninfluenza active comparator to provide benefit to subjects randomised to the comparator group. Specifically for this study the non-influenza active comparator was Meningococcal (Group ACWY) Conjugate Vaccine.

Actual start date of recruitment	17 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 195
Country: Number of subjects enrolled	Philippines: 1800
Country: Number of subjects enrolled	Thailand: 400
Country: Number of subjects enrolled	Poland: 298
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Estonia: 1198
Country: Number of subjects enrolled	Finland: 326
Country: Number of subjects enrolled	Lithuania: 292

Worldwide total number of subjects	4514
EEA total number of subjects	2119

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)	3244
Adolescents (12-17 years)	1270
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 39 centers in 8 countries

Pre-assignment

Screening details:

All enrolled subjects were included in the study

Period 1

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

Blinding implementation details:

The study was designed as an observer-blind study. Neither the subject nor any of the investigative site staff who were involved in the subjects' clinical evaluations or treatment were aware of the vaccine administered. Vaccine administration was shielded from the subject and blinded study personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	QIVc (≥ 2 years to < 18 years)

Arm description:

Cell-derived Seasonal Quadrivalent Influenza Vaccine

Arm type	Experimental
Investigational medicinal product name	QIVc
Investigational medicinal product code	
Other name	cell-derived Quadrivalent Influenza Vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

All subjects received a 0.5 mL intramuscular dose of QIVc at Day 1. Participants who were not previously vaccinated received a second 0.5 mL dose at Day 29.

Arm title	Comparator (≥ 2 years to < 18 years)
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Arm description:

Non-influenza comparator vaccine for intramuscular use.

Arm type	Active comparator
Investigational medicinal product name	Meningococcal Conjugate (Group ACWY) Vaccine
Investigational medicinal product code	
Other name	Men ACWY vaccine, Menveo
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

All subjects received a 0.5 mL intramuscular dose of Meningococcal (Group ACWY) Conjugate Vaccine. Subjects in the this group who were not previously vaccinated received placebo (0.9% w/v saline for injection) as second vaccination for blinding purposes.

Number of subjects in period 1	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)
Started	2258	2256
Completed	2249	2247
Not completed	9	9
Adverse event, serious fatal	-	1
Consent withdrawn by subject	3	3
Other	1	3
Lost to follow-up	5	2

Baseline characteristics

Reporting groups

Reporting group title	QIVc (≥2 years to <18 years)
Reporting group description: Cell-derived Seasonal Quadrivalent Influenza Vaccine	
Reporting group title	Comparator (≥2 years to <18 years)
Reporting group description: Non-influenza comparator vaccine for intramuscular use.	

Reporting group values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)	Total
Number of subjects	2258	2256	4514
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	1638	1606	3244
Adolescents (12-17 years)	620	650	1270
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	8.7	8.9	
standard deviation	± 4.0	± 4.1	-
Gender categorical Units: Subjects			
Female	1106	1082	2188
Male	1152	1174	2326

End points

End points reporting groups

Reporting group title	QIVc (≥2 years to <18 years)
Reporting group description: Cell-derived Seasonal Quadrivalent Influenza Vaccine	
Reporting group title	Comparator (≥2 years to <18 years)
Reporting group description: Non-influenza comparator vaccine for intramuscular use.	
Subject analysis set title	QIVc (≥3 years to <18 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Cell-derived Seasonal Quadrivalent Influenza Vaccine	
Subject analysis set title	Comparator (≥3 years to <18 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Non-influenza comparator vaccine for intramuscular use.	
Subject analysis set title	QIVc (≥2 years to <9 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Cell-derived Seasonal Quadrivalent Influenza Vaccine	
Subject analysis set title	Comparator (≥2 years to <9 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Non-influenza comparator vaccine for intramuscular use.	
Subject analysis set title	QIVc (≥4 years to <18 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Cell-derived Seasonal Quadrivalent Influenza Vaccine	
Subject analysis set title	Comparator (≥4 years to <18 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Non-influenza comparator vaccine for intramuscular use.	
Subject analysis set title	QIVc (≥9 years to <18 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Cell-derived Seasonal Quadrivalent Influenza Vaccine	
Subject analysis set title	Comparator (≥9 years to <18 years of age)
Subject analysis set type	Full analysis
Subject analysis set description: Non-influenza comparator vaccine for intramuscular use.	

Primary: Primary Efficacy: First occurrence of either RT-PCR- or culture-confirmed influenza (time-to-event analyses) due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine in subjects ≥2 to <18 yrs

End point title	Primary Efficacy: First occurrence of either RT-PCR- or culture-confirmed influenza (time-to-event analyses) due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine in subjects ≥2 to <18 yrs
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End point description:

The primary efficacy endpoint was defined as the time from the last study vaccination to the onset of the first occurrence of either RT-PCR- or culture-confirmed influenza (time-to-event analyses) due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.

The success criterion used for this primary objective was as follows: The efficacy of the QIVc was demonstrated if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for VE was above 20%.

Dataset Used: FAS-Efficacy = All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

End point type	Primary
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End point timeframe:

Day 14 to Day 180 or until the end of the influenza season, whichever is longer

End point values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2257	2252		
Units: Cases				
Any Strain	175	364		

Statistical analyses

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain
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Statistical analysis description:

Adjusted aVE for QIVc vs. comparator. Success criteria for the primary efficacy endpoint was met if the LL of the 2-sided 95% CI of the aVE estimate was greater than 20% (primary endpoint) using the protocol definition of ILI for the entire age range (2 to <18 years of age).

Comparison groups	Comparator (≥2 years to <18 years) v QIVc (≥2 years to <18 years)
Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	54.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.67
upper limit	62.12

Primary: Co-Primary Efficacy: First occurrence of either RT-PCR- or culture-confirmed influenza (time-to-event analyses) due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine in subjects 3 to <18 yrs

End point title	Co-Primary Efficacy: First occurrence of either RT-PCR- or culture-confirmed influenza (time-to-event analyses) due to
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any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine in subjects 3 to <18 yrs

End point description:

The co-primary efficacy endpoints were defined as the time from the last study vaccination to the onset of the first occurrence of either RT-PCR- or culture-confirmed influenza (time-to-event analyses) due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.

The co-primary efficacy objective was to be assessed on condition that the primary efficacy objective was successfully demonstrated. The success criterion used for this co-primary objective was as follows: The efficacy of the QIVc was demonstrated if the LL of the 2-sided 95% CI for VE was above 30%.

Dataset Used: FAS-Efficacy = All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

End point type	Primary
End point timeframe:	
Day 14 to Day 180 or until the end of the influenza season, whichever is longer	

End point values	QIVc (≥3 years to <18 years of age)	Comparator (≥3 years to <18 years of age)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2208	2201		
Units: Cases				
Any Strain	175	351		

Statistical analyses

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain
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Statistical analysis description:

Adjusted aVE for QIVc vs. comparator. Success criteria for the primary efficacy endpoint was met if the LL of the 2-sided 95% CI of the aVE estimate was greater than 30% (co-primary endpoint) using the protocol definition of ILI for the entire age range (3 to <18 years of age).

Comparison groups	Comparator (≥3 years to <18 years of age) v QIVc (≥3 years to <18 years of age)
Number of subjects included in analysis	4409
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	54.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.8
upper limit	61.71

Secondary: Secondary Efficacy: First occurrence of either RT-PCR- or culture-

confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine

End point title	Secondary Efficacy: First occurrence of either RT-PCR- or culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine
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End point description:

The endpoint was defined as the time from the last study vaccination to the onset of the first occurrence of either RT-PCR- or culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years.

Dataset Used: FAS-Efficacy = All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

End point type	Secondary
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End point timeframe:

Day 14 to Day 180 or until the end of the influenza season, whichever is longer

End point values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)	QIVc (≥2 years to <9 years of age)	Comparator (≥2 years to <9 years of age)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	2257	2252	1146	1142
Units: Cases				
Any	175	364	123	234

End point values	QIVc (≥4 years to <18 years of age)	Comparator (≥4 years to <18 years of age)	QIVc (≥9 years to <18 years of age)	Comparator (≥9 years to <18 years of age)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2045	2032	1111	1110
Units: Cases				
Any	154	310	52	130

Statistical analyses

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <18yrs
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Statistical analysis description:

Absolute Vaccine Efficacy (aVE) for 2 to <18 Years.

Comparison groups	QIVc (≥2 years to <18 years) v Comparator (≥2 years to <18 years)
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Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	54.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.67
upper limit	62.12

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <9yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 2 to <9 Years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	Comparator (≥ 2 years to <9 years of age) v QIVc (≥ 2 years to <9 years of age)
Number of subjects included in analysis	2288
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	50.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	38.43
upper limit	60.22

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 4 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 4 to <18 Years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥ 4 years to <18 years of age) v Comparator (≥ 4 years to <18 years of age)
Number of subjects included in analysis	4077
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	53.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	43.38
upper limit	61.54

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 9 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 9 to <18 Years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥9 years to <18 years of age) v Comparator (≥9 years to <18 years of age)
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	61.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.37
upper limit	72.34

Secondary: Secondary Efficacy: First occurrence of RT-PCR-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine

End point title	Secondary Efficacy: First occurrence of RT-PCR-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine
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End point description:

The endpoint was defined as the time from the last study vaccination to the onset of the first occurrence of RT-PCR-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years

Dataset Used: FAS-Efficacy = All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

End point type	Secondary
End point timeframe: Day 14 to Day 180 or until the end of the influenza season, whichever is longer	

End point values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)	QIVc (≥2 years to <9 years of age)	Comparator (≥2 years to <9 years of age)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	2257	2252	1146	1142
Units: Cases	175	364	123	234

End point values	QIVc (≥4 years to <18 years of age)	Comparator (≥4 years to <18 years of age)	QIVc (≥9 years to <18 years of age)	Comparator (≥9 years to <18 years of age)
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		age)		age)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2045	2032	1111	1110
Units: Cases	154	310	52	130

Statistical analyses

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 2 to <18 Years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	Comparator (≥ 2 years to <18 years) v QIVc (≥ 2 years to <18 years)
Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	54.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.67
upper limit	62.12

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <9yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 2 to <9 Years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥ 2 years to <9 years of age) v Comparator (≥ 2 years to <9 years of age)
Number of subjects included in analysis	2288
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	50.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	38.43
upper limit	60.22

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 4 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 4 to <18 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	

Comparison groups	QIVc (≥4 years to <18 years of age) v Comparator (≥4 years to <18 years of age)
Number of subjects included in analysis	4077
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	53.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	43.38
upper limit	61.54

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 9 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 9 to <18 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥9 years to <18 years of age) v Comparator (≥9 years to <18 years of age)
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	61.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.37
upper limit	72.34

Secondary: Secondary Efficacy: First occurrence of culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine

End point title	Secondary Efficacy: First occurrence of culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine
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End point description:

The endpoint was defined as the time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years.

Dataset Used: FAS-Efficacy = All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

End point type	Secondary
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End point timeframe:

Day 14 to Day 180 or until the end of the influenza season, whichever is longer

End point values	QIVc (≥ 2 years to <18 years)	Comparator (≥ 2 years to <18 years)	QIVc (≥ 2 years to <9 years of age)	Comparator (≥ 2 years to <9 years of age)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	2257	2252	1146	1142
Units: Cases	115	279	79	190

End point values	QIVc (≥ 4 years to <18 years of age)	Comparator (≥ 4 years to <18 years of age)	QIVc (≥ 9 years to <18 years of age)	Comparator (≥ 9 years to <18 years of age)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2045	2032	1111	1110
Units: Cases	101	237	36	89

Statistical analyses

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <18 yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 2 to <18 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥ 2 years to <18 years) v Comparator (≥ 2 years to <18 years)
Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	60.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.3
upper limit	68.46

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <9 yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 2 to <9 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥ 2 years to <9 years of age) v Comparator (≥ 2 years to <9 years of age)

Number of subjects included in analysis	2288
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	60.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.01
upper limit	69.83

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 4 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 4 to <18 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	Comparator (≥ 4 years to <18 years of age) v QIVc (≥ 4 years to <18 years of age)
Number of subjects included in analysis	4077
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	59.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.08
upper limit	68.05

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 9 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 9 to <18 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥ 9 years to <18 years of age) v Comparator (≥ 9 years to <18 years of age)
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	60.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	42.14
upper limit	73.33

Secondary: Secondary Efficacy: First occurrence of culture-confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine

End point title	Secondary Efficacy: First occurrence of culture-confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine
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End point description:

The endpoint was defined as the time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years.

Dataset Used: FAS-Efficacy = All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

End point type	Secondary
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End point timeframe:

Day 14 to Day 180 or until the end of the influenza season, whichever is longer

End point values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)	QIVc (≥2 years to <9 years of age)	Comparator (≥2 years to <9 years of age)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	2257	2252	1146	1142
Units: Cases	90	236	64	164

End point values	QIVc (≥4 years to <18 years of age)	Comparator (≥4 years to <18 years of age)	QIVc (≥9 years to <18 years of age)	Comparator (≥9 years to <18 years of age)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2045	2032	1111	1110
Units: Cases	81	200	26	72

Statistical analyses

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <18yrs
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Statistical analysis description:

Absolute Vaccine Efficacy (aVE) for 2 to <18 Years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints

Comparison groups	QIVc (≥2 years to <18 years) v Comparator (≥2 years to <18 years)
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Number of subjects included in analysis	4509
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	63.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.64
upper limit	71.48

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 2 to <9yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 2 to <9 Years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥2 years to <9 years of age) v Comparator (≥2 years to <9 years of age)
Number of subjects included in analysis	2288
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	63.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.66
upper limit	72.32

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 4 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 4 to <18 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥4 years to <18 years of age) v Comparator (≥4 years to <18 years of age)
Number of subjects included in analysis	4077
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	61.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.25
upper limit	70.33

Statistical analysis title	Absolute Vaccine Efficacy, Any Strain, 9 to <18yrs
Statistical analysis description: Absolute Vaccine Efficacy (aVE) for 9 to <18 years. Note that no prespecified criteria for success were defined for the secondary efficacy endpoints	
Comparison groups	QIVc (≥9 years to <18 years of age) v Comparator (≥9 years to <18 years of age)
Number of subjects included in analysis	2221
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	aVE
Point estimate	64.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.84
upper limit	77.51

Secondary: Secondary Immunogenicity: Geometric Mean Titers for 4 influenza strains (HI Assay)

End point title	Secondary Immunogenicity: Geometric Mean Titers for 4 influenza strains (HI Assay)
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End point description:

Immunogenicity was characterized by HI assay 3 weeks after the last vaccination in a subset of subjects 2 to <9 years of age enrolled in Season 2 (n=432) and Season 3 (n=319) who were immunized and had immunogenicity data at the assessed timepoints (FAS Immunogenicity). Immunogenicity was assessed at baseline (Day 1; all subjects in immunogenicity subset), at Day 22 (all "previously vaccinated" subjects receiving a single dose of the study vaccine), and at Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains using the HI assay.

Dataset used: FAS Immunogenicity (HI) = All subjects in the All Enrolled Set who received at least one dose of study vaccine and provided evaluable serum samples at both baseline and after the last vaccination.

End point type	Secondary
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End point timeframe:

Day 1 (all subjects), Day 22 (all previously vaccinated subjects) or Day 29 and Day 50 (all not previously vaccinated subjects receiving 2 doses)

End point values	QIVc (≥2 years to <9 years of age)	Comparator (≥2 years to <9 years of age)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210 ^[1]	212 ^[2]		
Units: geometric mean titre				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 HI GMT Season 2	50.83 (41.89 to 61.66)	47.51 (39.15 to 57.64)		
A/H1N1 Day 22/50 HI GMT Season 2	283.45 (249.22 to 322.38)	49.20 (43.24 to 55.98)		

A/H3N2 Day 1 HI GMT Season 2	97.02 (86.51 to 108.81)	94.40 (84.19 to 105.84)		
A/H3N2 Day 22/50 HI GMT Season 2	168.73 (150.87 to 188.70)	96.27 (86.05 to 107.70)		
B/Victoria Day 1 HI GMT Season 2	11.67 (9.97 to 13.67)	11.73 (10.02 to 13.73)		
B/Victoria Day 22/50 HI GMT Season 2	45.25 (39.73 to 51.54)	11.94 (10.48 to 13.60)		
B/Yamagata Day 1 HI GMT Season 2	10.87 (9.46 to 12.50)	12.17 (10.59 to 13.99)		
B/Yamagata Day 22/50 HI GMT Season 2	52.81 (45.77 to 60.94)	12.34 (10.68 to 14.24)		
A/H1N1 Day 1 HI GMT Season 3	36.62 (22.61 to 59.31)	31.76 (19.88 to 50.74)		
A/H1N1 Day 22/50 HI GMT Season 3	380.70 (283.12 to 511.91)	48.22 (36.14 to 64.32)		
A/H3N2 Day 1 HI GMT Season 3	20.85 (15.99 to 27.20)	20.74 (16.02 to 26.85)		
A/H3N2 Day 22/50 HI GMT Season 3	67.64 (57.03 to 80.24)	16.73 (14.17 to 19.77)		
B/Victoria Day 1 HI GMT Season 3	9.54 (7.25 to 12.54)	9.41 (7.22 to 12.28)		
B/Victoria Day 22/50 HI GMT Season 3	66.82 (51.29 to 87.04)	11.94 (9.23 to 15.44)		
B/Yamagata Day 1 HI GMT Season 3	23.98 (16.74 to 34.36)	27.33 (19.27 to 38.76)		
B/Yamagata Day 22/50 HI GMT Season 3	108.49 (85.16 to 138.22)	21.68 (17.11 to 27.46)		

Notes:

[1] - S2 n=210; S3 n=154

[2] - S2 n=212; S3 n=145

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: Percentage of subjects achieving seroconversion for 4 influenza strains (HI assay)

End point title	Secondary Immunogenicity: Percentage of subjects achieving seroconversion for 4 influenza strains (HI assay)
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End point description:

Immunogenicity was characterized by HI assay 3 weeks after the last vaccination in a subset of subjects 2 to <9 years of age enrolled in Season 2 (n=432) and Season 3 (n=319) who were immunized and had immunogenicity data at the assessed timepoints (FAS Immunogenicity). Immunogenicity was assessed at baseline (Day 1; all subjects in immunogenicity subset), at Day 22 (all "previously vaccinated" subjects receiving a single dose of the study vaccine), and at Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains using the HI assay.

Seroconversion was defined as: either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a prevaccination HI titer ≥1:10 and a ≥4 fold increase in postvaccination HI titer)

Dataset used: FAS Immunogenicity = All subjects in the All Enrolled Set who received at least one dose of study vaccine and provided evaluable serum samples at both baseline and after the last vaccination.

Data

End point type	Secondary
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End point timeframe:

Day 22 (all previously vaccinated subjects) or Day 29 and Day 50 (all not previously vaccinated subjects receiving 2 doses)

End point values	QIVc (≥ 2 years to < 9 years of age)	Comparator (≥ 2 years to < 9 years of age)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210 ^[3]	212 ^[4]		
Units: percentage of participants				
number (confidence interval 95%)				
A/H1N1 Season 2	59.5 (52.55 to 66.22)	1.9 (0.52 to 4.80)		
A/H3N2 Season 2	19.0 (13.97 to 25.02)	1.9 (0.52 to 4.80)		
B/Victoria Season 2	40.0 (33.32 to 46.97)	2.9 (1.06 to 6.11)		
B/Yamagata Season 2	49.5 (42.57 to 56.49)	4.8 (2.31 to 8.58)		
A/H1N1 Season 3	74.0 (66.35 to 80.75)	6.2 (2.88 to 11.46)		
A/H3N2 Season 3	51.9 (43.76 to 60.06)	1.4 (0.17 to 4.89)		
B/Victoria Season 3	58.4 (50.23 to 66.32)	3.4 (1.13 to 7.86)		
B/Yamagata Season 3	58.4 (50.23 to 66.32)	1.4 (0.17 to 4.89)		

Notes:

[3] - S1 n=210; S2 n=154

[4] - S1 n=212; S2 n=145

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: Geometric mean ratio for 4 influenza strains (HI assay)

End point title	Secondary Immunogenicity: Geometric mean ratio for 4 influenza strains (HI assay)
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End point description:

Immunogenicity was characterized by HI assay 3 weeks after the last vaccination in a subset of subjects 2 to < 9 years of age enrolled in Season 2 (n=432) and Season 3 (n=319) who were immunized and had immunogenicity data at the assessed timepoints (FAS Immunogenicity). Immunogenicity was assessed at baseline (Day 1; all subjects in immunogenicity subset), at Day 22 (all "previously vaccinated" subjects receiving a single dose of the study vaccine), and at Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains using the HI assay.

Geometric mean ratios (GMRs) measure the ratio in immunogenicity titers within subject\

Dataset used: FAS Immunogenicity = All subjects in the All Enrolled Set who received at least one dose of study vaccine and provided evaluable serum samples at both baseline and after the last vaccination.

End point type	Secondary
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End point timeframe:

Day 22/Day 1 (all previously vaccinated subjects) or Day 29/Day 1 and Day 50/Day 1 (all not previously vaccinated subjects receiving 2 doses)

End point values	QIVc (≥2 years to <9 years of age)	Comparator (≥2 years to <9 years of age)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210 ^[5]	212 ^[6]		
Units: ratio				
number (confidence interval 95%)				
A/H1N1 Season 2	5.76 (5.06 to 6.55)	1.00 (0.88 to 1.14)		
A/H3N2 Season 2	1.74 (1.56 to 1.95)	0.99 (0.89 to 1.11)		
B/Victoria Season 2	3.79 (3.33 to 4.32)	1.00 (0.88 to 1.14)		
B/Yamagata Season 2	4.63 (4.01 to 5.34)	1.08 (0.94 to 1.25)		
A/H1N1 Season 3	9.73 (7.24 to 13.09)	1.23 (0.92 to 1.64)		
A/H3N2 Season 3	4.14 (3.49 to 4.91)	1.02 (0.87 to 1.21)		
B/Victoria Season 3	7.01 (5.38 to 9.14)	1.25 (0.97 to 1.62)		
B/Yamagata Season 3	5.27 (4.14 to 6.72)	1.05 (0.83 to 1.33)		

Notes:

[5] - S1 n=210; S2 n=154

[6] - S1 n=212; S2 n=145

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: Percentage of subjects with HI titer ≥1:40 for 4 influenza strains (HI assay)

End point title	Secondary Immunogenicity: Percentage of subjects with HI titer ≥1:40 for 4 influenza strains (HI assay)
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End point description:

Immunogenicity was characterized by HI assay 3 weeks after the last vaccination in a subset of subjects 2 to <9 years of age enrolled in Season 2 (n=432) and Season 3 (n=319) who were immunized and had immunogenicity data at the assessed timepoints (FAS Immunogenicity). Immunogenicity was assessed at baseline (Day 1; all subjects in immunogenicity subset), at Day 22 (all "previously vaccinated" subjects receiving a single dose of the study vaccine), and at Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains using the HI assay.

The measures for assessing immunogenicity as determined by HI were as follows: Percentage of subjects with an HI titer ≥1:40 on Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.

Dataset used: FAS Immunogenicity = All subjects in the All Enrolled Set who received at least

End point type	Secondary
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End point timeframe:

Day 1 (all subjects), Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses)

End point values	QIVc (≥2 years to <9 years of age)	Comparator (≥2 years to <9 years of age)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210 ^[7]	212 ^[8]		
Units: percentage of participants				
number (confidence interval 95%)				
A/H1N1 Season 2	88.6 (83.47 to 92.54)	58.6 (51.59 to 65.31)		
A/H3N2 Season 2	90.0 (85.12 to 93.70)	92.4 (87.92 to 95.58)		
B/Victoria Season 2	54.3 (47.29 to 61.16)	24.3 (18.65 to 30.66)		
B/Yamagata Season 2	63.8 (56.91 to 70.31)	21.4 (16.08 to 27.60)		
A/H1N1 Season 3	94.8 (90.02 to 97.73)	55.2 (46.70 to 63.43)		
A/H3N2 Season 3	74.0 (66.35 to 80.75)	24.8 (18.03 to 32.68)		
B/Victoria Season 3	68.8 (60.88 to 76.04)	13.1 (8.08 to 19.70)		
B/Yamagata Season 3	79.2 (71.95 to 85.33)	46.2 (37.90 to 54.67)		

Notes:

[7] - Season 2 QIVc N = 210

Season 2 Comp N = 212

Season 3 QIVc N = 154

Season 3 Comp N = 145

[8] - Season 2 QIVc N = 210

Season 2 Comp N = 212

Season 3 QIVc N = 154

Season 3 Comp N = 145

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Safety: Percentage of subjects with solicited local and systemic adverse events for 7 days after vaccination

End point title	Secondary Safety: Percentage of subjects with solicited local and systemic adverse events for 7 days after vaccination
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End point description:

The secondary safety objective was to assess the safety and tolerability of QIVc.

The measures for assessing safety and tolerability were as follows: Percentage of subjects with solicited local and systemic adverse events (AEs) for 7 days after vaccination on Day 1 (for "previously vaccinated" subjects) or for 7 days after vaccination on Day 1 and Day 29 (for "not previously vaccinated" subjects) in the QIVc group and the non-influenza comparator vaccine group.

Dataset used: Solicited Safety Set = All subjects in the Exposed Set who had gone through any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics.

Note: Other solicited adverse events refer to use of analgesics / antipyretics for prophylaxis or treatment.

End point type	Secondary
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End point timeframe:

7 days after vaccination on Day 1 (for "previously vaccinated" subjects) or for 7 days after vaccination on Day 1 and Day 29 (for "not previously vaccinated" subjects)

End point values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2255	2254		
Units: Percentage				
number (not applicable)				
Solicited AEs	51.4	48.6		
Solicited Local AEs	36.8	33.6		
Solicited Systemic AEs	31.4	30.5		
Other	8.6	7.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Safety: Percentage of subjects with unsolicited AEs for 21 days after vaccination

End point title	Secondary Safety: Percentage of subjects with unsolicited AEs for 21 days after vaccination
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End point description:

The secondary safety objective was to assess the safety and tolerability of QIVc.

The measures for assessing safety and tolerability were as follows: Percentage of subjects with unsolicited AEs assessed from Day 1 to Day 22 (for "previously vaccinated" subjects) or from Day 1 to Day 50 (for "not previously vaccinated" subjects) in the QIVc group and the non-influenza comparator vaccine group.

Dataset used: Unsolicited Safety Set = All subjects in the Exposed Set who had gone through any AE assessments, ie, a subject did not have to have any AEs to be included in this population.

End point type	Secondary
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End point timeframe:

Day 1 to Day 22 (for "previously vaccinated" subjects) or from Day 1 to Day 50 (for "not previously vaccinated" subjects)

End point values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2258	2255		
Units: Percentage				
number (not applicable)				
Any AE	28.0	27.9		

Any AE (Mild)	24.4	24.6		
Any AE (Moderate)	4.8	4.5		
Any AE (Severe)	0.5	0.5		
Related AE	4.3	3.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Safety: Percentage of subjects with SAEs, AEs leading to withdrawal from vaccination and/or the study, MAAEs, and NOCDs reported

End point title	Secondary Safety: Percentage of subjects with SAEs, AEs leading to withdrawal from vaccination and/or the study, MAAEs, and NOCDs reported
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End point description:

The secondary safety objective was to assess the safety and tolerability of QIVc.

The measures for assessing safety and tolerability were as follows: Percentage of subjects with SAEs, AEs leading to withdrawal from vaccination and/or the study, New Onset of Chronic Diseases (NOCDs), medical attended AEs (MAAE) within 30 days of ILI, AEs leading to death reported during the subject's entire participation in the study (ie, from Day 1 to Day 181 [for "previously vaccinated" subjects] or from Day 1 to Day 209 [for "not previously vaccinated" subjects]), or until the end of influenza season, whichever was longer, and all medications associated with these events.

Medically-attended AEs were collected through the first 30 days after the first occurrence of influenza-like illness.

Dataset used: Unsolicited Safety Set = All subjects in the Exposed Set who had gone through any AE assessments, ie, a subject did not have to have any AEs to be included in this popul

End point type	Secondary
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End point timeframe:

from Day 1 to Day 181 [for "previously vaccinated" subjects] or from Day 1 to Day 209 [for "not previously vaccinated" subjects]), or until the end of influenza season, whichever was longer

End point values	QIVc (≥2 years to <18 years)	Comparator (≥2 years to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2258	2255		
Units: percentage				
number (not applicable)				
SAE	1.1	1.3		
Related SAE	0	0		
AE leading to study withdrawal	0	0		
MAAE	27.2	30.1		
NOCD	0.4	0.5		
Death	0	0.04		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through end of study

Adverse event reporting additional description:

Nonserious Unsolicited AEs and SAEs are reported

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	QIVc
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Reporting group description:

A single dose of approximately 0.5 mL of QIVc was administered on Day 1. (QIVc = Quadrivalent Influenza Vaccine, cell-based). For those subjects who were not previously vaccinated, a second dose was administered on Day 29. For subjects randomized in the QIVc-arm, the second dose was QIVc.)

Reporting group title	Non-influenza Comparator Vaccine
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Reporting group description:

A single dose of approximately 0.5 mL of non-influenza comparator vaccine was administered on Day 1. (Non-influenza comparator vaccine is (meningococcal [Groups A, C, W-135, and Y] oligosaccharide diphtheria CRM197 conjugate vaccine [Men ACWY]. For those not previously vaccinated, a second dose was administered on Day 29.

For subjects randomized in the non-influenza comparator group, the second dose was a placebo (saline for injection).

Serious adverse events	QIVc	Non-influenza Comparator Vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 2258 (1.11%)	30 / 2255 (1.33%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			

subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder developmental			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Loss of consciousness			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status migrainosus			

subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
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			
Unevaluable event			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (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 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
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			
Epistaxis			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
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			
Drug eruption			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			

subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (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			
Pharyngitis			
subjects affected / exposed	1 / 2258 (0.04%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis bacterial			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 2258 (0.22%)	3 / 2255 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	2 / 2258 (0.09%)	2 / 2255 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	2 / 2258 (0.09%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 2258 (0.04%)	2 / 2255 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 2258 (0.04%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue haemorrhagic fever			
subjects affected / exposed	1 / 2258 (0.04%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal gastroenteritis			
subjects affected / exposed	1 / 2258 (0.04%)	0 / 2255 (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 / 2258 (0.04%)	0 / 2255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			

subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 2258 (0.00%)	2 / 2255 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
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	0 / 2258 (0.00%)	3 / 2255 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Type 1 diabetes mellitus			

subjects affected / exposed	0 / 2258 (0.00%)	1 / 2255 (0.04%)
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: 5 %

Non-serious adverse events	QIVc	Non-influenza Comparator Vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	871 / 2258 (38.57%)	963 / 2255 (42.71%)	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	791 / 2258 (35.03%)	894 / 2255 (39.65%)	
occurrences (all)	1194	1252	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	97 / 2258 (4.30%)	121 / 2255 (5.37%)	
occurrences (all)	111	135	
Upper respiratory tract infection			
subjects affected / exposed	216 / 2258 (9.57%)	216 / 2255 (9.58%)	
occurrences (all)	298	270	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2016	This amendment included updates to support regulatory submissions in additional global regions and to satisfy CHMP requests made after review of the study synopsis. These changes consisted of the following: extending the age range include subjects ≥ 2 years of age; a co-primary objective was added to the revised protocol, for evaluation of efficacy in subjects 2 to <18 years of age; secondary endpoints were aligned with the cohort distribution of 3 to <18 , 2 to <18 , 3 to <9 , 2 to <9 , and 9 to <18 years of age, to allow for evaluation per age cohort; monitoring of ILI cases was to continue until the end of the influenza season in the revised protocol, instead of until the end of study participation; blood drawn from the immunogenicity subset was lowered from 10 mL to 7 mL per visit to reduce subject burden; pregnancy testing was scheduled to occur prior to each vaccination; the end of study definition was adapted for reporting purposes and the number of immunogenicity subset subjects was clarified as 666 subjects.
30 November 2017	This amendment described an adjustment of the assumptions underlying the sample size calculation to maintain the protocol-defined power for demonstration of the efficacy objective in subjects 3 to <18 years of age. The assumed event rate in non-influenza comparator arm was updated from 4% to 8% and additional updated assumptions included: reducing the original absolute VE (aVE) assumption from 60% to 50%; the co-primary aVE assumption (aVE = 55%) was changed to aVE = 45%; the primary and co-primary endpoints were reversed; adjustments to the sample size and the required number of influenza events were needed in order to maintain study power. The number of influenza-confirmed cases needed to proceed to final analysis increased from 144 to 381. An interim analysis was planned after the majority of the cases for the second influenza season were collected; the total number of healthy subjects planned to be enrolled was updated from 6368 to 7692; allocation strategy was changed from a 2:1 to a 1:1; immunogenicity subset enrollment was to be performed during the second and subsequent seasons, and not limited to the second season only; given the changes in subject allocation for the immunogenicity subset, and because of the descriptive nature of the secondary immunogenicity objective, the immunogenicity sampling strategy was further clarified. Sample size for secondary immunogenicity objectives has been modified and redistributed in the revised protocol and as a consequence of changes in the allocation ratio and enrollment was to be performed during the second and subsequent seasons, the number of subjects was increased.

20 June 2018	<p>Multiple reasons for this amendment included: 1) adjusting the timing, scope and conditionality of the interim analysis (IA), 2) enrolment in a third season was planned despite the fact the total number of cases approached the minimal number of cases estimated for analysis, 3) Added 2 age cohorts to evaluate efficacy, immunogenicity, and safety Compliance to EU GDPR was also added to Data Management 4) an exploratory objective has been added to further describe vaccine efficacy against antigenically matched A/H3N2 influenza cases and the microneutralization assay may be used to characterize the immune response of QIVc.</p> <ol style="list-style-type: none"> 1. The prespecified interim analysis after the second season was removed and updated to an interim analysis performed a) when a sufficient number of influenza-confirmed cases have occurred and b) conditional to the needs of the Sponsor. 2. The test for futility was removed from the interim analysis, as vaccine efficacy and influenza strain distribution could vary widely between influenza seasons. 3. Enrolment in a third season was planned and reasons provided in the amendment. 4. The following exploratory efficacy objective was added: To describe the absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by occurrence of culture confirmed illness caused by influenza H3N2 virus strains antigenically matched to the influenza H3N2 A/Singapore/GP2050/2015 (cell seed) strain. 5. Although antigenic characterization of influenza viruses using HI assay was still successful for the antigenic characterization of influenza A(H1N1) and B-viruses, problems had arisen for A(H3N2) viruses mainly due to evolutionary changes in agglutination properties. As an alternative, a MN assay might be used to evaluate the immunogenicity of QIVc.
13 December 2018	<p>This amendment included changes to address regulatory feedback in regards to the intended use of microneutralization assay data and to reduce the overall number of planned subgroup analyses. Specifically, to reflect regulatory feedback, the microneutralization (MN) assay was kept for Exploratory Immunogenicity Endpoints and removed from the Secondary Immunogenicity Endpoints and total number of age categories for subgroup analyses was reduced.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported